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Cues and sensory manipulations to modulate long-range autocorrelations in gait variability among patients with Parkinson's disease

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Summary

Parkinson's disease causes gait disorders in terms of both spatiotemporal parameters (speed, step length, cadence) and variability (magnitude, temporal organization), increasing the risk of falls and their consequences. The use of external stimuli (tactile, auditory, visual) is recommended to treat these disorders. These "cueings" have positive effects on spatiotemporal parameters, but there are many questions concerning their impact on the temporal organization of patients' gait, measured via long-range autocorrelations (LRA) computation.

In this thesis, the patients' senses were manipulated (touch, hearing, vision) to determine their effects on the LRA present in their gait. Firstly, tactile cueing showed similar effects to auditory cueing on patients' LRA. With regard to auditory cueing, we have established that a cueing frequency that fluctuates according to a structured variability may be the best choice for maintaining a good level of LRA. Concerning vision, virtual reality makes it easy to manipulate visual feedbacks. Via a systematic review of the literature with meta-analysis, we showed that virtual reality is effective in improving patients' balance. Next, we manipulated patients' vision by adding natural optic flow in immersive virtual reality during treadmill walking. This ecological addition enabled us to restore LRA similar to those measured during overground walking, possibly increasing the validity of this measurement when analyzing it in a laboratory setting.

Keywords: Parkinson, cueing, gait, variability, long-range autocorrelations, virtual reality

Résumé

La maladie de Parkinson provoque des troubles de marche aussi bien en terme de paramètres spatiotemporels (vitesse, longueur du pas, cadence) que de variabilité (grandeur, organisation temporelle) augmentant le risque de chutes et leurs conséquences. L'utilisation de stimuli externes (tactiles, auditifs, visuels) est recommandée pour traiter ces troubles. Ces « indiçages » ont des effets positifs sur les paramètres spatiotemporels mais beaucoup de questions se posent concernant leur impact sur l'organisation temporelle de la marche des patients, mesurée via le calcul des autocorrélations à long terme (ALT).

Dans cette thèse, les sens des patients ont été manipulés (toucher, audition, vision) pour en déterminer les effets sur les ALT dans leur marche. Premièrement, l'indiçage tactile présente des effets semblables à l'indiçage auditif sur les ALT des patients. Concernant l'indiçage auditif, nous avons établi qu'une fréquence d'indiçage fluctuant selon une variabilité structurée pourrait être le meilleur choix pour maintenir une bon niveau de ALT. À propos de la vision, la réalité virtuelle permet d'aisément manipuler les feedbacks visuels. Via une revue systématique de la littérature avec méta-analyse, nous avons montré que la réalité virtuelle est efficace pour améliorer l'équilibre des patients. Ensuite, nous avons manipulé la vision des patients en ajoutant un flux optique naturel en réalité virtuelle immersive durant la marche sur tapis roulant. Cet ajout écologique nous a permis de restaurer des ALT semblables à celles mesurées lors de la marche sur sol plat, augmentant possiblement la validité de cette mesure lors d'analyses en laboratoire.

Mots-clés : Parkinson, indiçage, marche, variabilité, autocorrélations à long terme, réalité virtuelle

General Introduction

Parkinson's Disease

Parkinson's Disease (PD) was first described by James Parkinson in his 1817 "An essay on the shaking palsy".[1] Some of the patients he described were people seen in the streets of London. At that time, this pathology did not yet bear his name and was described as "paralysis agitans". It was not until later in the 19th century that Jean-Martin Charcot finally gave the name Parkinson's disease to this syndrome. Charcot even enhanced the definition of Parkinson's disease and described forms of the disease without tremors but he also put the emphasis on the slowness of movements of these patients.[2] The neuron degeneration in substantia nigra, part of the basal ganglia, was first described in 1919, the role of dopamine was first discussed only in 1957[3] and decreased dopamine concentrations in striatum was found in 1960[4], more than 140 years after Parkinson's first clinical description. Concerning etiology of the disease and favoring factors, genetic factors and other environmental elements are still debated.[5]

From an epidemiological point of view, PD is the second most frequent neuro-degenerative disease after Alzheimer's disease.[6,7] Prevalence in Europe is estimated for all ages at 66 to 1500 per 100,000.[8] Regarding incidence, it is multiplied by 5 to 10 times between 30 and 90 years of age, going from 5/100,000 to 35/100,000 new cases per year.[9] Even if this figure already seems important, it could double by 2040.[10]

Most known motor clinical features related to PD results from dopamine-producing neurons degeneration with Lewy bodies formation (aggregate of α-synuclein) in substantia nigra pars compacta, part of the basal ganglia, brain structure situated in the midbrain and involved in movement regulation.[11,12] Motor symptoms are key elements for the clinical diagnosis but these may be preceded by non-motors symptoms between 10 to 20 years before motor manifestations in a heterogeneous way (hyposmia, constipation, depression,…)[11,13–16] (Figure 1.1). Since prodromal symptoms begin years before diagnosis, it is estimated that up to 80% of the dopaminergic cells are lost before classic motor symptoms appearance.[17]

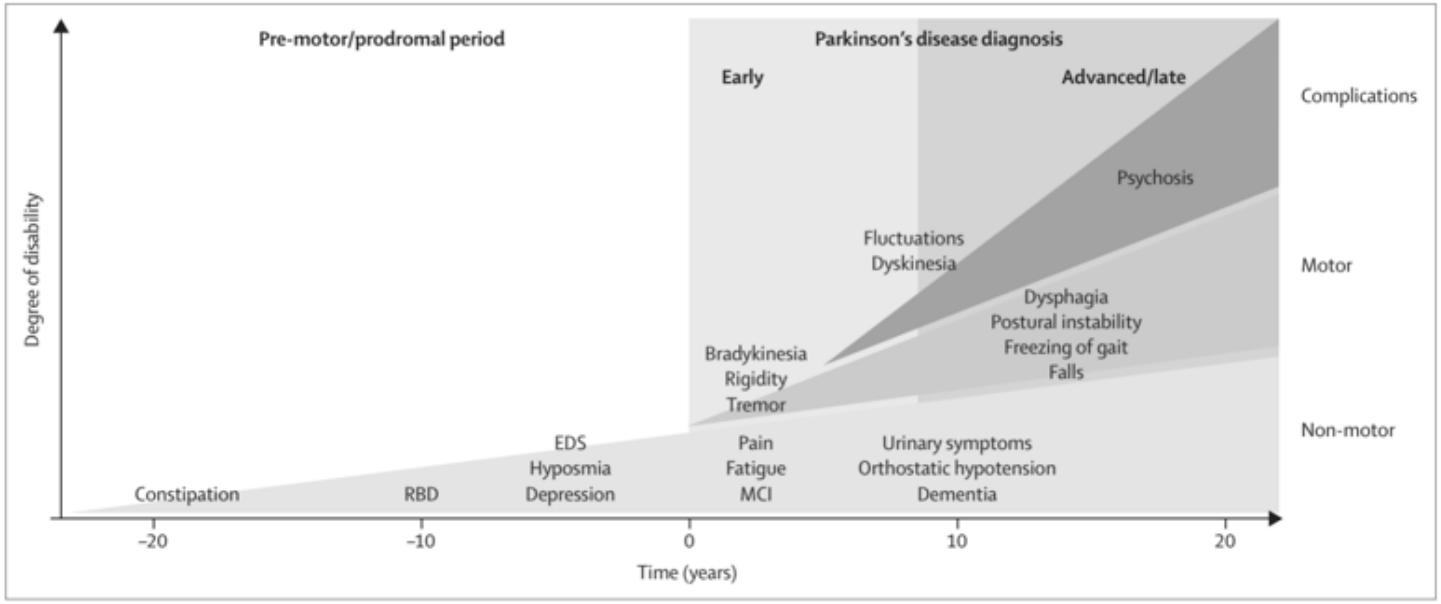

Figure 1.1. *Clinical manifestations of Parkinson's disease since diagnosis. Adapted from Kalia et al (2015).*[15]

General description of the symptoms

Clinically, Parkinson's disease is characterized by non-motor and motor symptoms (Figure 1.2).

Non-motor symptoms are divers and divided into multiple subtypes (neuropsychiatric, cognitive, autonomic, sleep disorders).[17] These are major elements interfering with PD patients' quality of life but will not be discussed in this manuscript, which focuses primarily on motor symptoms and gait.

Among motor symptoms, the classic motor tetrad is composed of rest tremor, stiffness, bradykinesia and postural instability. PD patients could be divided into three disease subtypes : tremor-dominant (with relative absence of other motor symptoms), non-tremor-dominant (akineto-rigid syndrome and postural/gait disorders) and a mixed subtype with several motor symptoms combined.[15] Classically, tremor-dominant patients would present with slower evolution than akineto-rigid patients.[18] The non-tremor-dominant patients often present with gait disorders combined with postural instability that could lead to falls and their consequences: bone fractures, hemorrhages, post-fall syndrome, kinesiophobia,… The prevalence of falls is enormous since 80% of PD patients with more than 15 years since diagnostic would experience falls.[19]

Before discussing gait disorders specific to PD, it is important to determine how gait can be analyzed in general.

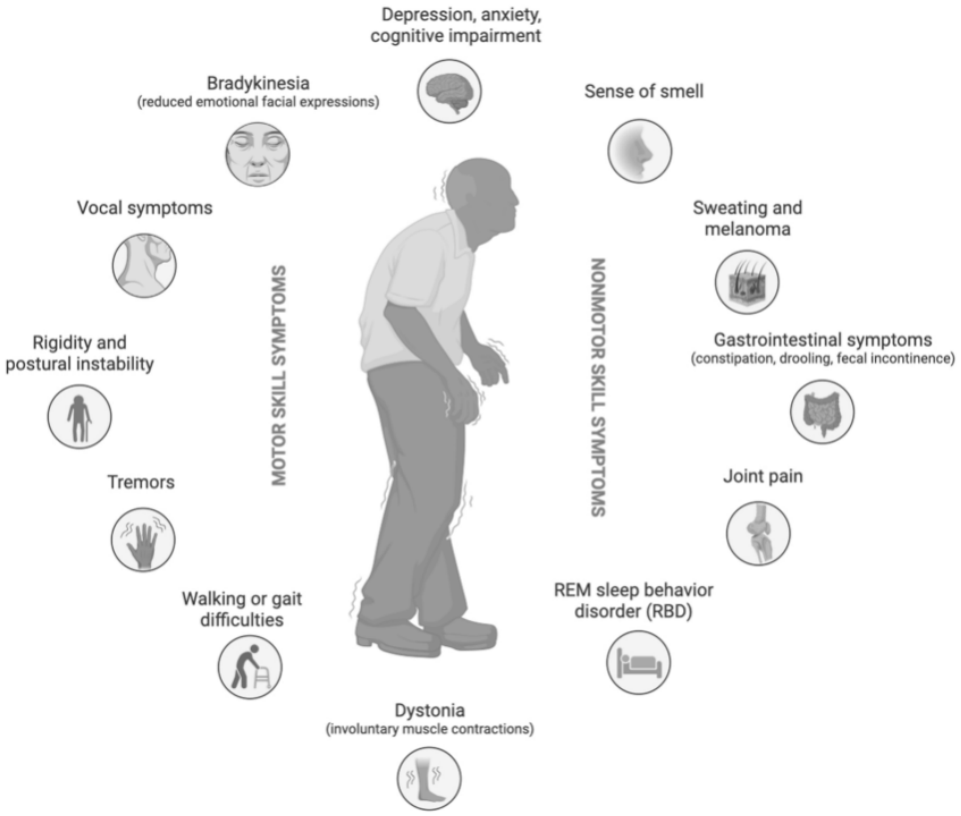

Figure 1.2. *Symptoms of Parkinson's disease. Adapted from Leite Silva et al. (2023).*[17]

A general introduction to linear and non-linear analysis of gait variability (Long-Range Autocorrelations computation)

Gait can be analyzed via the study of spatiotemporal parameters (speed, cadence, step length), the study of kinematics (amplitudes of movements) or even the study of gait dynamics (muscular moments, energy cost). These analyses are called "linear" because no relationship is sought between the different variables at different time-points. This way of analyzing human movement, and more particularly gait, provides valuable information for monitoring patients with objective measurements. Although useful, these linear analyses do not account for the important complexity of a movement such as walking. By complexity, it is understood that gait is a system hard to understand and difficult to predict in time. This complexity in gait is sought to be the result of multiple interactions between the internal components generating it (brain, spinal cord, central pattern generator, peripheral nerves, musculoskeletal system) and external components (sensory inputs, interaction with the environment, characteristics of the ground,…).[20]

Some physiological signals exhibit fluctuations that appear stochastic at first glance, but actually vary according to non-linear dynamics.[21] For example, this is the case with the heart rate of a healthy subject, which fluctuates over time in a structured fractal pattern (Figure 1.3), losing this complexity in the event of a pathological situation (too random or loss of variation) (Figure 1.4).[22] The same way, it is now known that different gait parameters such as step length or stride duration (the most studied) fluctuate over time in the long term in an organized fashion (Figure 1.5). In this idea, dynamic analyses of

non-linear systems such as gait have been proposed to study the temporal variability of a given parameter.

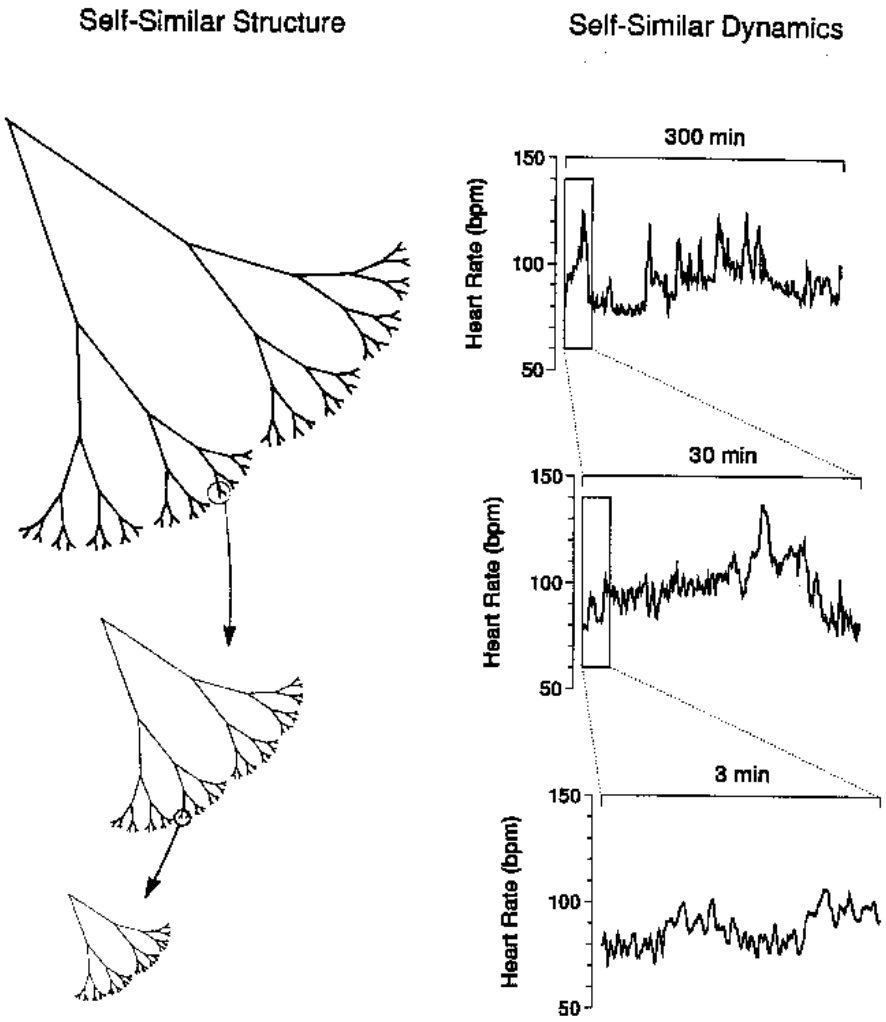

Figure 1.3. *Left, schematic of a tree-like fractal has self-similar branchings such that the small scale (magnified) structure resembles the large scale form. Right, a fractal process such as heart rate regulation generates fluctuations on different time scales (temporal "magnifications") that are statistically self-similar. Adapted from Goldberger et al. (1996).*[23]

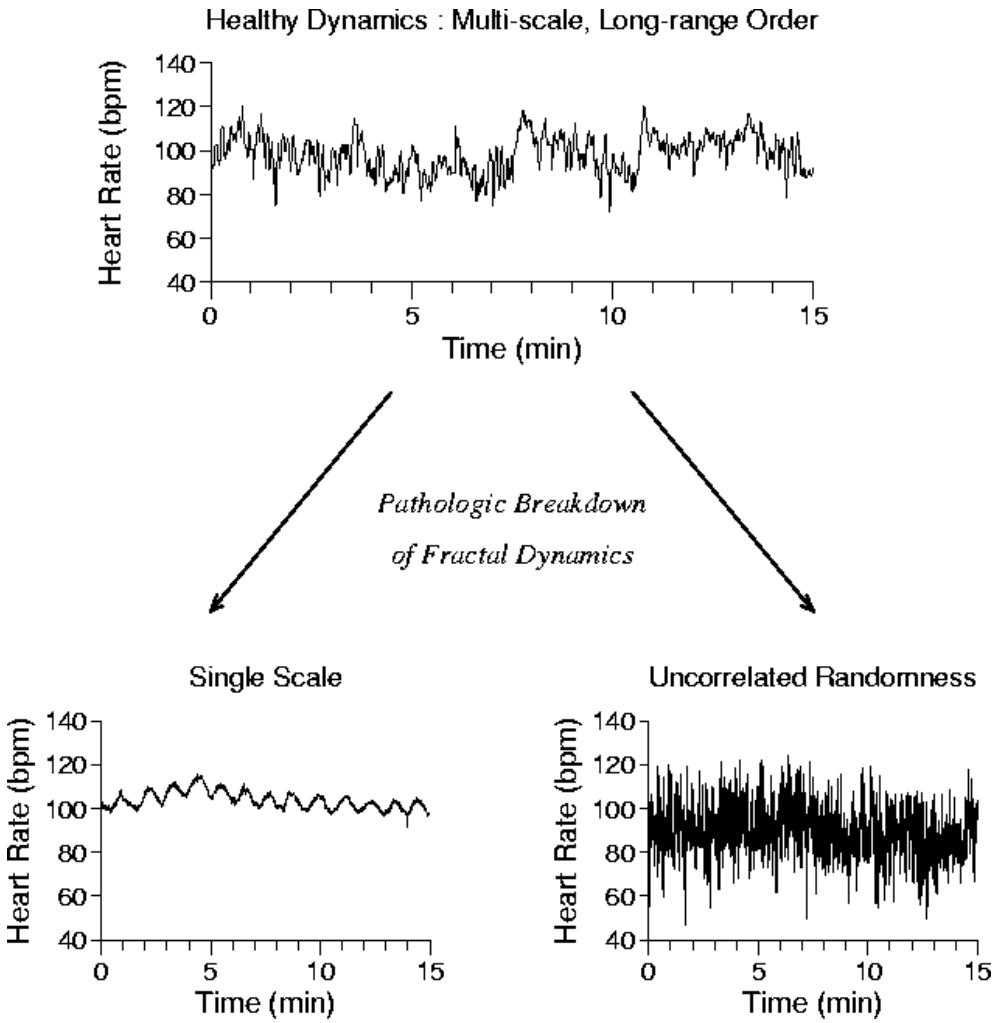

Figure 1.4. *Breakdown of a fractal physiological control mechanism can lead ultimately either to a highly periodic output dominated by a single scale or to uncorrelated randomness. The top heart rate time series is from a healthy subject; bottom left is from a subject with heart failure; and bottom right from a subject with atrial fibrillation. Adapted from Goldberger et al. (1996).*[23]

One way to perform this non-linear analysis is to evaluate the predictability of a data value over time, looking for a fractal-like temporal behavior. In the context of gait and using these non-linear analysis, a certain temporal order in variability can be observed demonstrating the presence of what can be called Long-Range Autocorrelations (LRA).[24–26] The presence of LRA in the temporal organization of stride duration variability could be interpreted as a sign of a long term memory in the locomotor system.[27] LRA then would imply persistence in the fluctuations, some kind of predictability. Large fluctuations tend to be followed by other large fluctuations and small fluctuations tend to be followed by other small fluctuations.

Various methods for LRA computation have been used throughout the studies (Rescaled Range Analysis, Power Spectral Density, Detrended Fluctuation Analysis, ARFIMA, etc.). Among these methods, the evenly spaced averaged Detrended Fluctuation Analysis (DFA) is probably the most widely used. Indeed, it is one of the most robust against stationary and non-stationary processes, but also in the case of missing data, and one of the most reliable for short time series with good intraday and interday reliability.[28]

As for heart rate, this « structured variability » in gait could be a sign of its healthy state, meaning sufficient predictability to carry out a steady walk but with enough adaptability to respond to disruptive elements, what could be called a homeostasis.[27,29,30] According to this theoretical framework, a deviation of this homeostasis towards a too rigid behavior of the system (too stable) or on the contrary a too unpredictable one could translate a pathological state.[30,31] Using the DFA, the α exponent is computed and interpretation of it could be made. LRA are present when α exponent is between 0.5 and 1 which implies persistence in the variations. This means

that large stride duration fluctuations tend to be followed by other large fluctuations, and vice-versa. An α exponent <0.5 is the sign of anti-persistence and α exponent = 0.5 corresponds to complete randomness in the fluctuations (i.e., white noise). An α exponent = 1 (i.e., 1/f noise) is the boundary between stationarity and non-stationarity.[32] In this context, 1/f noise is interpreted as "a 'compromise' between the complete unpredictability of white noise (α = 0.5) (very rough 'landscape') and the very smooth 'landscape' of Brownian noise (α = 1.5)".[33] Then, α exponent = 1 could be considered as the optimal state of variability characterizing healthy gait according to the theoretical framework of optimal movement variability.[28,34] When data from healthy and pathological patients are pooled from several studies to establish thresholds of healthy variability, we tend to observe an α exponent close to 0.8 rather than 1.[28]

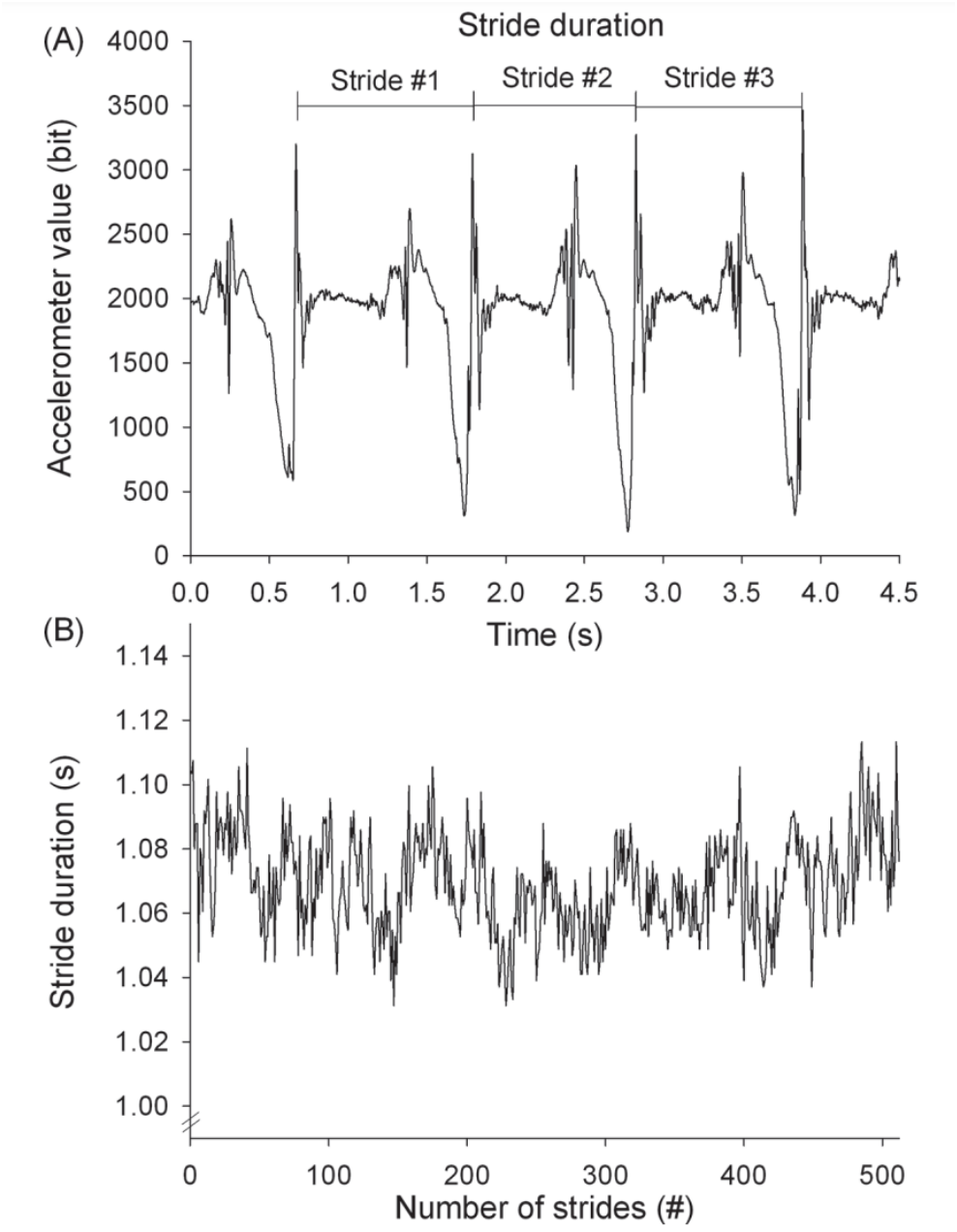

Figure 1.5. *Peak detection method and typical trace of stride duration over time during healthy gait. Adapted from Warlop et al. (2016).*[35]

Origins of Long-Range Autocorrelations

The study of this parameter in the context of diseases such as Parkinson's disease allows us to theorize about the origin of LRA. The origin and control of the LRA in human gait is largely debated. The main hypothesis suggests an internal centrally controlled process since LRA are affected in central nervous system pathologies such as Huntington's disease, amyotrophic lateral sclerosis and Parkinson's disease.[32,35,36] More specifically, the basal ganglia could be involved given their role in the generation of rhythmic movements but also in the regulation of gait and posture.[12,37,38] Also, the LRA are affected in PD, a pathology where this brain region is specifically impaired.[29,39–41] Others attribute its origin to biomechanical structures[42,43] or even to the presence of Central Pattern Generators (CPGs) in the spinal cord.[44] Other authors have studied LRA in patients with peripheral nerve damage and found no change in LRA[45], further emphasizing its potential central origin.

Gait impairments in Parkinson's disease

Regarding PD, linear and non-linear analyses are of interest.

PD gait is characterized by reduced gait speed and step length, freezing of gait (sudden and relatively brief episodes of inability to produce steps) and increased randomness in stride duration variability in terms of temporal organization.[27] Indeed, non-linear analysis of PD gait allows to demonstrate a breakdown of LRA.[35,46] Following the theory of the homeostasis in complex systems described earlier, this increased randomness in the temporal organization of gait (α exponent close to 0.5) could then be a pathological feature of PD. More interestingly, previous studies demonstrated strong correlations between this breakdown of LRA, balance impairments and

disease progression.[35,46] Therefore, analysis of temporal organization of stride duration variability by LRA computation has been suggested as an objective biomarker of postural instability, fall risk and disease progression in PD patients.[35,37,47] Furthermore, recent research showed possibility to distinguish PD patients from healthy participants using LRA computation.[48,49] Also, LRA measurement would make it possible to separate different disease severity groups according to Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr scale (Figure 1.6) using non-linear measures computed during long acquisition periods[35,48,49] better than linear analysis of spatiotemporal parameters, such as stride length, measured during short time frames.[49] Despite these previous interesting results concerning the clinical interest of LRA measurement, it should be remembered that LRA calculation is not yet implemented in routine clinical practice. For this reason, further research is needed to increase our knowledge of the subject and, if possible, to implement it in our practice as a complementary gait outcome to follow.

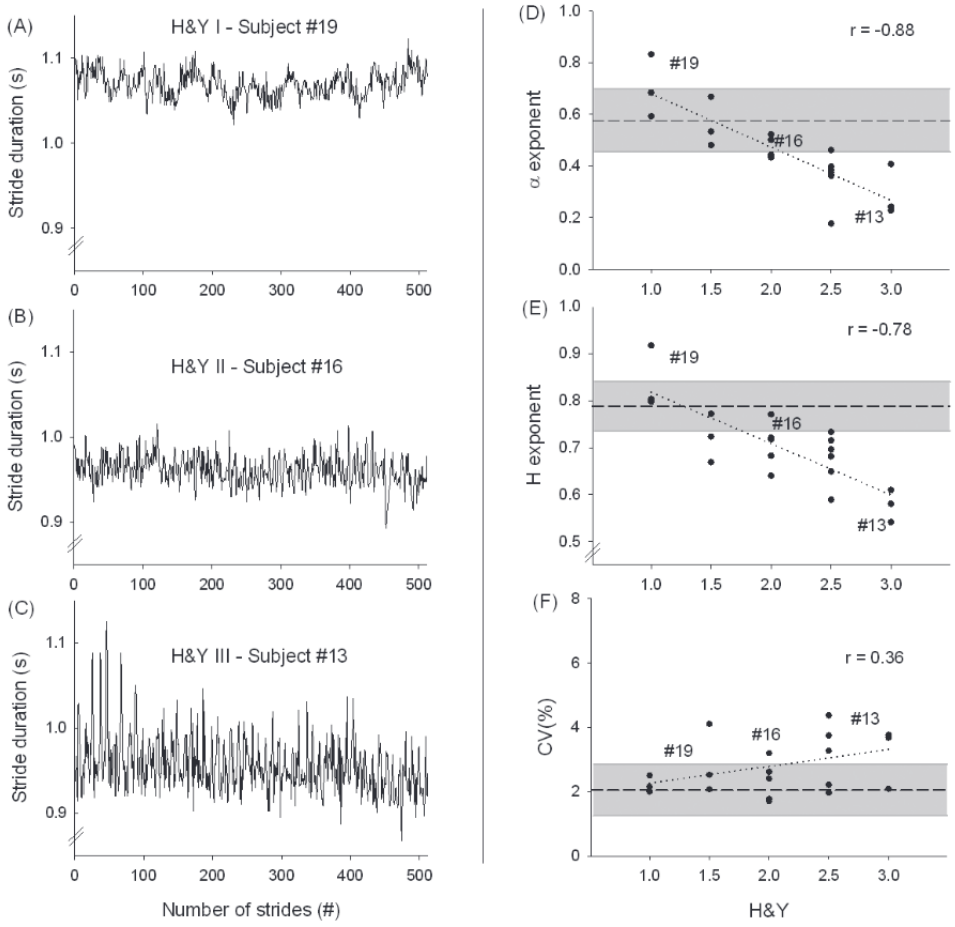

Figure 1.6. *Selected typical traces of stride duration variability of patients with Parkinson's disease (PD) according to disease severity (Hoehn & Yahr scale; H&Y scale) (A–C). On the right side, the evolution of individual values of the α and Hurst exponents (D–E) and coefficient of variation (CV) of stride duration (F) with disease severity. Grey area indicates values from normative data set of healthy subjects (9, 27). r = Spearman's correlation coefficient. Adapted from Warlop et al. (2016).*[35]

Now that these gait impairments are known, how should they be treated?

The basic treatment of motor symptoms in PD is pharmacological. Although effective on tremors and plastic rigidity, these treatments are only partially effective on patients' postural stability and gait.[50–53] It is in this context that researchers and clinicians are seeking ever more innovative non-pharmacological rehabilitation treatments to improve these parameters and reduce patients' risk of falling. The use of cueing is one such treatment.

External factors to regulate gait: manipulation of the senses and introduction to the concept of cueing

Although internally generated, gait is influenced by external factors involving the patient's senses and interacting with the internal elements. For this reason, research has focused for years on influencing patient's senses in order to improve their gait. Among these external factors, “cueing” is one way to influence patients’ senses. Cueing is defined as rhythmic stimulations (punctual stimulations separated by a time or space interval) and have been extensively studied in the context of Parkinson's disease. These stimuli can therefore be of a spatial or temporal nature, facilitating the initiation and continuation of movements such as walking.[54]

Among the senses that can be easily manipulated by cueing, three have been particularly studied: touch, hearing and vision. Vibrations on the skin[55], walking on a treadmill[56], the repetitive sound of a metronome[57], groovy music[58], lines on the ground placed in a parallel fashion[59], ... All these techniques are as many methods allowing to carry out cueing with PD patients.

Studied for about 30 years in the context of Parkinson's disease, the positive effects of cueing on spatiotemporal gait parameters are now well known.[60] It is also recognized that auditory cueing can be used and possibly effective with PD patients presenting with mild cognitive impairment (Mini-Mental State Examination between 15 and 26/30) highlighting its applicability to the majority of PD patients.[61] This method of treatment is also practical because whatever its modality (somatosensory, auditory, visual), cueing is usable and effective at the patient's home[62] and makes it possible to increase the total daily amount of physical activity of patients using it.[63] To complete the picture, cueing can be used and is effective in improving gait in patients who are not on medication[64], allowing to suggest that its use could make it possible to decrease the doses of drug to be administered.

How does cueing work?

As mentioned above, cues are external rhythmic outputs designed to facilitate internal motor control inputs. The oldest theory suggests that cueing allows movement to be generated by bypassing the basal ganglia and the supplementary motor area and instead passing through the premotor cortex.[62,65,66] Also, a Magnetic Resonance Imaging (MRI) study has shown that cueing alleviates the overload on the parietal operculum which is dysfunctional in Parkinson's disease.[67] A complementary theory suggests that cue-guided movement results in enhanced cortical activity that decreases rather than bypasses pathological basal ganglia activity.[59,68–70] This increase in cortical activity would be due to the patient's attention being focused on the cues rather than on the generation of the gait itself.[71–73]

External stimulations and cueing effects on Long-Range Autocorrelations

In addition to cueing effects on spatiotemporal gait parameters, some studies have evaluated their effects on LRA in PD patients.

Touch

Regarding haptic/somatosensory cueing, some studies were interested in the effect of the treadmill on LRA by showing an increase of the LRA of PD patients when walking on it.[56,74] However, to our knowledge, no study has evaluated the effects of rhythmic vibrotactile stimulations (vibrating units in contact with the patients' skin) on LRA. The practicality of this type of cueing is that it allows somatosensory cueing to be carried out during overground walking in situations of the patient's daily life. On the other hand, PD patients are known to have a deficit in the integration of somatosensory information and kinesthesia, as shown by the study of somatosensory evoked potentials[75,76] and positron emission tomography[77], potentially influencing the effects of this type of cueing on patients' gait and perhaps on LRA.

Hearing

Although PD patients present hearing deficits linked to their sometimes advanced age and also central auditory processing deficits linked to the pathology itself[78], auditory cueing remains the most widely used external stimulation for treating patients' gait. As stated before, auditory cueing generally has a positive effect on spatiotemporal gait parameters.[60] On the other hand, these seem to further alter the LRA present in PD patients' gait.[57,79] This observation is applicable to isochronous auditory cueing

(constant inter-beat intervals) which is unfortunately the most common form of auditory cueing used in research but also in clinical practice. Dotov et al. (2017)[57] have already attempted to evaluate the effect of auditory cues presenting with variable rhythms on PD patients' LRA. They confirmed that isochronous auditory cueing alters LRA, and that cueing with a beat frequency varying in a biological fashion would preserve LRA in PD patients' gait at a level similar to that during walking without cueing. Unfortunately, their methods included acquisition times insufficient to perform a robust LRA computation[28,80–83], making their results debatable.

Vision

Regarding vision, it has been shown that PD patients suffer from vision disorders directly linked to damage to the basal ganglia and reduced dopamine levels in peripheral visual structures.[84,85] On the other hand, these same patients have difficulties with proprioception and kinesthesia[86–89], making them highly dependent on visual information to guide their balance and walking, to a greater extent than healthy subjects..[86,90–99] However, this presents a disadvantage since PD patients would rely too much on visual elements and also since they overreact to them.[86,100–102] In contrast, this makes patients potentially very receptive to this type of external stimulations/cueing and there are quite a few vision-related elements to influence. The cues in this case can be either spatial and/or temporal. Lines on the ground placed parallel to each other and perpendicular to the patient's walking direction constitute spatial cues. Light flashes triggered at regular time intervals represent a temporal cueing, like the beat of a metronome. Finally, some researchers have been interested in the manipulation of optic flow, which is a non-rhythmic external stimulation that can be differentiated from cueing.

Optic flow could be defined as the impression that the environment is passing before our eyes when we walk, defined as self-motion perception, which is essential for maintaining our balance and walking in our environment.[103–105] The manipulation of optic flow is interesting since some authors believe that this element is central in the regulation of gait in PD patients.[59,86,90,91] Older to more recent studies have attempted to generate an optic flow during treadmill walking.[86,106–112] Indeed, during treadmill walking, the sensation of optic flow is completely absent. Therefore, an essential ecological element is missing during such a walk, which could be even more confusing for PD patients who rely heavily on it. It is known that treadmill walking modifies the spatiotemporal gait parameters[113,114] and LRA.[56,74,115] Treadmill-based analyses of PD patients' gait could then not reflect their natural gait regarding these parameters. The question is therefore: could this lack of ecological visual elements partly explain these changes during treadmill walking?

As mentioned above, some studies have partly addressed these questions but with means that seem archaic to this day and insufficient to create the illusion of optic flow. The current technologies, by means of immersive Virtual Reality (VR) headsets, allow to erase these defects and to create the illusion of a realistic optic flow. Although VR is a young technology whose effectiveness remains to be further studied in the context of Parkinson's disease, it offers possibilities never seen before. In addition to these technological considerations, no study to our knowledge has evaluated the effects of adding an optic flow during treadmill walking on LRA.

Aims and content of the thesis

As previously developed, cueing has been studied for their effects on PD patients' gait. However, their effects on the LRA present in the gait of these patients still need to be studied in greater depth. The aim of this thesis is to increase our knowledge of the effects of cueing on PD patients' gait in terms of spatiotemporal parameters and variability by exploring the three main senses on which to influence: touch, hearing and vision.

In **Chapter 1**, the effects of vibrotactile cueing on LRA have been studied in PD patients. The aim was to compare these vibrotactile cues with already well-known auditory cues. Our hypothesis was that, despite somatosensory integration impairments in PD, this type of temporal somatosensory cueing would enable us to obtain results similar to those obtained with auditory cueing on spatiotemporal parameters but also on the LRA present in PD patients' gait.

Isochronous auditory cueing is probably the most studied and used cueing in Parkinson's disease. Since isochronous auditory cueing (constant inter-beat intervals) is known to further degrade LRA in PD patients[57,79], question raises of their use since altered LRA have been correlated with poor balance performance in PD.[35,46] The problem could stem from the temporal structure of the isochronous rhythm. Therefore, it remains to be determined whether applying a variation in inter-beat intervals has an impact on LRA of PD patients. In **Chapter 2**, we compared various auditory cues presenting with different inter-beat interval variabilities in terms of temporal organization: isochronous, random, and "autocorrelated" organizations. As discussed earlier, a similar previous study exists[57] but their results required confirmation

using sufficient acquisition times[28,80–83], which was achieved in our study. The hypothesis here was that auditory cueing presenting with an autocorrelated/biological temporal organization would make it possible to maintain the LRA while maintaining the positive effects of cueing on spatiotemporal parameters.

Regarding visual cueing, the arrival of VR headsets allows us to propose a realistic optic flow during treadmill walking. In **Chapter 3**, we performed a systematic review and meta-analysis focusing on the effectiveness of VR rehabilitation on PD patients' functional mobility and balance. The aim was to subgroup the results according to VR types (VR specifically created for a neurorehabilitation purposes or commercial VR) and to assess the fulfilment of neurorehabilitation principles in the included studies. Our hypothesis was that neurorehabilitation-specific VR solutions were more effective than commercial VR to improve the outcomes by fulfiling more principles important for neurorehabilitation.

Finally, **Chapter 4** focused on the effects of the addition of an immersive VR optic flow during treadmill walking on the spatiotemporal gait parameters and the LRA present in PD patients' gait. Since treadmill walking is known to modify LRA in PD gait, the main hypothesis was that incorporating a natural VR optic flow during treadmill walking would enable a more ecological and accurate measurement of LRA in individuals with PD during treadmill walking, similar to LRA computed when walking overground.

Chapter 1

Touch

Comparison of the Effects of Rhythmic Vibrotactile Stimulations and Rhythmic Auditory Stimulations on Parkinson's Disease Patients' gait variability: A Pilot Study

Chapter 1

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Comparison of the Effects of Rhythmic Vibrotactile Stimulations and Rhythmic Auditory Stimulations on Parkinson's Disease Patients' gait variability: A Pilot Study

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Abstract

Introduction

Parkinson's Disease patients' gait is characterized by shorter step length, reduced gait velocity and deterioration of temporal organization of stride duration variability (modified Long Range Autocorrelations). The objective of this study was to compare effects of Rhythmic Auditory Stimulations (RAS) and Rhythmic Vibrotactile Stimulations (RVS) on Parkinson's disease patients' gait.

Methods

Ten Parkinson's Disease patients performed three walking conditions lasting 5-7 minutes each: Control Condition (CC), RAS condition and RVS condition. Inertial measurement units were used to assess spatiotemporal gait parameters. Stride duration variability was assessed in terms of magnitude using coefficient of variation and in terms of temporal organization (i.e. Long Range Autocorrelations computation) using the evenly spaced averaged Detrended Fluctuation Analysis (α-DFA exponent).

Results

Gait velocity was significantly higher during RAS condition than during CC (Cohen's d=0.52) and similar to RVS condition (Cohen's d=0.17). Cadence was significantly higher during RAS (Cohen's d=0.77) and RVS (Cohens' d=0.56) conditions than during CC. Concerning variability, no difference was found either for mean coefficient of variation or mean α-DFA between conditions. However, a great variability of individual results between the RAS and the RVS conditions is to be noted concerning α-DFA.

Conclusions

In conclusion, RAS and RVS improved similarly PD patients' spatiotemporal gait parameters, without modifying stride duration variability in terms of magnitude and temporal organization at group level. Future studies should evaluate the relevant parameters for administering the right cueing type for the right patient.

ClinicalTrial.gov registration number NCT05790759, date of registration: 16/03/2023, retrospectively registered.

Keywords: Rhythmic Auditory Stimulations, Rhythmic Vibrotactile Stimulations, Parkinson's Disease, gait, Long Range Autocorrelations

Introduction

Parkinson's disease (PD) is manifested by motor symptoms such as rest tremor, plastic rigidity, bradykinesia[116] but also postural and gait disorders leading to fall risk, morbidity and mortality.[117] PD gait is characterized by lowered gait velocity and step length and changes in stride duration variability in terms of magnitude [increased coefficient of variation (CV)] and temporal organization.[35,118] Non-linear analysis such as long-range autocorrelations (LRA) computation allows analyzing the temporal organization of stride duration variability.[24] Although stride duration varies over time, this variability follows a structured fractal pattern[30,119] that could be a sign of long term memory in the locomotor system[120] and that is representative of an adaptative healthy system.[29,31,119] Also, temporal organization of stride duration variability could be the result of interactions between internal (nervous system, biomechanical structures, central pattern generators) and external (visual, somatosensory, auditory information) elements.[36,42,44,57,121,122] Some authors theorized that a breakdown in LRA would represent a pathological state[28,29,31] as seen in PD gait.[35,46] Indeed, stride duration variability in PD gait presents with diminished fractal scaling α exponent that could be the result of basal ganglia degeneration[29,40,41,120] which are involved in the regulation of gait and posture.[12] This breakdown of LRA in PD gait could have clinical correlates since strong correlations between diminished α exponent and balance impairments, but also disease progression were highlighted.[35,46,118] LRA computation was proposed as an objective and quantitative biomarker of postural instability, possibly fall risk and disease progression in PD patients.[37]

As mentioned, gait organization depends on interactions between internal and external elements. Rehabilitative approaches using external cues, such as isochronous Rhythmic Auditory Stimulations (RAS), have been studied for their positive effects on PD patients' spatiotemporal gait parameters.[60] By using alternative cortical pathways to facilitate the initiation and continuation of movement, cueing by means of RAS would bypass the basal ganglia emitting defective internal rhythms in PD.[112,123] Unlike spatiotemporal parameters, isochronous RAS (i.e. same interbeat intervals) is known to deteriorate LRA in PD gait.[57,124] Although previous studies investigated the effects of Rhythmic Vibrotactile Stimulations (RVS) on spatiotemporal gait parameters[55,125,126], the effect of RVS on temporal organization of PD gait remains unknown. Even though PD patients present with abnormal somatosensory perception[127], vibrotactile cues could be more easily implemented for a daily use. Indeed, vibrations on the skin seem more convenient for a daily use than auditory or visual cues that interfere with hearing and vision.

The purpose of this pilot study was to compare the effect of isochronous RVS and isochronous RAS on PD patients' spatiotemporal gait parameters and stride duration variability. Our hypothesis was that both isochronous cueings would similarly improve spatiotemporal parameters and would alter LRA compared to a control condition in PD patients.

Methods

Ethics, Consent, and Permissions

This pilot study obtained ethical approval from the local ethical board (B403201318916/clinicaltrials.gov registration: NCT05790759). Participant

gave written informed consent prior to data collection in accordance with the Declaration of Helsinki prior to data collection.

Participants

Inclusion criteria were: PD diagnosis made according to United Kingdom Brain Bank criteria[128], stages I–III on the modified Hoehn and Yahr scale[129], ability to walk 256 gait cycles in a row without walking aids, stable dopaminergic medication for a minimum of 4 weeks before assessments, no other pathology that could interact with motor capacities and gait performance, a minimum of 24/30 on the Mini-Mental State Examination (MMSE)[130], being in ON medication state during the experiment, non-presenting with freezing of gait. The absence of freezing of gait[†] was also checked with the item 2.13 of the MDS-UPDRS. Exclusion criteria were: other pathological state interfering with gait, important hearing impairment.

Procedure

The experiments took place at Cliniques universitaires Saint-Luc (Bruxelles, Belgium). Patients were asked to walk on a 63.2 m rectangular track with rounded corners for at least 256 gait cycles (5-7 min), in their preferred direction, which was maintained throughout all conditions. They walked in three conditions in a randomized order. The control condition (CC) consisted in walking at patients' self-selected comfortable gait velocity without any cueing. During the RAS condition, patients were asked to "walk accordingly to the rhythm", each step corresponding to an auditory stimulation, like

[†]Absence of freezing of gait was asked by phone at the inclusion, asked via item 2.13 of the part II of MDS-UPDRS and checked clinically with item 3.11 of the part III of MDS-UPDRS.

"beeps" listened through earphones (MDR-XB550AP, Sony, Japan) plugged to a smartphone (Galaxy A40, SAMSUNG, South Korea) placed in a patient's pocket. During the RVS condition, PD patients were also asked to "walk accordingly to the rhythm", each step corresponding to a vibration felt on the skin through a vibrotactile unit (Pulse, Soundbrenner, China/Germany) attached to the wrist located on each patient's most affected side. The wrist was chosen for stimulation, given the positive effect on spatiotemporal parameters and arm swing found in a previous study for this stimulation site.[126] The side most affected was chosen to specifically focus the patient's attention on the side most in need of improvement. Both RAS and RVS frequencies were selected using the same smartphone app (Soundbrenner, China/Germany) and were the same during the two cueing conditions of the same patient. For each patient, the interbeat interval of the RAS and the RVS was isochronous meaning that there was no time variability between intervals. The RAS and RVS frequency was set 10% higher than each patient's comfortable gait cadence determined before the experiments during the 10 meters walking test. This frequency was chosen because previous studies showed better effects on spatiotemporal parameters if the RAS pace was set 10% higher than the patient's comfortable gait cadence.[60,120] Between each condition, patients followed a 5-minute rest period.

Functional assessment

Patients completed the Activities-Specific Balance Confidence Scale (ABC scale)[131], the Mini Balance Evaluation Systems Test (Mini-BESTest)[132], the Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale Revision (MDS-UPDRS)[133], the modified Hoeh & Yahr scale[129], the Mini Mental State Examination[134], and a 10 Meters Walking Test.

Data acquisition

During each condition, two Inertial Measurement Units (IMeasureU Research, VICON, United Kingdom) were taped on patients' lateral malleoli to record ankle accelerations at a sample of 500 Hz in antero-posterior direction. Before data acquisition, patients were asked to walk one lap of the track to accustom with each condition. Data was then transferred onto a computer and stride durations were determined using a peak detection method.[135]

Gait assessment

Gait outcomes were assessed in terms of spatiotemporal parameters, magnitude and temporal organization of stride duration variability. Data was extracted from 256 consecutive gait cycles which is the minimum recommended to correctly assess the temporal organization of stride duration variability.[81]

Spatiotemporal gait parameters were assessed as follow:

$$\textit{Gait velocity } (m.s^{-1}) = \frac{Total\ walking\ distance\ (m)}{Total\ acquisition\ time\ (s)}$$

$$\textit{Cadence } (\#steps.min^{-1}) = \frac{Total\ number\ of\ steps\ (\#)}{Total\ acquisition\ time\ (min)}$$

$$\textit{Step length } (m) = \frac{Gait\ velocity\ (m.s^{-1})}{Cadence\ (Hz)}$$

$$\textit{Mean stride duration } (s) = \frac{Total\ acquisition\ time\ (s)}{Total\ number\ of\ strides\ (\#)}$$

Coefficient of variation (CV) was used to assess magnitude of stride duration variability and calculated using the mean stride duration and standard deviation (SD):

CV (%) = $[\frac{SD}{mean}]$.100.

Temporal organization of stride duration variability was assessed by LRA computation using the evenly spaced averaged Detrended Fluctuation Analysis (DFA) [136] to obtain α-DFA exponent. This method was chosen among others given its robustness regarding stationary and non-stationary processes.[28,137] The original time series size was N ≥ 256. Then, the series was divided in subsets of size t, from t = 10 to t = N/2. The number of points used to calculate the slope in evenly spaced averaged DFA was based on Almurad and Delignières (2016).[136] This method consists in selecting the data used for the regressions as follows:

$$\begin{cases} n_1 = n_{min} \\ n_i = \left[n_{i-1} 10^{\frac{log_{10}(n_{max}) - log_{10}(n_{min})}{k-1}} \right] \end{cases}$$

Where k represents the number of points to include in the diffusion plot, the k interval lengths are noted [n_i (i = 1, 2,. . .k)] and n_{max} and n_{min} correspond to the maximum and the minimum interval lengths. We used n_{min} = 10, n_{max} = N/2 and k = 18 to follow the study by Almurad and Delignières (2016).[136] After selecting evenly spaced data points, the linear regressions can be performed on the average data across the data points that are between selected points (evenly spaced averaged). LRA are present when α-DFA is between 0.5 and 1 which implies persistence in the variations meaning that large stride duration fluctuations tend to be followed by other large fluctuations, and vice-

versa. An α-DFA = 0.5 corresponds to randomness (i.e., white noise). An α-DFA = 1 (i.e., 1/f noise) is the boundary between stationarity and non-stationarity.[32] In this context, 1/f noise is interpreted as "a 'compromise' between the complete unpredictability of white noise (α = 0.5) (very rough 'landscape') and the very smooth 'landscape' of Brownian noise (α = 1.5)".[33] Then, α-DFA = 1 is considered as the optimal state of variability characterizing healthy gait according to the theoretical framework of optimal movement variability.[28,34]

Statistical analysis

To conduct statistical analysis and create graphics, Sigmaplot 13.0 was used. Before analysis, a Shapiro Wilk test was performed to verify normality. Then a one-way repeated measures ANOVA was applied to compare gait parameters between each condition. If significant difference between groups was detected, a post hoc Holm-Sidak test was performed. The results were considered statistically different for $p < 0.05$.

Regarding α-DFA, results were also normalized using Z-scores. The mean α-DFA of the healthy population used to compute Z-scores was taken from the meta-analysis of Ravi et al. (2020)[28] (α-DFA = 0.81 ± 0.14).

Results

Ten PD patients participated in this pilot study. Table 2.1 summarizes their clinical characteristics.

Table 2.1. Patients' clinical characteristics and anthropometric.

	PD patients (n = 10)
Age (years)	68.3 ± 9.3
Height (m)	1.7 ± 0.1
Weight (kg)	71.4 ± 15.9
Gender (male/female)	6/4
Most affected side (right/left)	5/5
Time since diagnostic (years)	5.6 ± 3.2
MDS-UPDRS (/260)	62.8 ± 26.2
MDS-UPDRS part III (/132)	44.3 ± 17.8
Modified Hoehn & Yahr scale [1-5]	2 [1-3]
10 Meter Walking Test ($m.s^{-1}$)	1.2 ± 0.2
Mini-BESTest (/28)	22.5 ± 2.7
ABC scale (%)	83.3 ± 20.9
MMSE (/32)	26.9 ± 2.8

Mean ± SD, Median [interquartile range]; ABC-Scale, Activities-Specific Balance Confidence Scale; Mini-BESTest, Mini Balance Evaluation Systems Test; MDS-UPDRS, Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale Revision; MMSE, Mini Mental State Examination

Spatiotemporal gait parameters

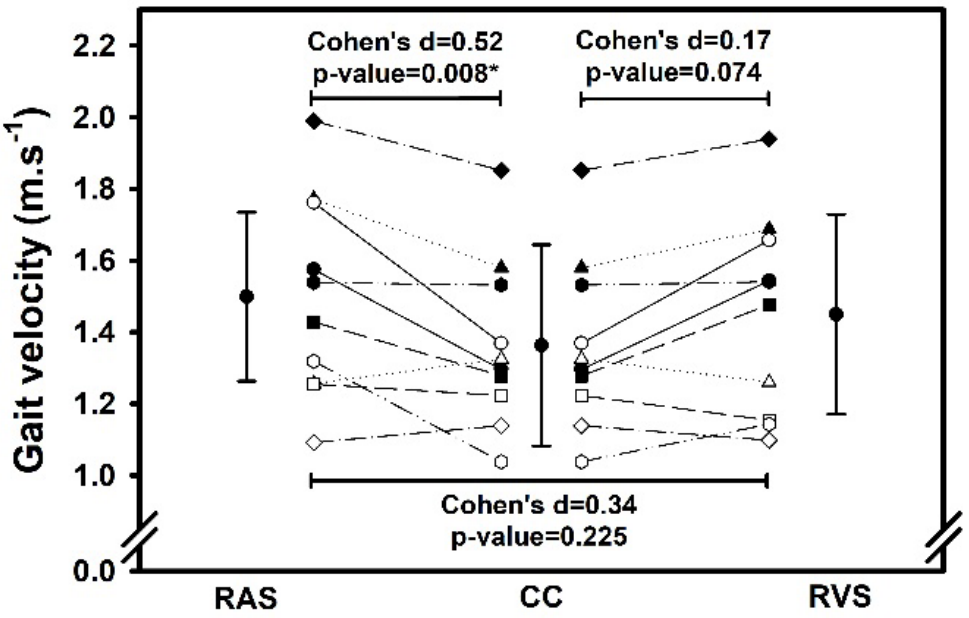
Regarding gait velocity, a significant statistical difference was found between conditions [$F(2,9)$: 6.295; p = 0.008]. During RAS condition, mean gait velocity (1.50±0.28) was significantly higher than during CC (1.36±0.24) but not different from during RVS condition (1.45±0.28) (Table 2.2 and Figure 2.1).

Similarly, a significant difference was found between conditions concerning cadence [$F(2,9)$: 9.077; p = 0.002]. RAS (121.6 ±8.4) and RVS (119.8±8.1) increased significantly gait cadence in comparison to CC (115.3±7.7). No difference was found between RAS and RVS conditions for this outcome (Table 2.2 and Figure 2.1).

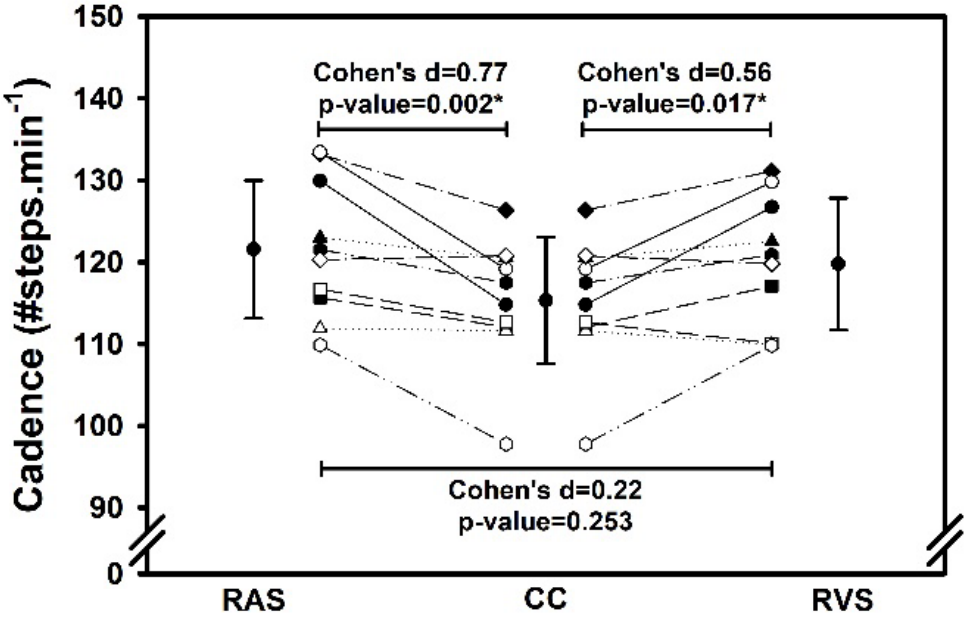
On the contrary, there was no significant difference regarding step length [$F(2,9)$: 2.517; p = 0.109] (Table 2.2 and Figure 2.1).

Stride duration was significantly different between conditions [$F(2,9)$: 8.123; p = 0.003]. RAS (0.99±0.07) and RVS (1.00±0.07) decreased significantly stride duration in comparison to CC (1.04±0.08). No difference was found between RAS and RVS conditions for this outcome (Table 2.2 and Figure 2.1).

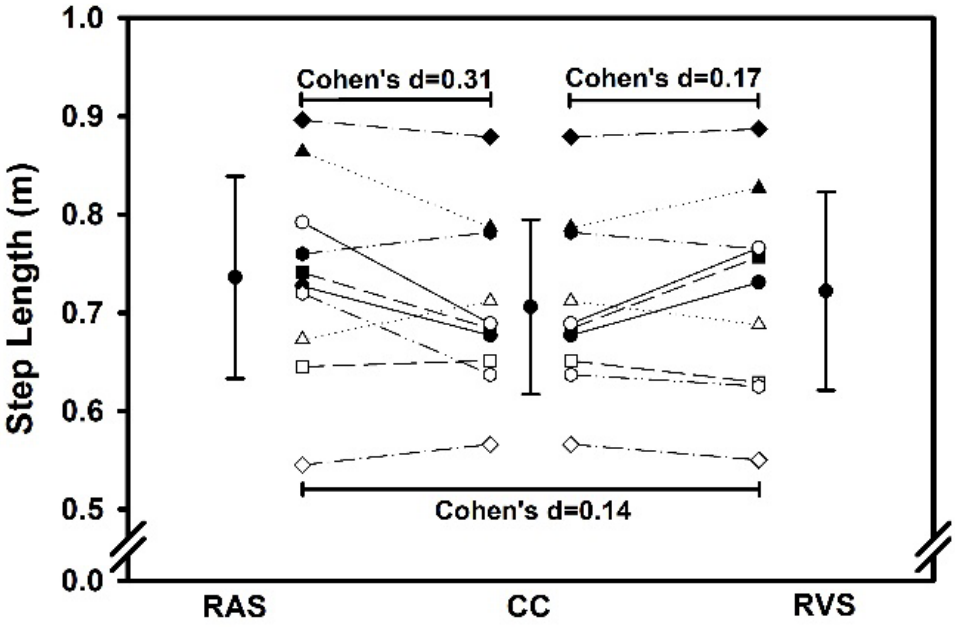
A


Gait velocity (m.s-1)
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.0
Cohen's d=0.52
p-value=0.008*
Cohen's d=0.17
p-value=0.074
Cohen's d=0.34
p-value=0.225
RAS
CC
RVS

B


Cadence (#steps.min-1)
150
140
130
120
110
100
90
0
Cohen's d=0.77
p-value=0.002*
Cohen's d=0.56
p-value=0.017*
Cohen's d=0.22
p-value=0.253
RAS
CC
RVS

C


Step Length (m)
1.0
0.9
0.8
0.7
0.6
0.5
0.0
Cohen's d=0.31
Cohen's d=0.17
Cohen's d=0.14
RAS
CC
RVS

D

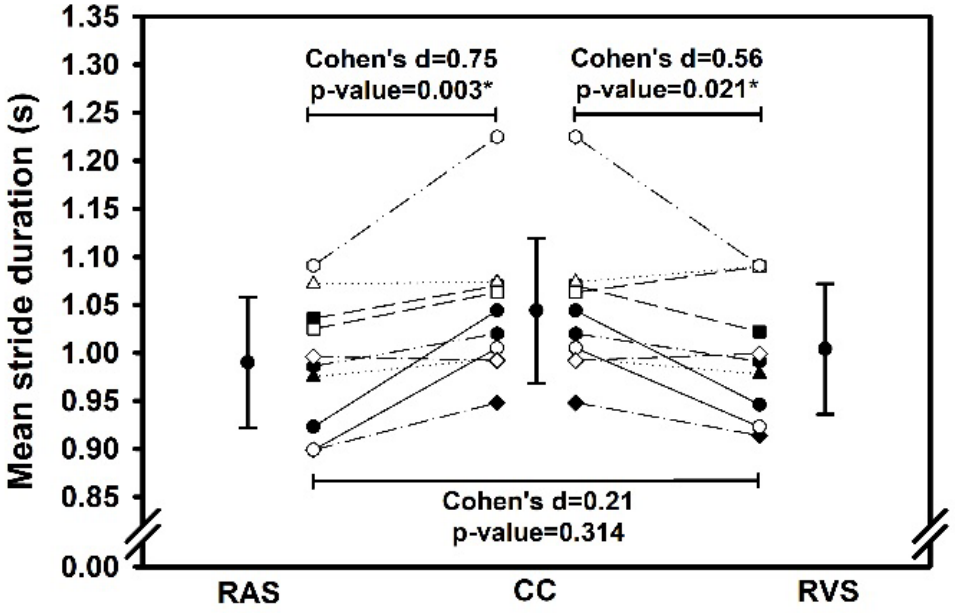

Mean stride duration (s)
1.35
1.30
1.25
1.20
1.15
1.10
1.05
1.00
0.95
0.90
0.85
0.00
Cohen's d=0.75
p-value=0.003*
Cohen's d=0.56
p-value=0.021*
Cohen's d=0.21
p-value=0.314
RAS
CC
RVS

Figure 2.1. *Mean (±1 SD) and individual spatiotemporal gait parameters values during Control Condition (CC), Rhythmic Auditory Stimulations condition (RAS), and Rhythmic Vibrotactile Stimulations condition (RVS). (A) Gait velocity. (B) Cadence. (C) Step Length. (D) Mean stride duration.*

Stride duration variability

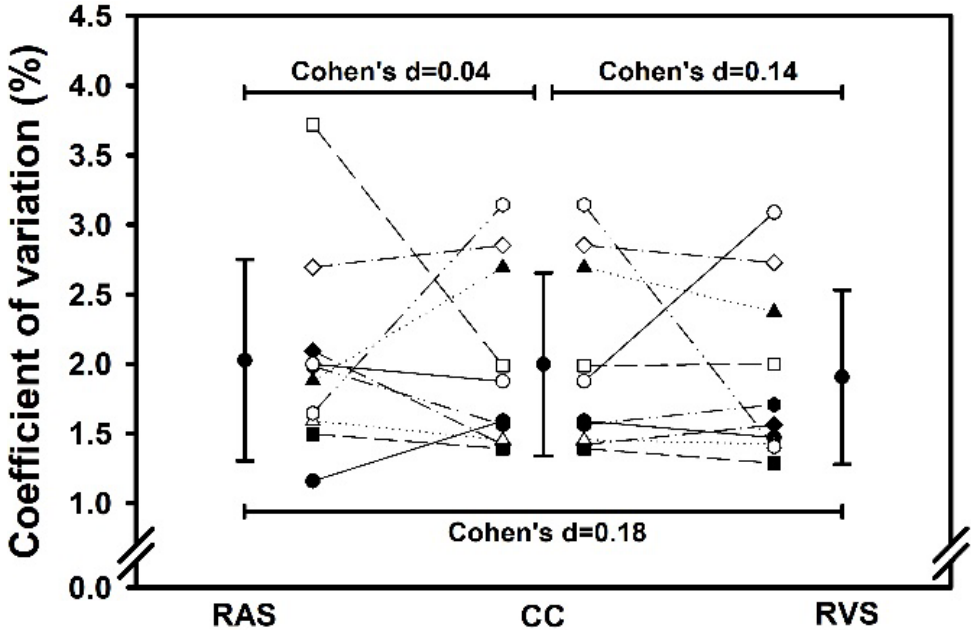
The results regarding CV did not pass the normality test, a Friedman Repeated Measures Analysis of Variance on Ranks was then applied.

No significant difference was found between conditions regarding CV ($p = 0.670$) and α-DFA [$F(2,9): 2.867$; $p = 0.083$] (Table 2.2 and Figure 2.2).

During CC, all participants presented with LRA, meaning persistence in temporal organization of stride duration variability ($0.5<\alpha\text{-DFA}<1$), and with normal mean α-DFA expressed in absolute value (mean α-DFA = 0.76 ± 0.05) and in Z-score (-0.34 ± 0.38) (Table 2.2 and Figure 2.2).

Conversely, three participants during RAS condition (mean α-DFA = 0.62 ± 0.19) and one participant during RVS condition (mean α-DFA = 0.73 ± 0.15) presented with $\alpha\text{-DFA}<0.5$ meaning disappearance of the LRA and anti-persistence. Seven of the ten patients during RAS condition and six of the ten patients during RVS condition had decreased α-DFA compared to CC. Seven out of the ten patients presented with higher α-DFA during RVS condition than during RAS condition and the other three presented the opposite trend (Figure 2). To further emphasize the differences in individual results, coefficient of variation of α-DFA during RAS (31%) and RVS (21%) conditions was markedly greater than during CC (6%) (Table 2.2 and Figure 2.2).

A


Coefficient of variation (%)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.0
Cohen's d=0.04
Cohen's d=0.14
Cohen's d=0.18
RAS
CC
RVS

B

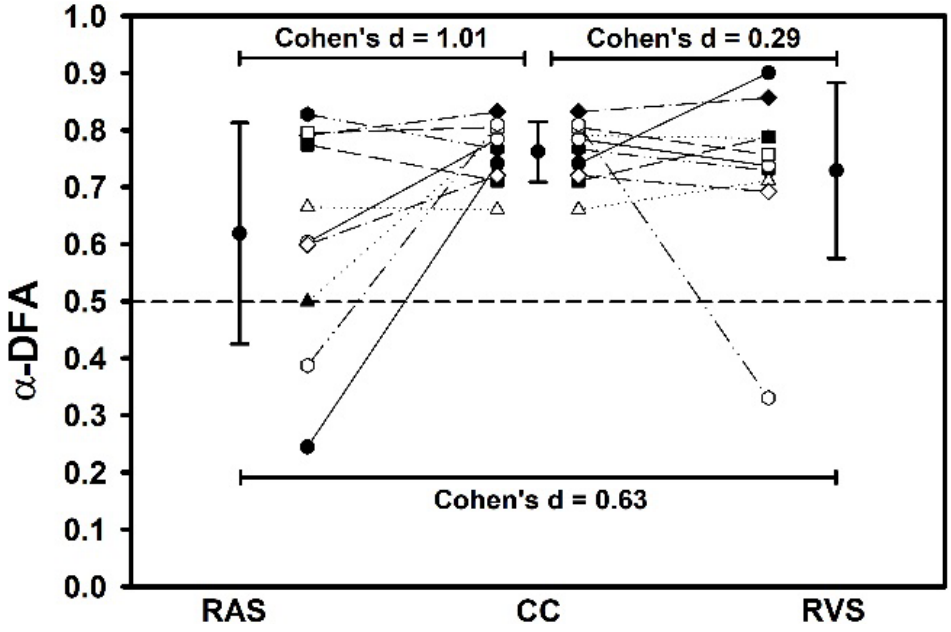

α-DFA
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Cohen's d = 1.01
Cohen's d = 0.29
Cohen's d = 0.63
RAS
CC
RVS

Figure 2.2. *Mean (±1 SD) and individual gait variability parameters values during Control Condition (CC), Rhythmic Auditory Stimulations condition (RAS), and Rhythmic Vibrotactile Stimulations Condition (RVS). (A) Coefficient of variation. (B) α-DFA (dashed line corresponding to the limits above which there are LRA).*

Table 2.2. Results for spatiotemporal gait parameters and stride duration variability parameters.

	CC	RAS	RVS	Post-hoc test between RAS and RVS
Gait velocity ($m.s^{-1}$)	1.36 ± 0.24	1.50 ± 0.28*	1.45 ± 0.28	p=0.225
Cadence ($\#steps.min^{-1}$)	115.3 ± 37.73	121.56 ± 8.41*	119.78 ± 8.05*	p=0.253
Step length (m)	0.71 ± 0.09	0.74 ± 0.10	0.72 ± 0.10	
Mean stride duration (s)	1.04 ± 0.08	0.99 ± 0.07*	1.00 ± 0.07*	p=0.314
Coefficient of variation in stride duration variability (%)	2.00 ± 0.66	2.03 ± 0.72	1.91 ± 0.63	
α-DFA	0.76 ± 0.05	0.62 ± 0.19	0.73 ± 0.15	
α-DFA Z-score	-0.34 ± 0.38	-1.37 ± 1.39	-0.58 ± 1.10	

Mean ± SD ; α-DFA, α exponent calculated using the evenly spaced averaged Detrended Fluctuation Analysis; CC, Control Condition; RAS, Rhythmic Auditory Stimulations condition; RVS, Rhythmic Vibrotactile Stimulations condition.

*Significant difference with CC ($p<0.05$)

Discussion

The objective of this pilot study was to compare the effects of RAS and RVS with a control condition on spatiotemporal gait parameters and on stride duration variability in terms of magnitude and temporal organization in PD patients. First, gait velocity was higher during RAS condition than during CC, but similar to RVS condition. Secondly, cadence and stride duration were higher during RAS and RVS conditions than during CC. Step length was not different between the three conditions. Regarding stride duration variability, there was no difference between conditions.

Based on a recent meta-analysis, increased gait velocity was expected during RAS.[60] Less was known regarding RVS and this study did not demonstrate a significant difference between RVS et RAS conditions regarding this parameter. The increase in velocity in both cueing conditions could be explained by cueing frequency set 10% higher than patients comfort gait cadence. Rochester et al. (2010)[125] found a higher gait velocity using RAS and RVS than during their CC with no difference between cueing conditions but found it after a three-weeks training program and using patients' preferred cueing frequency.

As for gait velocity, gait cadence was significantly higher and mean stride duration was significantly lower during RAS condition than during CC as intended regarding previous results[60] and were similar between RVS and RAS conditions. Regarding RAS, this was expected given the chosen higher cueing frequency.[120,138] Concerning RVS, this is different from the study of van Wegen et al. (2006)[55] in which a reduced cadence and increased step length were found using RVS but cueing frequency was set 10% lower than patients'

preferred gait cadence. This difference could be important since it could mean that PD patients would be able to adapt their walking pace according to different external cueing frequencies. Depending on the desired effect on gait, vibrotactile cueing could be proposed either 10% lower to improve stride length, or 10% higher to increase speed and cadence. Interestingly, Thompson et al. (2017)[126] found a reduced gait cadence using RVS set 20% faster than PD patients' preferred arm swing pace but contrarily to this study, patients were not explicitly asked to synchronize to the cues.

Magnitude of stride duration variability measured by the CV was similar between conditions. Regarding RAS, this is in agreement with previous studies[124,139] whereas other studies[57,120] showed an increase in CV. To our knowledge, this is the first study investigating the effect of RVS on CV. The CV is known to be increased in PD patients[118] and is coupled with postural reflex disorder since it is considered as a marker of attentional load.[46] Since CV was similar between gait conditions, it could be assumed that RAS and RVS did not produce an attentional overload.

Similar mean α-DFA values during isochronous RAS and RVS conditions, at the group level, are in line with our hypothesis. But results are highly variable from one subject to another. This could imply that some patients could be more receptive to RVS than to RAS, and vice-versa. In the future, it could be interesting to pay attention to patient's preferences and in the relation between these preferences and gait parameters. Regarding RVS, this is the first study to our knowledge investigating LRA while using somatosensory cueing with PD patients. As for RAS[57,124], future studies should investigate different temporal organizations of rhythm variability of RVS and their impact on LRA in PD patients.

Limitations should be acknowledged. First, this pilot study only included ten patients presenting with α-DFA within normative data of healthy patients as it has been the case in previous studies.[28,81] Second, patients were mildly impaired by PD. Future transversal and longitudinal studies with more impaired PD patients should be conducted to compare the clinical relevance of RVS versus RAS. RVS were given on patients' wrists, future studies should investigate the best anatomical place to administrate RVS to improve spatiotemporal parameters and LRA. Third, levodopa equivalent daily dose has not been recorded at baseline. Although gait and balance disorders are relatively resistant to dopaminergic medication[50,52,53], this constitutes missing baseline information. It was decided to test patients in the ON state. Future studies could compare the effects of RAS and RVS for patients in the OFF state, given that cueing can also be effective in patients without pharmacological treatment.[64]

In conclusion, similar results were found between RAS and RVS regarding PD patients' spatiotemporal gait parameters and stride duration variability in terms of magnitude and temporal organization. More transversal and longitudinal studies including more PD patients are needed to confirm these results. Studies evaluating effects of different external cues on PD gait and correlations with patients' preferences must be conducted.

Funding and competing interests

The authors have no financial or non-financial interests to disclose.

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Informed consent

Participants gave written informed consent prior to data collection.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Cliniques universitaires Saint-Luc (Bruxelles, Belgium) (No: B403201318916).

Consent to participate and consent to publish

Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding publishing their data.

Data availability

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

Chapter 2

Hearing

Influence of Autocorrelated Rhythmic Auditory Stimulations on Parkinson's Disease Gait Variability: Comparison with Other Auditory Rhythm Variabilities and Perspectives

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Influence of Autocorrelated Rhythmic Auditory Stimulations on Parkinson's Disease Gait Variability: Comparison with Other Auditory Rhythm Variabilities and Perspectives

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Abstract

Parkinson's Disease patients suffer from gait impairments such as reduced gait speed, shortened step length, and deterioration of the temporal organization of stride duration variability (i.e., breakdown in Long-Range Autocorrelations). The aim of this study was to compare the effects on Parkinson's Disease patients' gait of three Rhythmic Auditory Stimulations (RAS), each structured with a different rhythm variability (isochronous, random, and autocorrelated). Nine Parkinson's Disease patients performed four walking conditions of 10–15 min each: Control Condition (CC), Isochronous RAS (IRAS), Random RAS (RRAS), and Autocorrelated RAS (ARAS). Accelerometers were used to assess gait speed, cadence, step length, temporal organization (i.e., Long-Range Autocorrelations computation), and magnitude (i.e., coefficient of variation) of stride duration variability on 512 gait cycles. Long-Range Autocorrelations were assessed using the evenly spaced averaged Detrended Fluctuation Analysis (α-DFA exponent). Spatiotemporal gait parameters and coefficient of variation were not modified by the RAS. Long-Range Autocorrelations were present in all patients during CC and ARAS although all RAS conditions altered them. The α-DFA exponents were significantly lower during IRAS and RRAS than during CC, exhibiting anti-correlations during IRAS in seven patients. α-DFA during ARAS was the closest to the α-DFA during CC and within normative data of healthy subjects. In conclusion, Isochronous RAS modify patients' Long-Range Autocorrelations and the use of Autocorrelated RAS allows to maintain an acceptable level of Long-Range Autocorrelations for Parkinson's Disease patients' gait.

Chapter 2

Keywords: gait disorders, rhythmic auditory stimulations, cueing, gait variability, long range autocorrelations, Parkinson's disease, fractals

Introduction

Several physiological signals, apparently randomly organized, are in fact governed by dynamic phenomena organized between order and disorder.[29,140] This complex self-organization is the result of multiple interactions between different elements of the system.[20,141] Such complexity of organization is visible in the study of the temporal organization of human gait.[31,121,142] Indeed, gait variability organization is the result of multiple interactions between internal (nervous system, biomechanical structure) and external (proprioceptive, visual, auditory information) components.[36,42,44,57,121,122] The study of the magnitude (using linear mathematical methods) and of the temporal organization (using non-linear mathematical methods) constitute complementary ways to assess gait variability, and stride duration variability in particular.[31,143] Stride duration varies in the short and long term according to a complex dynamic of temporal variations.[27] These variations present Long-Range Autocorrelations (LRA)[27,30,119] involving a long-memory process which means that every stride duration depends on the duration of the previous strides.[27,121] Nevertheless, the origin and control of LRA in human locomotion remain elusive. While some attribute their origin to biomechanical structures[42], the most common theory is that LRA reflect a control from the central nervous system.[36] Indeed, a degradation of LRA has been shown in Parkinson's and Huntington's disease suggesting that the phenomenon would come from supraspinal centers.[35,37,40] Other theories suggest the existence of Central Pattern Generators (CPGs) at spine level to describe dynamics of human gait.[44] After years of research, some authors have suggested that LRA are markers of healthy stable but still adaptive gait

and a breakdown of LRA would be a sign of gait disorders and loss of adaptability as suggested in Parkinson's Disease (PD).[29,31,119]

Among motor symptoms, PD patients suffer from gait disorders such as shorter step length, reduced gait speed, and increased randomness in temporal organization of gait.[27] Indeed, a breakdown of LRA (reduced fractal scaling α exponent) in stride duration variability in PD gait and strong correlations between LRA, disease severity and postural instability were demonstrated.[35,46] Diminished α exponent would be linked to basal ganglia degeneration[27,29,40,41] involved in the regulation of gait, posture and rhythm control.[37,144] LRA measurement would therefore be a biomarker of gait instability and risk of falling, which is of particular clinical interest in PD.[35,37] Given that PD patients' gait disorders are partially responsive to medication[62,145], there is a need for rehabilitative approach.[146]

As previously mentioned, gait is organized according to the interactions between internal and external components, such as proprioceptive, visual or auditory information. Rhythmic Auditory Stimulations (RAS) acting as an external cue by means of a metronome, have been studied for years for their effects on PD patients' gait.[60] This cueing would act like an external rhythm generator bypassing the basal ganglia that can no longer properly act as an internal rhythm generator in PD patients.[62] It is then suggested that a broader use of isochronous RAS should be beneficial in PD patients' gait rehabilitation.[147] However, it has been demonstrated that the use of isochronous RAS modify LRA in young[148,149] and older[148] healthy subjects and in PD patients.[57,150]

Some authors tried to study the effects of autocorrelated RAS (i.e., rhythm variability presenting with LRA) on healthy subjects'[148,149] and PD patients' LRA computed from gait tasks.[57,79] Although some studies showed that autocorrelated RAS are beneficial for stride duration variability, these results should be interpreted with caution given the short acquisition times used (except for Marmelat et al., 2020[79]). Indeed, a long acquisition time (at least 512 gait cycles) is necessary to show the presence of LRA with a high level of evidence.[28,80–83] Series length has a clear effect on the statistical precision and the sensitivity of scaling exponents.[81] Shorter series lengths lead to loss of accuracy and are too short to be statistically different from short-range correlated processes.[81,83] In this sense, there is a risk that LRA computations using short series could not reflect the results on long series.[81,83]

Dotov et al. (2017) and Marmelat et al. (2020) tested autocorrelated RAS on PD patients.[57,79] Dotov et al. (2017) showed that autocorrelated RAS allow to maintain similar level of LRA (similar α exponent) than during their control condition without RAS and that isochronous RAS deeply modify LRA.[57] However, their findings require confirmation given their short acquisition time (5 min per condition). It should also be noted that their method to produce their autocorrelated RAS remains unknown and that their RAS frequency was set 10% faster than each participant's preferred cadence, which will both differ in this present study. Also, Dotov et al. (2017) used a 21.6 m track, probably imposing a constant strong steering while our 42 m track should allow smoother steering.[57] This could be of importance since steering is known to influence LRA.[151] Unlike Dotov et al. (2017)[57], Marmelat et al. (2020) found significantly higher α exponent values during their autocorrelated RAS condition (the 1:1 step-to-beat ratio version)

compared to their control condition.[79] In their study, music was used to deliver RAS when a simple beat will be used in this study. This is not negligible since music is composed of multiple "layers" including the rhythmic beat itself, melody and harmony. Furthermore, Marmelat et al. (2020) used an α exponent = 1.02 as a reference[79] while an α exponent similar to normative data of healthy subjects will be used in this study.

The purpose of this pilot study is to analyze the effects of three different RAS (isochronous, random and autocorrelated RAS) on PD patients' spatiotemporal gait parameters and stride duration variability (magnitude and temporal organization) using suitable acquisition times to compute LRA. Our main hypothesis is that the autocorrelated RAS will be more efficient than the isochronous RAS and the random RAS to maintain LRA in the temporal organization of stride duration variability of PD patients.

Methods

Ethics, Consent, and Permissions

This study obtained ethical approval from the local ethical board (B403201318916/clinicaltrials.gov registration: NCT03716674). Participants gave written informed consent prior to data collection and this study adhered to the Declaration of Helsinki.

Participants

Nine PD patients were included in this pilot study. Inclusion criteria were: PD diagnosis made according to United Kingdom Brain Bank criteria[128], stages I–III on the modified Hoehn and Yahr scale[129], ability to walk for a minimum

of 512 gait cycles (±15 min) in a row without walking aids[‡], stable dopaminergic medication for a minimum of 4 weeks before assessments, no other pathology that could interact with motor capacities and gait performance, a minimum of 24/30 on the Mini-Mental State Examination (MMSE).[130]

Patients' anthropometric and clinical characteristics are summarized in Table 3.1.

[‡] Absence of freezing of gait was asked by phone at the inclusion, asked via item 2.13 of the part II of MDS-UPDRS and checked clinically with item 3.11 of the part III of MDS-UPDRS.

Table 3.1. Characteristics of the study population.

	PD patients (*n*=9)
Age (years)	66.6 (±8.17)
Height (cm)	170.1 (±11.96)
Weight (kg)	69.7 (±19.43)
Gender (male/female)	4/5
Hoehn & Yahr (modified)	2 [1 – 2.5]
Mini Mental State Examination (/30)	28.9 (±0.92)
10 Meter Walk Test (m/s)	1.3 (±0.22)
ABC Scale (%)	77.3 (±13.94)
BESTest (%)	78.7 (±10.62)
MDS-UPDRS (/260)	45.7 (±25.72)
PIGD (/20)	3.7 (±2.69)
Number of falls (#/6 months)	0.6 (±1.33)

Mean (±SD); Median [interquartile range].

ABC-Scale, Activities-Specific Balance Confidence Scale; BESTest, Balance Evaluation Systems Test; MDS-UPDRS, Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale Revision; PIGD, Postural Instability and Gait Disorder.

Stimulus

In addition to a control walking condition without cueing [i.e., Control Condition (CC)], three conditions involved walking with three different RAS: Isochronous RAS (IRAS), Random RAS (RRAS), and Autocorrelated RAS (ARAS). Each of them was composed with an internally developed software (Matlab 2014R, Mathworks, United States) and adapted to each patient according to their spontaneous cadence determined before the experiment with 10 Meters Walking Tests. For each patient, these three RAS had the same mean interbeat duration [Mean (s) = 0.54 ± 0.05] but different magnitude (i.e., coefficient of variation, CV) and temporal organization of rhythm variability. During IRAS, the RAS presented no variation of the interbeat intervals [CV (%) = 0.00 ± 0.00][§]. During ARAS, autocorrelated interbeat intervals were used with α exponent similar to healthy subjects' data of α exponent measured during gait in a previous study using the evenly spaced averaged Detrended Fluctuation Analysis [α-DFA = 0.78 ± 0.00; CV (%) = 0.92 ± 0.00].[56] During RRAS, a random variability of the interbeat intervals was used and obtained by shuffling the interbeat intervals used for each patient during the ARAS [α-DFA = 0.46 ± 0.00; CV (%) = 0.92 ± 0.00].

Procedure

Prior to data collection, patients listened to the RAS and were asked to mark the rhythm with a finger tapping task to ensure that the rhythm of the RAS was detected. Then, each patient walked in the four conditions in a randomized order. During RAS conditions, patients were listening to the RAS through earphones by the mean of a MP3 player. Standardized instructions to

[§] α used to produce the temporal organization of interbeat duration variability = 0.5(± 0,00).

"walk accordingly to the proposed rhythm," the foot contact of each step corresponding to each beat of the metronome, were given to each participant. During each condition, patients walked around on an oval indoor track of 42 m during ±15 min. The heading direction (clockwise or counterclockwise) was randomized but each patient kept the same heading direction for all conditions. A maximum of two conditions were tested during 1 day with a minimum break of 5 min between each of the conditions to avoid a fatigue effect and to limit a potential order effect. Patients came back a second day (2–14 days apart from the first session) to perform the other two conditions. The experiment was always performed at the same time of the day for the same patient during ON phase of dopaminergic treatment to avoid drug effect.

Data Acquisition

Two unidimensional accelerometers were taped on patients' both lateral malleoli in the antero-posterior direction and connected to a recording device (Vitaport 3 – Temec Instruments B.V., Kerkrade, The Netherlands) attached to the patients' waist. Ankle accelerations were recorded while walking at a sample of 512 Hz and were then transferred onto a computer. Each peak of acceleration, corresponding to each foot contact, was detected by an homemade software to determine stride durations (i.e., peak detection method[152]).

Functional Assessment

Functional assessment was performed before the beginning of the first walking condition. A 10 Meters Walk Test was used to calculate the patients' spontaneous cadence used to individually adapt the RAS. Patients also completed the Activities-Specific Balance Confidence Scale (ABC scale)[131]

to assess their balance-confidence, the Balance Evaluation Systems Test (BESTest)[153] to test their balance, the Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale Revision (MDS-UPDRS)[133] to globally assess the severity of motor and non-motor symptoms, the Postural Instability and Gait Disorder (PIGD)[154] which groups five items (#13–15 and #29–30) of the UPDRS and the number of falls during the last 6 months before the experiment (see Table 1).

Gait Assessment

Gait was assessed through the measurement of the spatiotemporal gait variables, the magnitude and the temporal organization of the stride duration variability.

The data was extracted from 512 consecutive gait cycles which is recommended to assess temporal organization of the stride duration variability.[28,80,81]

Spatiotemporal gait parameters were assessed as follow:

$$Gait\ speed\ (m.s^{-1}) = \frac{Total\ walking\ distance\ (m)}{Total\ acquisition\ time\ (s)};$$

$$Cadence\ (\#steps.min^{-1}) = \frac{Total\ number\ of\ steps\ (\#)}{Total\ acquisition\ time\ (min)};$$

$$Step\ length\ (m) = \frac{Gait\ speed\ (\mathrm{m.s^{-1}})}{Cadence\ (Hz)};$$

$$Mean\ stride\ duration\ (s) = \frac{Total\ acquisition\ time\ (s)}{Total\ number\ of\ strides\ (\#)}.$$

To assess magnitude of stride duration variability, CV was calculated using the mean stride duration and standard deviation (SD): $CV\ (\%) = \left[\frac{SD}{mean}\right].100$.

Temporal organization of stride duration variability was assessed by LRA computation using the evenly spaced averaged DFA[155] to obtain α-DFA exponent. This method was chosen among others given its robustness regarding stationary and non-stationary processes.[28,137]

The original time series size was N ≥ 512. Then, the series was divided in subsets of size t, from *t* = 10 to *t* = N/2. The number of points used to calculate the slope in evenly spaced averaged DFA was based on Almurad and Delignières (2016).[155] This method consists in selecting the data used for the regressions as follows:

$$\begin{cases} n_1 = n_{min} \\ n_i = \left[n_{i-1} 10 \dfrac{log_{10}(n_{max}) - log_{10}(n_{min})}{k-1}\right] \end{cases}$$

Where k represents the number of points to include in the diffusion plot, the k interval lengths are noted [n*i* (*i* = 1, 2,. . .k)] and n*max* and n*min* correspond to the maximum and the minimum interval lengths. We used n*min* = 10, n*max* = N/2 and *k* = 18 to follow the study by Almurad and Delignières (2016).[155] After selecting evenly spaced data points, the linear regressions can be performed on these selected points (evenly spaced), or on the average data across the data points that are between selected points (evenly spaced averaged).

LRA are present when α-DFA is between 0.5 and 1 which implies persistence in the variations meaning that large stride duration fluctuations tend to be

followed by other large fluctuations, and vice-versa. α-DFA <0.5 is the sign of anti- persistence and α-DFA = 0.5 corresponds to randomness (i.e., white noise). An α-DFA = 1 (i.e., 1/f noise) is the boundary between stationarity and non-stationarity.[32] In this context, 1/f noise is interpreted as "a 'compromise' between the complete unpredictability of white noise (α = 0.5) (very rough 'landscape') and the very smooth 'landscape' of Brownian noise (α = 1.5)".[33] Then, α-DFA = 1 is considered as the optimal state of variability characterizing healthy gait according to the theoretical framework of optimal movement variability.[28,34]

Statistical Analysis

A power analysis was made based on a previous study of Dotov et al. (2017)[57] using PASS software, in the idea of performing a one-way repeated measures ANOVA. Total sample of nine participants achieved 80% power to detect differences among the means vs. the alternative of equal means using an *F*-test with a 0.05 significance level.

Statistical analyses were conducted using Sigmaplot 13.0. After verification with a Shapiro-Wilk normality test, a one- way repeated measures ANOVA was applied to determine the effect of each RAS type on all the gait parameters. When a significant difference between groups was detected, a *post- hoc* Tukey Test was performed. Effect size between conditions regarding α exponents was assessed using Cohen's d. For the linear measures of stride duration variability, the results of the coefficient of variation (CV) did not pass the normality test ($p < 0.05$). A Friedman Repeated Measures ANOVA on ranks was then applied. The results were considered statistically different for $p < 0.05$. Results of α-DFA were also normalized using Z-scores.

The mean α-DFA of the healthy population used to compute Z-scores was taken from the meta-analysis of Ravi et al. (2020) (α-DFA = 0.81 ± 0.14).[28] They studied the effect of PD on α-DFA by compiling the results of 7 studies including a total of 177 PD patients and 135 healthy subjects.

Results

Spatiotemporal Gait Variables

No significant difference was found between each condition for gait speed [$F(3, 8)$: 1.427; $p = 0.260$], gait cadence [$F(3, 8)$: 0.709; $p = 0.556$], step length [$F(3, 8)$: 1.224; $p = 0.323$], and mean stride duration [$F(3, 8)$: 0.674; $p = 0.577$] (Table 3.2).

Stride Duration Variability

Regarding the magnitude of the stride duration variability, CV [$F(3, 8)$: 1.787; $p = 0.177$] was similar in all four conditions (Table 3.2).

Concerning temporal organization of stride duration variability, α-DFA during ARAS was higher than during RRAS and IRAS and was the highest during CC. Indeed, a significant difference was found [$F(3, 8)$: 21.487; $p < 0.001$] (Table 3.2 and Figure 3.1). LRA were present for all patients during CC (Figure 3.2). The mean α-DFA was the highest during this condition (0.76 ± 0.09) and within normative data of healthy population according to Z-scores (Table 3.2 and Figures 3.1, 3.2). Also, Cohen's d was always >1 between CC and the three other RAS conditions, indicating large effect sizes (Figure 3.1).

During ARAS, LRA were present for all patients (Figure 3.2) and mean α-DFA (0.66 ± 0.09) was lower than α-DFA during CC but remained above −1.96 Z-scores, indicating LRA within the normative data (Table 3.2 and

Figures 3.1, 3.2). Furthermore, α-DFA during ARAS was significantly higher than during IRAS and RRAS.

During IRAS, LRA were lowered (α-DFA = 0.44 ± 0.09) compared to CC and Z-scores were below −1.96 which means below normative data (Table 2 and Figure 3.1). During this condition, α-DFA was <0.5 for seven patients, meaning anti- persistence. Similarly, α-DFA was close to 0.5 for the last two patients suggesting that stride duration variability was getting closer to complete randomness during IRAS (Figure 3.2).

During RRAS, α-DFA (0.54 ± 0.18) was significantly lower than during CC, close to 0.5 and not significantly higher than during IRAS for α-DFA (Table 3.2 and Figures 3.1, 3.2). Z-scores were very close to −1.96 Z-scores during this condition suggesting that α-DFA during RRAS was almost out of the normative data (Table 3.2).

Table 3.2. Absolute mean values of the spatiotemporal gait parameters and stride duration variability assessed during Control Condition (CC), Isochronous Rhythmic Auditory Stimulations condition (IRAS), Random Rhythmic Auditory Stimulations condition (RRAS) and Autocorrelated Rhythmic Auditory Stimulations condition (ARAS) and comparison between these walking conditions.

	CC	IRAS	RRAS	ARAS
Gait speed ($m.s^{-1}$)	1.30 (±0.26)	1.29 (±0.25)	1.27 (±0.24)	1.27 (±0.26)
Step length (m)	0.69 (±0.10)	0.69 (±0.10)	0.68 (±0.10)	0.68 (±0.11)
Cadence ($\#steps.min^{-1}$)	113.01 (±8.01)	112.03 (±9.22)	111.89 (±9.06)	111.86 (±9.07)
Mean stride duration (s)	1.07 (±0.07)	1.08 (±0.09)	1.08 (±0.09)	1.08 (±0.09)
Coefficient of variation (%)	1.87 (±0.71)	1.53 (±0.34)	1.66 (±0.25)	1.78 (±0.40)
α-DFA	0.76 (±0.09)†	0.44 (±0.09)*†	0.54 (±0.18)*†	0.66 (±0.09)*
Z-score α-DFA	-0.33 (±0.63)	-2.64 (±0.66)	-1.91 (±1.30)	-1.05 (±0.64)

Absolute value is expressed as mean (±SD)

α-DFA: α exponent calculated using the evenly spaced averaged version of the Detrended Fluctuation Analysis

*: significant difference with CC ($p<0.05$)

†: significant difference with ARAS ($p<0.05$)

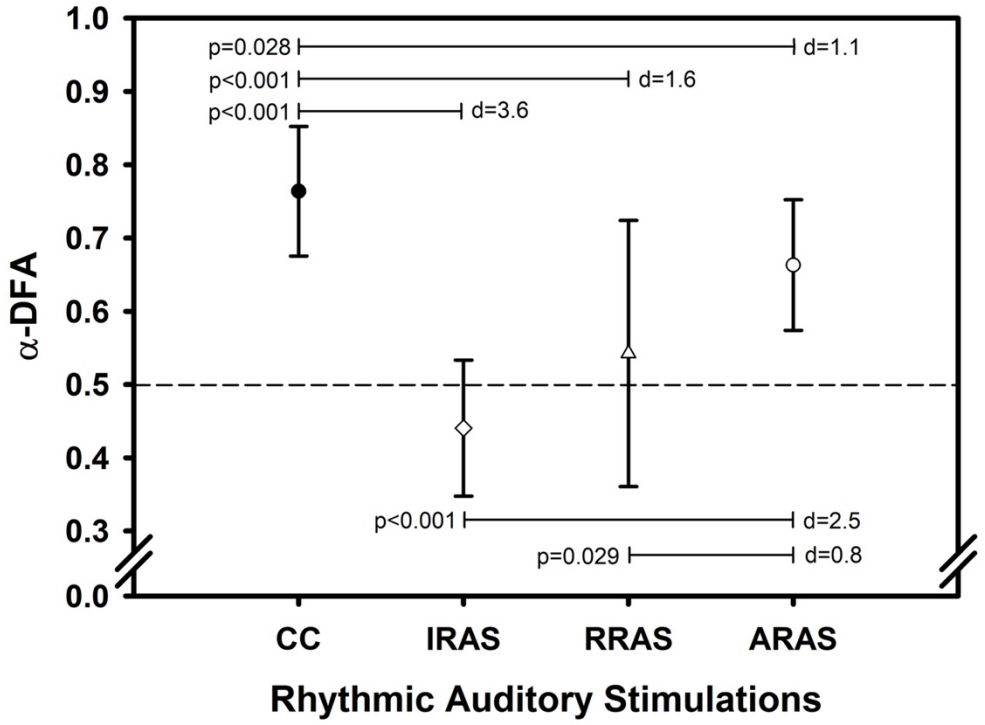

Figure 3.1. *Error bars comparing mean values ± standard deviation of α-DFA obtained during each condition. X axis represents the walking conditions. Y axis represents mean α exponent value during each condition and calculated using the evenly spaced averaged version of the Detrended Fluctuation Analysis (α-DFA). Horizontal lines represent significant differences between conditions. Each p-value is indicated on the left of each line and Cohen's d represents the effect size between conditions on the right (d). The black dashed line placed at 0.5 on the Y axis delimit the area above which there are LRA.*

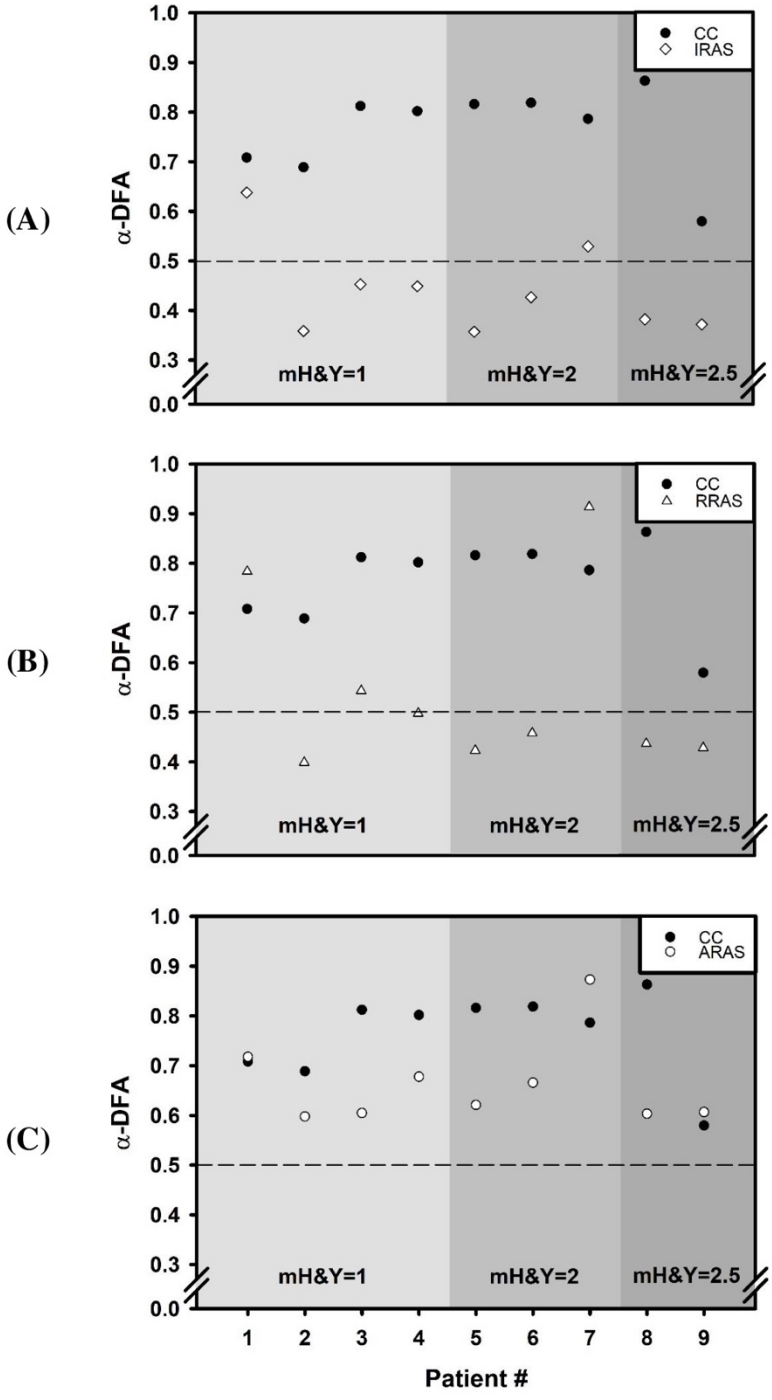
(A)
(B)
(C)
α-DFA
CC
IRAS
RRAS
ARAS
mH&Y=1
mH&Y=2
mH&Y=2.5
Patient #
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.0
1
2
3
4
5
6
7
8
9

Figure 3.2. *Scatter plots comparing α exponent of each of the nine patients during Control Condition (CC) to α exponents obtained during each walking condition: (A) Isochronous Rhythmic Auditory Stimulations condition (IRAS), (B) Random Rhythmic Auditory Stimulations condition (RRAS) and (C) Autocorrelated Rhythmic Auditory Stimulations condition (ARAS). X axis represents the subject number, and the Y axis represents α exponent value during each condition and calculated using the evenly spaced averaged version of the Detrended Fluctuation Analysis (α-DFA). The black dashed line placed at 0.5 on the Y axis delimit the area above which there are LRA. Each graph is divided into three parts representing a stage of the modified Hoehn & Yahr scale (mH&Y) from smallest (left) to largest (right).*

Discussion

This study investigated the extent to which auditory stimuli with different temporal organizations could influence PD gait. First, this study did not show difference concerning spatiotemporal gait parameters and magnitude of stride duration variability between all conditions. On the contrary, this study highlighted that the three RAS influenced the temporal organization of stride duration variability differently. Indeed, LRA were markedly modified during IRAS and RRAS, whereas α-DFA was maintained within normative data and less modified during ARAS.

The spatiotemporal gait parameters were similar between all conditions. These results are reassuring since these parameters have not been degraded during the RAS conditions, whatever the rhythm used. In other studies, PD patients presenting with spatiotemporal gait disorders have improved these parameters using isochronous RAS over several weeks.[156,157] Likewise, improvements were obtained when the RAS had a frequency 10% higher than patients' spontaneous gait cadence.[157]

The analysis of stride duration variability using linear mathematical methods (mean, CV) revealed that the magnitude of the fluctuations was not influenced by the conditions (Table 3.2). These results are in agreement with those of Uchitomi et al. (2013)[139] but contrary to those of Dotov et al. (2017)[57] and Marmelat et al. (2020)[79] who had shown an increase in the CV.

On contrary, all RAS influenced PD patients' temporal organization of stride duration variability differently highlighting further the importance of supraspinal centers in the regulation of gait variability given the influence of these interacting external stimulations. LRA were present in all patients

during CC with normal α-DFA according to the normative data of healthy population.[28,81] This study showed that the use of IRAS led to anti-persistence among seven out of the nine patients. For the others, during IRAS, α-DFA was close to 0.5 indicating a temporal organization close to randomness. As stated in the introduction, it has been shown LRA were positively correlated with balance status (BESTest and ABC scale).[35] In this hypothesis, PD patients' postural stability could be impaired when α-DFA is lowered. As a corollary, the use of an isochronous metronome would potentially induce greater postural instability for these patients.[27] This should be confirmed with longitudinal clinical studies. Unlike during IRAS and RRAS, LRA were present for all patients during ARAS. Although a significant decrease in α-DFA could be demonstrated during this condition compared to CC, the results remained within the normative data of healthy population.[28,81]

Recently, it has been suggested that the presence of LRA in biological systems would represent its healthy status marked by abilities to flexibly adapt to the daily stresses imposed on the body.[27,29,30] While the metronome is widely used in PD patients' gait rehabilitation, this study confirmed that it could lead to less persistence in the temporal organization of gait, whatever the rhythm used. According to Stergiou et al. (2006), among other biological signals, healthy gait would present with an "optimal movement variability".[30] Deviation from this optimal level in either the direction of randomness or over-regularity would represent a loss of adaptative capabilities of the locomotor system.[30,31] The next line of reasoning will follow this theoretical model. Each RAS imposed a rhythm on the patients, a limiting constraint that reduced degrees of freedom during gait. Indeed, patients were asked to synchronize steps with the RAS and had to readjust the timing of each step in

relation to the next in accordance with the imposed rhythms. This could therefore explain why α-DFA during each condition is close to that of the different RAS. In this context, the absence of variation of the isochronous metronome would be contrary to the natural fluctuations present in healthy subjects' gait and compels the patient to synchronize to stereotyped and less complex RAS.[27,148] In the same way, the use of a random metronome would make the temporal organization of gait noisier and more unstable because of a complete lack of structure in the RAS. Both situations are marked by an absence or decrease in persistence. Whether it is an excess of order or complete disorder, this could induce a loss of adaptability in patients' gait.[30] Then, the compromise between excessive order and disorder would be the use of an autocorrelated metronome. Autocorrelated RAS would allow PD patients to have a necessary structure during walking while giving them a certain freedom in carrying out gait, a repertoire of adaptative motor behaviors for the same situation. This is illustrated by an α-DFA within the normative data of healthy subjects during ARAS and therefore closer to 1. According to this theoretical framework[28,33,34], α-DFA close to 1 (i.e., 1/f noise) would be considered as an optimal state of variability and a sign of a strong coordination between the sub-elements composing the system generating and organizing gait. Therefore, getting closer to 1 could be a rehabilitation goal for these patients. Previous studies supported this assumption since it would be possible to discriminate elderly fallers from non-fallers using LRA computation[27] and as mentioned above, correlations were found between a low α- DFA and poor balance test scores in PD patients.[35,46] Further longitudinal studies should be conducted to confirm this hypothesis.

Several authors also studied the effects of different RAS on gait variability among healthy young[148,149] and old[148] subjects' and on PD patients' LRA.[57,79] On one hand, their results clearly showed that the use of an isochronous metronome lead to less persistence in gait.[57,148,149] On the other hand, the use of autocorrelated RAS allowed either to maintain α exponent at the level of non-cued gait, or even to have a more persistent stride-to-stride variability. However, these results cannot be compared perfectly with those of the present study since some of these studies[148,149] only included healthy subjects and since the acquisition times used were all short to compute LRA in a robust manner (5–6 min).

Dotov et al. (2017)[57] and Marmelat et al. (2020)[79] also tested ARAS on PD patients. As already discussed in the Introduction section, this study differs methodologically from theirs. Indeed, this study differs with the one of Dotov et al. (2017): longer acquisition time, RAS frequency set according to participants' comfort cadence, known α-DFA used to create ARAS and longer track with less steering.[57] Lastly, Dotov et al. (2017) did not asked patients to synchronize their step to the beats while this was the case for this present study.[57] On the other hand, despite these differences, our results were similar. Unlike our results and those of Dotov et al. (2017)[57], Marmelat et al. (2020) found significantly higher α-DFA values during ARAS (the 1:1 step-to- beat ratio version) compared to their CC.[79] In their study, music was used to deliver ARAS when a simple beat was used in this study. As notified in the Introduction, music is composed of multiple "layers" giving music multiple frequency ranges making it a more complex auditory cue. This greater complexity could offer more degrees of freedom to patients compared to an usual metronome that could constitute a more rigid framework, even with an

autocorrelated rhythm organization.[119] This could partly explain why Marmelat et al. (2020) noticed an increase in the α-DFA during their ARAS.[79] Also, music evokes emotions[158], improves motivation[159] and it is not currently possible to rule out potential effects of these features on the LRA. The second difference lies in the α-DFA used to produce the ARAS. Indeed, Marmelat et al. (2020)[79] used an α-DFA ∼ 1 which is believed to be an optimal state of variability.[28,33,34] The present study opted for an α-DFA = 0.78 representing the natural temporal organization of healthy gait as seen in previous studies[56,81] and confirmed by the meta-analysis of Ravi et al. (2020).[28] Based on the results of this study, that of Dotov et al. (2017)[57] and Marmelat et al. (2020)[79], the question that remains is which α-DFA to choose to get the optimal temporal organization of the autocorrelated RAS to be used with PD patients. This should be answered with future transversal and longitudinal studies evaluating the long-term effects of RAS using different α exponents as references.

This pilot study included nine mildly impaired patients with α-DFA within normative data of healthy patients.[28,81] It would then be interesting to analyze the influence of the different RAS on a greater number of PD patients and at more advanced stages of the disease. Also, the long-term effect of RAS should be analyzed following a training program to determine whether short-term results are maintained or changed over the long term. Third, no analysis of synchronization between steps and RAS has been performed. This should be done in future similar studies. Lastly, even though the PD patients served as their own control group with CC, no control group composed with healthy subjects was included in this study. One of the prospects for the future is the use of new technologies, such as the smartphone, to produce RAS. These

technologies would be able to assess patient's gait continuously and to deliver ARAS structured with α-DFA adapted in real-time to the patient's needs and situations as suggested by Hove et al. (2012)[150] and Hristovski & Balagué (2012).[160] Such a system should be tested with PD patients in future studies.

In conclusion, the temporal organization of the RAS has a marked impact on temporal organization of stride duration variability among PD patients. IRAS and RRAS lead to less persistence, whereas ARAS allowed to maintain gait variability closer to baseline. Given the results of this study and those of previous ones, the use of an autocorrelated metronome could therefore be an alternative when proposing auditory cueing to patients. However, future transversal and longitudinal studies must be conducted in order to determine the optimal α exponent used to produce autocorrelated RAS and to investigate the clinical utility of this type of metronome in comparison with each other RAS.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

Ethics statement

The studies involving human participants were reviewed and approved by the Comité d'Ethique Hospitalo-facultaire of Cliniques universitaires Saint-Luc. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AL handled data analysis, interpretation of the results, and wrote the manuscript. TW handled the creation of study protocol, managed patient recruitment, participated in the interpretation of the results, and revised the manuscript. CC helped with patient recruitment, data collection, data analysis, and interpretation of the results. BC provided methodological inputs to the study and participated in the interpretation of the results. GS participated in the interpretation of the results and revised the manuscript. CD provided methodological and statistical inputs to the study, helped to the application of mathematical methods, participated in the interpretation of the results, and revised the manuscript. TL was the chief investigator, provided methodological inputs to the study, participated in the interpretation of the results, greatly assisted in writing the manuscript, and revised the final manuscript. All authors approved the final manuscript.

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Chapter 3

Vision: Virtual reality as rehabilitation

Is Pathology-Specific Virtual Reality Rehabilitation Better Than Commercial Virtual Reality to Improve Balance and Functional Mobility in Parkinson's Disease Patients? A Systematic Review and Meta-Analysis

Chapter 3

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Is Pathology-Specific Virtual Reality Rehabilitation Better Than Commercial Virtual Reality to Improve Balance and Functional Mobility in Parkinson's Disease Patients? A Systematic Review and Meta-Analysis

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Abstract

Background

Virtual Reality (VR) rehabilitation is an innovative way to treat balance and mobility impairments in Parkinson's Disease (PD) individuals. Studies use VR designed for rehabilitation (Specific Virtual Reality; SVR) and others use commercial VR (Non-Specific Virtual Reality; NSVR). Also, neurorehabilitation principles have been proposed to identify what potentially make VR interventions effective.

Objective

To perform a systematic review with meta-analysis comparing VR effectiveness versus Conventional Therapy (CT) for balance, functional mobility and quality of life in PD. Second objectives are to assess SVR over NSVR effect and analyze fulfiled neurorehabilitation principles across included studies.

Methods

Randomized control trials studying VR versus CT effects on balance, functional mobility and quality of life outcomes in PD adults were selected from PubMed and Embase. Subgroup analyses were conducted according to VR type, disease severity and treatment duration. Risk of bias was assessed using PEDro checklist and Cochrane's Risk of Bias tool 2 (RoB-2). Percentages of fulfiled neurorehabilitation principles across studies were extracted. GRADE approach was used to define certainty of evidence.

Results

Twenty studies were included for quantitative analysis. VR results were superior to CT for balance but similar for functional mobility and quality of life. SVR and NSVR were similar for balance and functional mobility outcomes. Finally, SVR studies did not fulfil more neurorehabilitation principles than NSVR studies.

Conclusions

VR could enhance balance rehabilitation in PD but with a low certainty of evidence. SVR solutions were not superior to NSVR and should fulfil more relevant neurorehabilitation principles in the future.

Keywords: Parkinson's disease, Virtual reality, Exergaming, Rehabilitation

Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disease[6] with a prevalence in Europe of 66 to 1500 per 100,000.[8] Clinically, PD is mostly characterized by the motor triad: tremor, plastic rigidity, bradykinesia/akinesia.[17] As a consequence, individuals present with limitation of mobility (gait impairments, postural instability) and activities, having repercussions on quality of life.[19]

Drug therapies are only partially effective in improving PD patients' gait and balance.[50–52] Therefore, rehabilitation is an essential part of the treatment of these disorders. As such, clinicians and researchers have been looking for ever more effective rehabilitation treatments.

Virtual Reality (VR) is an innovative rehabilitation method that have been studied for over 10 years in PD. VR is a computer-driven technology that engage individuals with a simulated environment that appeals to multiple senses.[161] VR can be categorized into immersive and non-immersive experiences.[161] In non-immersive VR, participants interact with a digital environment displayed on a standard screen, maintaining their awareness of the physical world. Immersive VR, on the other hand, utilizes VR headsets to completely immerse individuals in a virtual environment.[161] VR is an ideal medium for exergaming with known effectiveness on balance in PD.[162] "Exergame" is a combination of "exercise" and "game." It refers to a type of video game that combines interactive entertainment with physical exercise as a primary purpose. Exergaming is a rehabilitation method with a playful component, providing patients with performance feedback, problem solving, adapting to their functional level and involving motion to interact with the

virtual environment rather than simply pressing buttons.[163] Some searchers or specialized companies create VR exergames specifically for neurorehabilitation purposes (Specific Virtual Reality, SVR).

In contrast, video game manufacturers create off the shelf games (Non-Specific Virtual Reality; NSVR) which are not necessarily dedicated to rehabilitation and especially not pathology-specific. In the literature, it therefore seems relevant to distinguish studies using SVR from those using NSVR. Maier et al (2019)[164] showed that SVR was more effective than NSVR in improving post-stroke upper limb outcomes. They also established a list of 15 neurorehabilitation principles to identify features that make VR effective.[165] They suggested that SVR treatments were superior to NSVR treatments as more of these principles were fulfiled.[164] They also suggested that these neurorehabilitation principles could be potentially applied to PD.[165]

Previous meta-analyses already showed the positive effects of VR on patients' gait and balance, potentially surpassing those of conventional therapy (CT) with a certainty of evidence depending on the study ranging from ‘low’ to ‘high’ according to GRADE approach.[162,166–169] In addition, a previous meta-analysis carried out a subgroup analysis on Berg Balance Scale results, demonstrating the superiority of SVR over NSVR.[167] However, these results are sometimes contradictory, indicating a certain variability in the interventions. Moreover, further analyses are needed to assess the influence of the VR type used (SVR versus NSVR), the degree of disease severity, the total treatment duration, and the fulfilment of the neurorehabilitation principles on other outcomes such as functional mobility. Consequently, the aim of this study is to carry out a systematic review of the literature with meta-analysis in order to:

1) evaluate the efficacy of VR on PD adults according to the World Health Organization's International Classification of Function, Disability, and Health (ICF-WHO) activity and participation categories, fundamental to rehabilitation:[170] balance, functional mobility and quality of life

2) performing subgroup analysis based on VR type (SVR or NSVR), disease severity (Hoehn & Yahr scale) and total treatment duration

3) investigate the fulfilment of neurorehabilitation principles among each study to characterize their VR intervention.

Our primary hypotheses were that SVR would be more effective than NSVR in improving balance, functional mobility and quality of life in PD patients, and would fulfil more neurorehabilitation principles. As secondary hypotheses, we believe that patients who were more affected by the disease would benefit more from VR treatments as they have greater range of improvements, and that prolonged interventions would lead to greater outcomes.

Methods

Study Design

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[171] (Supplementary Material 4.1) and was registered at PROSPERO database (CRD42020151886).

Literature Search

Two independent investigators (AG and AS) screened MEDLINE (PubMed) and EMBASE databases (Supplementary Material 4.2). In addition, previous reviews' reference lists were checked. In case of disagreement or doubt, a third reviewer (AL) intervened in the final inclusion decision. Search strategies are presented in Supplementary Material 4.2.

Eligibility Criteria

Studies were included if our PICOS criteria were fulfiled : (P) idiopathic PD adults at any stage of the disease; (I) VR exergames used for balance or functional mobility rehabilitation and conducted in substitution or in addition of CT (treatments were considered as VR rehabilitation if they involved patients interacting with computer-based technology involving motion-gaming); (C) CT (physical or occupational therapy) or other treatments deemed conventional (balance training, treadmill walking,…) or no treatment; (O) relevant outcomes were measured to assess the ICF-WHO activity (balance, functional mobility) or participation (quality of life) components; (S) RCT design, written in English or French and published before September 19th, 2022.

Data Extraction

The following data were extracted from included studies by two reviewers (AG and AS): VR type (SVR or NSVR), interventions, total treatment duration, number of participants, mean age, delay since diagnostic, mean stage according to Hoehn & Yahr scale, design of the VR intervention, principal aim of the study, scales used according to ICF-WHO categories (Supplementary Material 4.3), follow-up duration, main finding, fulfiled

neurorehabilitation principles. For activities: Berg Balance Scale[172], Sensory Organization Test[173], Timed Up & Go[174] and Dynamic Gait Index[175] were considered. For participation: Parkinson's Disease Questionnaire-39[176] and Parkinson's Disease Questionnaire-8[177] were considered. Absolute mean and SD were extracted for each outcome at the end of the treatment of each group in each study.

In case of missing information, authors were contacted. If they did not reply, the studies were excluded from the quantitative analysis.

Quality Appraisal and Risk-of-Bias Assessment

Included RCTs were assessed using the PEDro checklist (AL, AG, AS). Afterwards, version 2 of the Cochrane Collaboration's Risk of Bias tool (RoB-2) was used to assess the methodological content in each studies included (AL).

Content Analysis of Included Neurorehabilitation Principles

Maier et al (2019)[165] have compiled a list of fifteen neurorehabilitation principles (Supplementary Material 4.4). Three authors (AG, AS, AL) reviewed the studies included in the qualitative analysis to determine which neurorehabilitation principles were fulfiled. All the principles have been retained as in the study of Maier et al. (2019).[165] The meaning of the item "Modulate effector selection", which in the context of PD does not concern the use of a paretic limb but the use of the side most affected by the disease, was changed accordingly. Percentage of neurorehabilitation principles fulfilment of each study was calculated separately for SVR and NSVR.

For some VR methods, certain principles were verified by carrying out searches on the internet to understand their nature and content. This way of proceeding was chosen when it was suspected that certain principles were not explicitly communicated, aiming for the highest level of accuracy possible.

Certainty of Evidence

The GRADE approach was used to determine the certainty of evidence regarding the effect of VR interventions on each outcome of interest.[178] The certainty of evidence was classified as very low, low, moderate, or high depending on the design of the included studies, their overall risk of bias, inconsistency, indirectness, imprecision, publication bias and effect size.

Statistical Analysis

The methodological guidelines of the Cochrane Handbook were followed for the following statistical analyses.[179] Forest-plots and statistical analyses were realized using Review Manager software (RevMan 5.3.). For each outcome of interest, after assessment of equivalence between groups before intervention, treatment effectiveness was assessed by comparing post-intervention scores of the included studies between experimental and control groups, taking into account their related standard deviations and number of participants. A standardized mean difference (SMD) and 95% confidence interval was computed when different scales were reported for the same outcome. The SMD is calculated as a ratio where the numerator represents the mean difference in outcome between group and the denominator, the standard deviation of outcome among participants. The effect size was categorized as low for $0.2 < SMD \leq 0.5$, moderate for $0.5 < SMD \leq 0.8$ or large for $SMD > 0.8$, according to Cohen's guidelines.[180] In addition, the I^2

test was performed to estimate between-studies statistical heterogeneity: heterogeneity might not be important when I^2 ranges from 0 to 40%, heterogeneity may be moderate when I^2 is between 30 and 60%, heterogeneity may be substantial when I^2 is between 50 and 90%, and heterogeneity may be considerable when I^2 is between 75 and 100%.[179] Owing to the uncertainty of the I^2 value in some specific scenarios (when the number of studies is small for instance), we also assessed heterogeneity by visual inspection of forest-plots (looking at the overlaps between the confidence intervals of included studies) and through chi-square tests results. A sensitivity analysis was performed before excluding potential outlier studies.[181]

Funnel plots were also used to detect small study effects, which may suggest publication biases (in case of asymmetry).

For each forest-plot, we chose to use a random-effects analysis as this model takes no account of heterogeneity and is more indicated if no asymmetry is present within the funnel plot. When possible, we also performed subgroup analyses based on VR types (SVR or NSVR), total intervention duration ($\geq$15 or <15 hours), and disease stage (mean Hoehn & Yahr scale $\leq$2 or >2).

An unpaired Student t test was performed to determine a difference of principles fulfilment between SVR and NSVR studies.

Results

Study Identification

After using our search equation in the databases, 1004 studies were identified. Two additional records were identified through other sources.[182,183] After removing duplicates and reading titles and abstracts, 31 studies were selected

for full-text reading. In the end, 25 studies (10 SVR; 15 NSVR) were included in the qualitative analysis and 20 (6 SVR; 14 NSVR) in the quantitative results.[184–188] All studies used non-immersive VR. The total number of participants was 1009 with mean age ranging from 52.5 to 75.6 years, mean PD duration from 4 to 10.3 years, and mean Hoehn & Yahr scale from 1.25 and 3.4. Intervention duration ranged from 4 to 12 weeks, with an average of 7.2 weeks for SVR and 8.7 weeks for NSVR. The total number of treatment hours ranged from 4 to 45 hours, with a mean of 13.5 for SVR and 22.7 for NSVR. The number of treatment hours per week ranged from 0.75 to 6 hours, with a mean of 2.2 hours (1.8 for SVR and 2.2 for NSVR). The Berg Balance Scale (BBS) was the most frequent outcome measure, with 7 studies focusing on SVR and 9 on NSVR (Tables 4.1 and 4.2). The study by Song et al (2018)[189] is the only included study whose control group received no treatment.

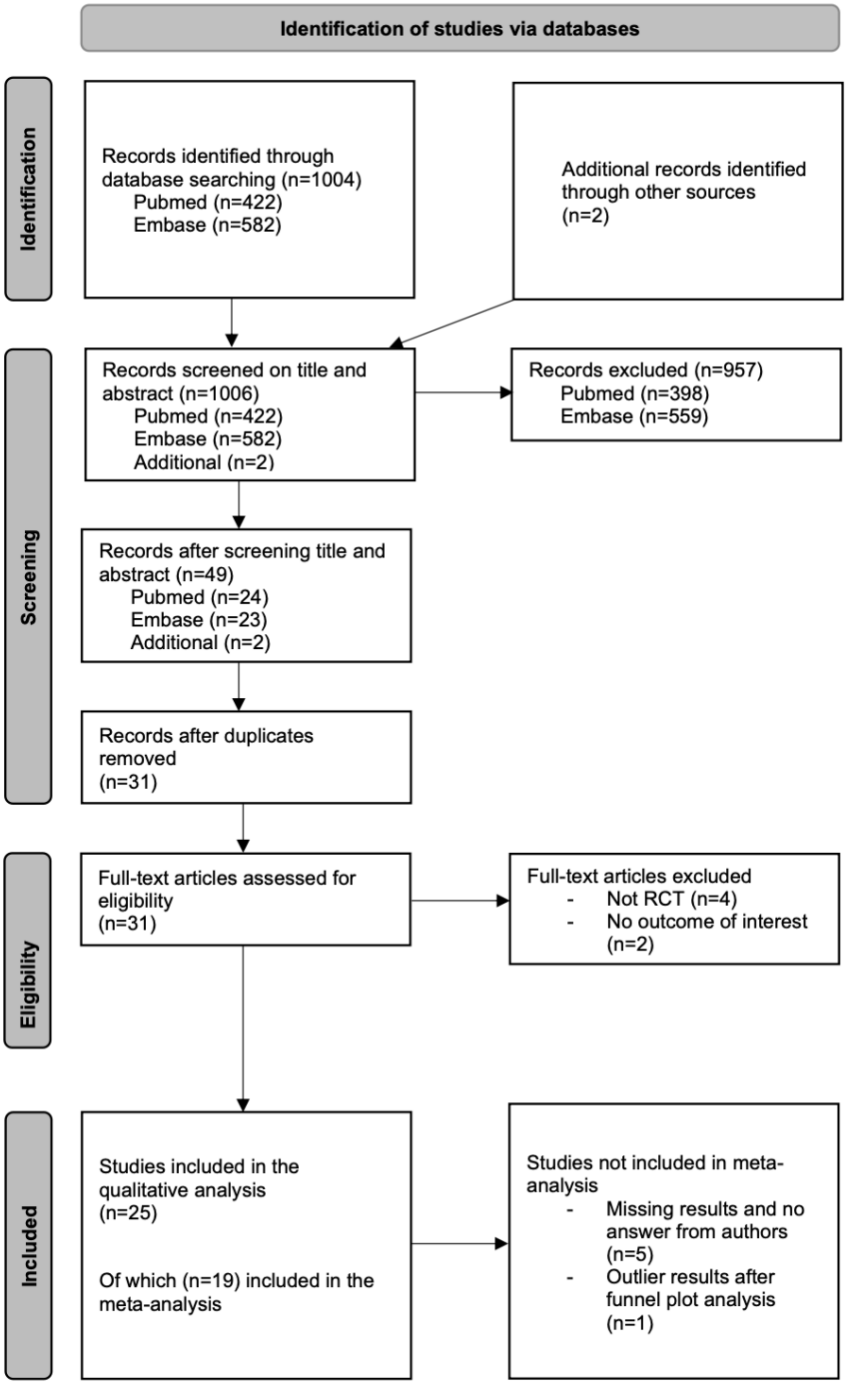

Figure 4.1. *PRISMA flow chart representing the studies selection process.*

Risk of Bias Assessment

The median PEDro score was 7 [6-7]. No study included blinding of patients and therapists, and few studies proposed ‘intention-to-treat’ analysis when drop-outs occurred. A summary of results regarding the RoB-2 is shown in Figure 4.2. Since the two publications by Kashif et al (2022)[190,191] referred to one single trial applying the same treatment among the same cohort of patient, it was decided to apply RoB-2 to a single study only. The same was done with the two studies by Liao et al (2015).[192,193] The overall risk of bias across all studies was primarily categorized as either 'high risk' or 'some concerns'. Only 4 were considered to have a ‘low risk’ of bias[188,189,194,195] (Figure 4.2).

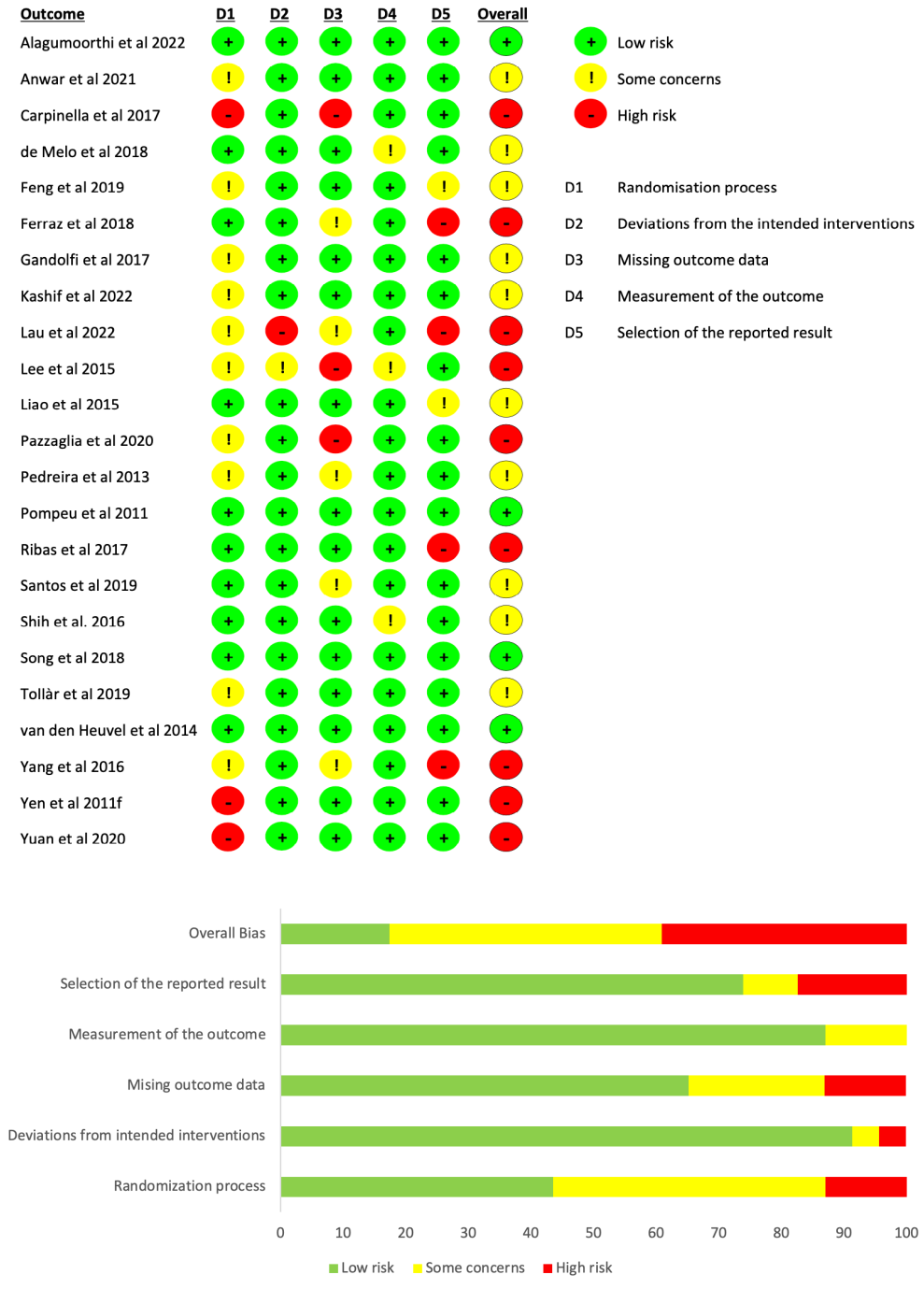

Figure 4.2. *Risk of bias assessment using the Cochrane's RoB-2.*

Effects of VR Interventions on Balance

Fourteen studies were used for quantitative analysis. A funnel plot indicated asymmetry and one outlier[196] was removed from the final analysis (sensitivity analysis: *P*=0.61) (Supplementary Material 4.5). VR rehabilitation showed greater effect over CT on balance outcomes with moderate effect size (SMD=0.59; 95% CI=0.30 to 0.88; *P*<0.0001) (Figure 4.3).

A subgroup analysis based on VR types (*P*=0.78) highlighted that SVR (SMD=0.56; 95% CI=0.21 to 0.91; *P*=0.002) and NSVR (SMD=0.64; 95% CI=0.22 to 1.06; *P*=0.003) showed similar efficacy (Figure 4.3). A subgroup analysis based on total treatment duration (*P*=0.41) highlighted that interventions with a treatment duration ≥15 hours (SMD=0.72; 95% CI=0.25 to 1.19; *P*=0.003) and those with a treatment duration <15 hours (SMD=0.47; 95% CI=0.11 to 0.82; *P*=0.009) showed similar efficacy (Figure 4.4). A subgroup analysis based on disease severity (*P*=0.62) highlighted that patients with a mean Hoehn & Yahr ≥2 (SMD=0.51; 95% CI=0.11 to 0.92; *P*=0.01) and those with a mean Hoehn & Yahr <2 (SMD=0.73; 95% CI=-0.03 to 1.49; *P*=0.06) obtained similar outcomes (Figure 4.5). GRADE approach revealed a low certainty of evidence regarding VR effect on balance outcomes, owing for a moderate heterogeneity and unclear risk of bias (Table 4.3).

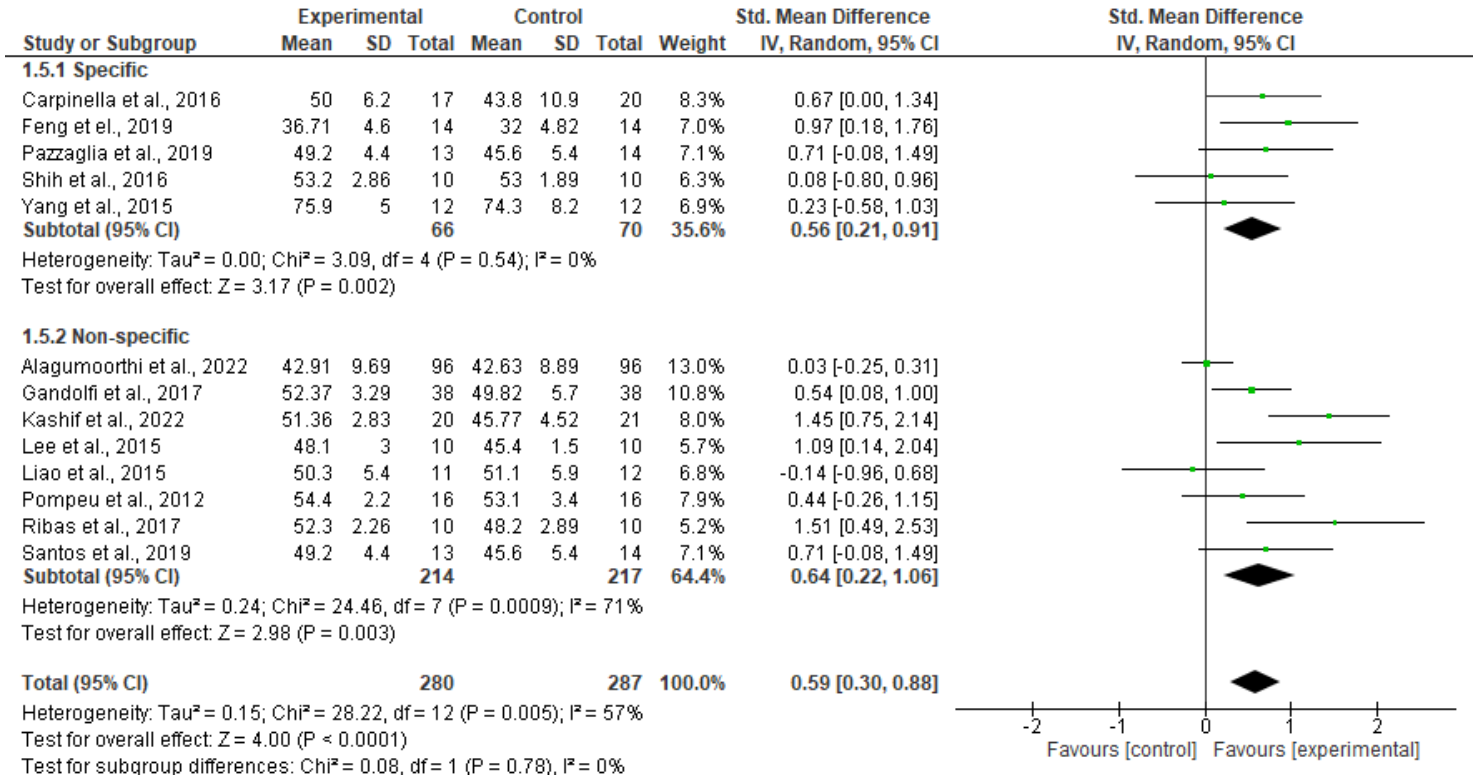

Figure 4.3. *VR rehabilitation effect on balance and subgroup analysis based on VR types represented through a forest plot.*

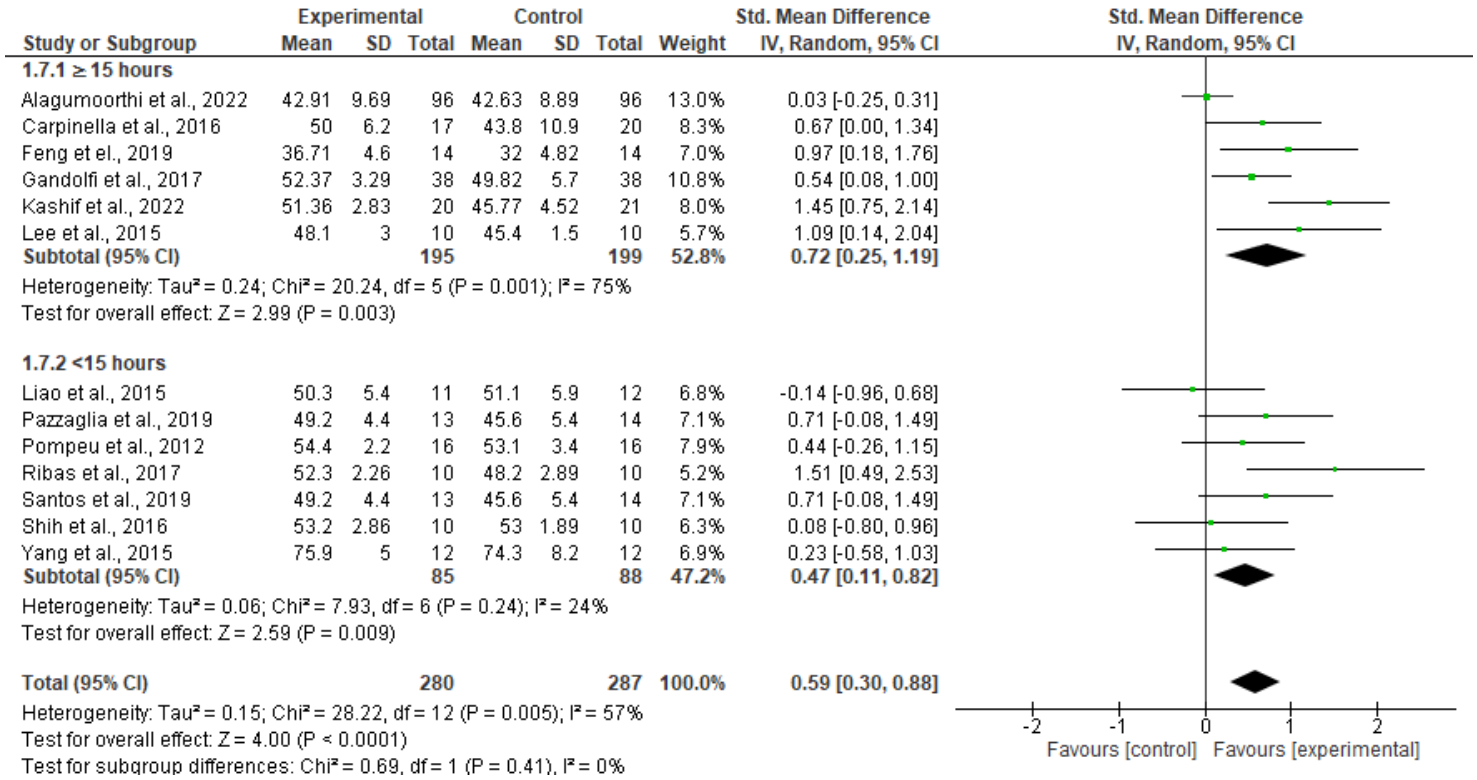

Figure 4.4. *VR rehabilitation effect on balance and subgroup analysis based on total intervention duration represented through a forest plot.*

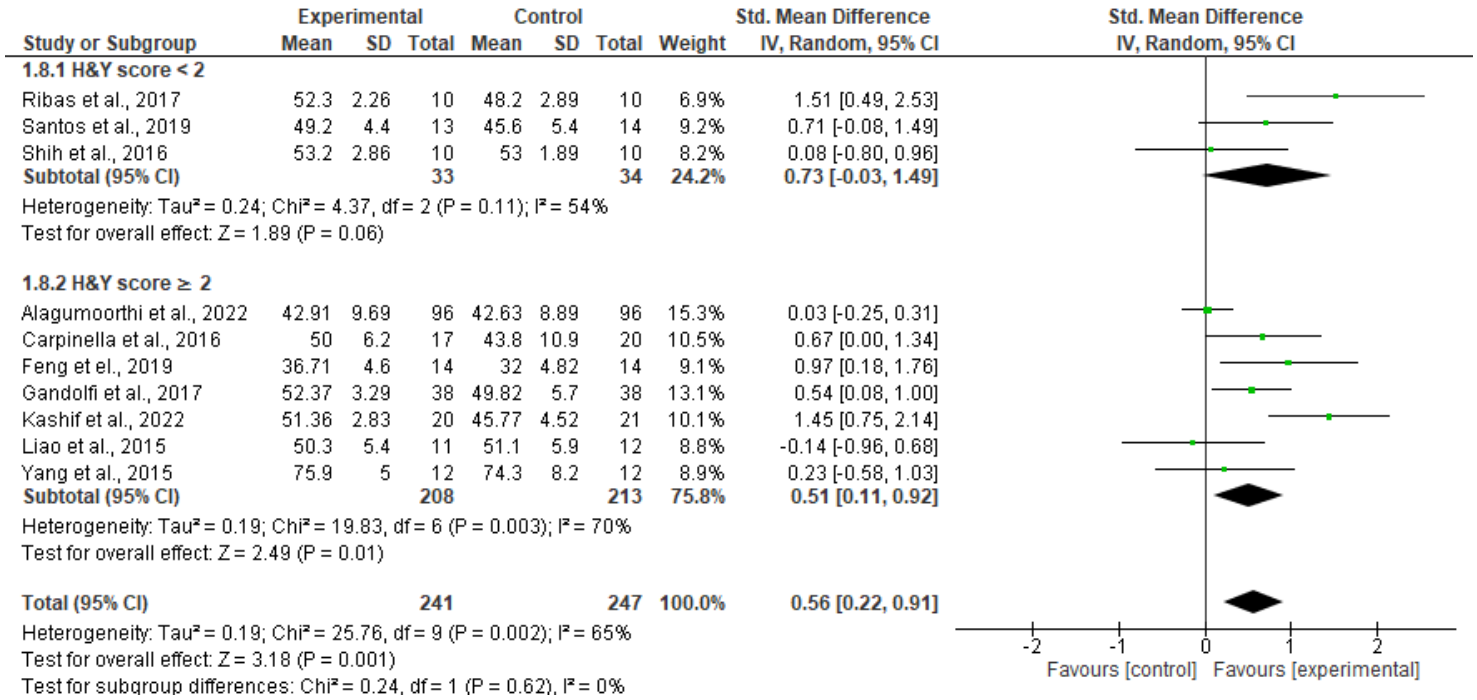

Figure 4.5. *VR rehabilitation effect on balance and subgroup analysis based on disease severity according to Hoehn & Yahr scale, represented through a forest plot.*

Effects of VR Rehabilitation on Functional Mobility

Eleven studies were included in quantitative analysis. One outlier[196] was removed from the meta-analysis because funnel plot showed asymmetry (sensitivity analysis: *P*=0.30) (Supplementary Material 4.5). VR rehabilitation did not lead to a significant benefit over CT to improve functional mobility (SMD=0.14; 95% CI=-0.08 to 0.36; *P*=0.20) (Figure 4.6).

A subgroup analysis based on VR type (*P*=0.45) highlighted that SVR (SMD=0.23; 95% CI=-0.16 to 0.61; *P*=0.25) and NSVR (SMD=0.06; 95% CI=-0.16 to 0.28; *P*=0.62) showed similar efficacy (Figure 4.6). A subgroup analysis based on total treatment duration (*P*=0.20) highlighted that interventions with a treatment duration ≥15 hours (SMD=0.45; 95% CI=-0.09 to 0.99; *P*=0.10) and those with a treatment duration <15 hours (SMD=0.03; 95% CI=-0.17 to 0.23; *P*=0.20) showed similar efficacy (Figure 4.7). GRADE approach revealed a moderate certainty of evidence regarding VR effect on functional mobility outcomes, owing for a low effect size (Table 4.3).

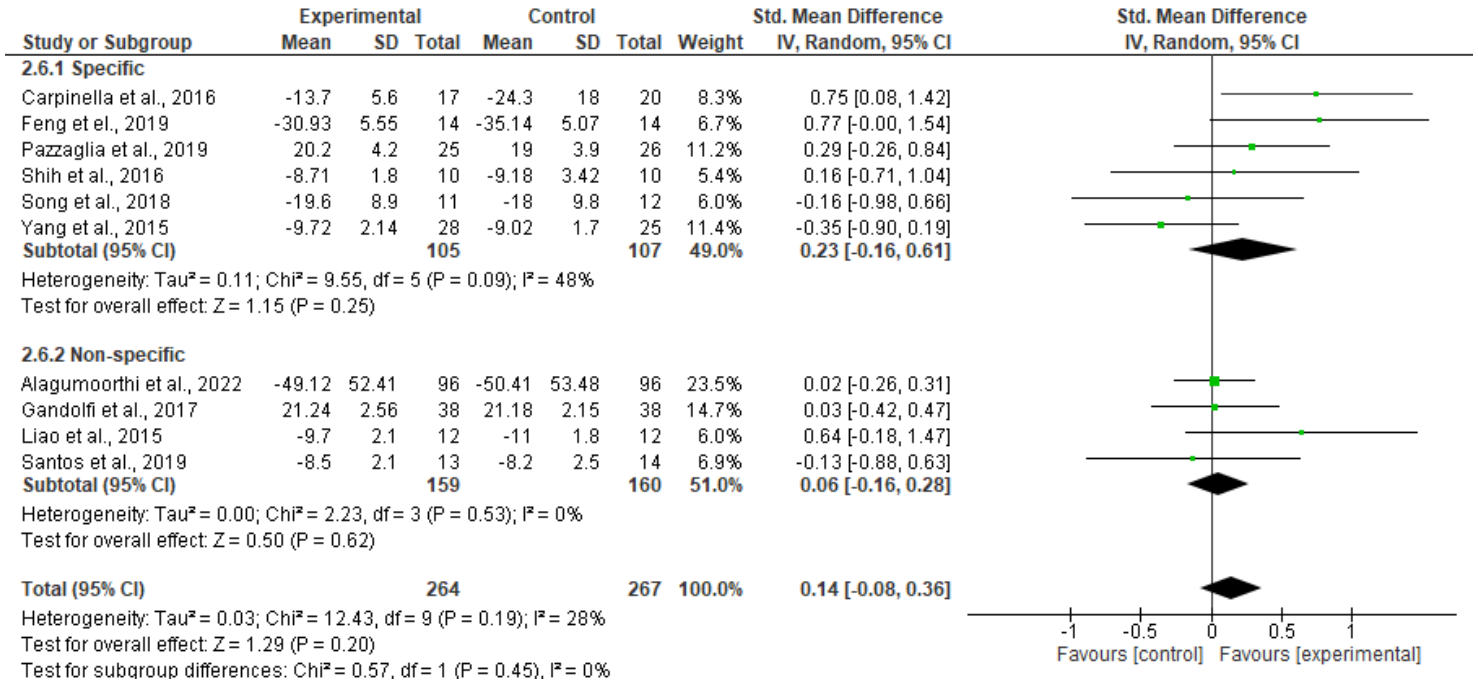

Figure 4.6. *VR rehabilitation effect on functional mobility and subgroup analysis based on VR types represented through a forest plot.*

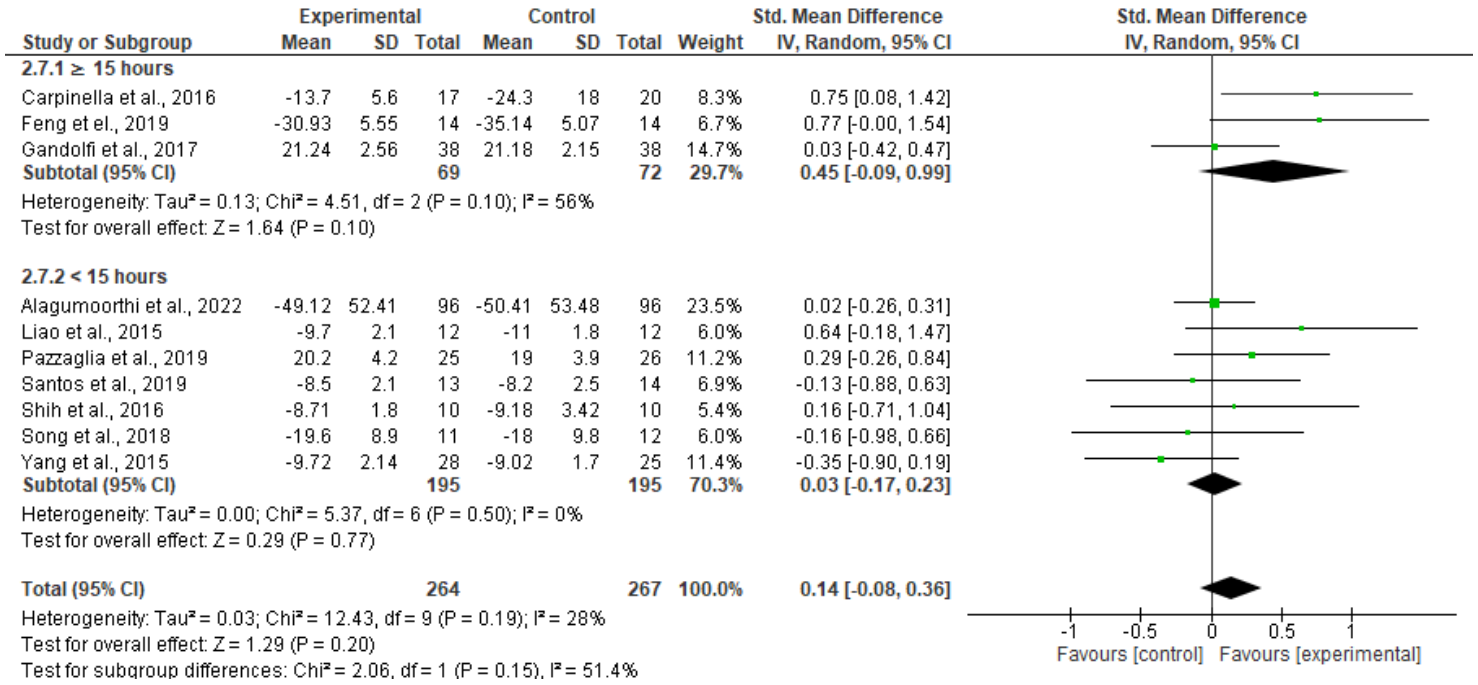

Figure 4.7. *VR rehabilitation effect on functional mobility and subgroup analysis based on total intervention duration, represented through a forest plot.*

Effects of VR Rehabilitation on Quality of Life

Eleven studies were included in the analysis. VR rehabilitation did not lead to a significant benefit over CT to improve quality of life (SMD=0.04; 95% CI=-0.15 to 0.22; *P*=0.70) (Figure 4.8). Given the small number of SVR studies, no subgroup analysis could be performed. GRADE approach revealed a low certainty of evidence regarding VR effect on quality of life outcomes, owing for a low effect size and serious risk of bias (Table 4.3).

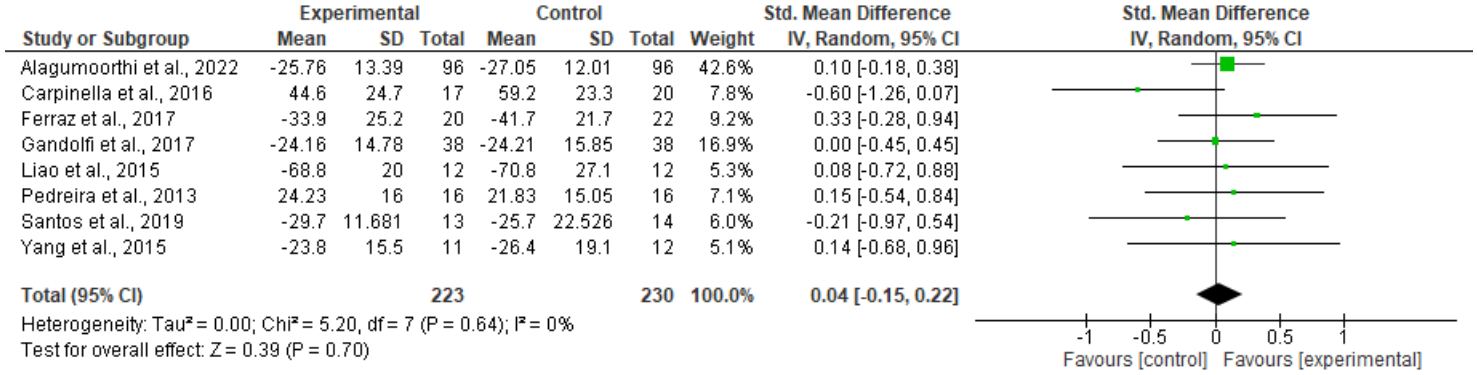

Figure 4.8. *VR rehabilitation effect on quality of life represented through a forest plot.*

Included Principles of Neurorehabilitation

Table 4.2 gives details of the principles fulfiled by each study. Figure 4.9 summarizes the amount of neurorehabilitation principles fulfiled across studies. Mean number of fulfiled principles was 6.9(2.1) for SVR studies and 6.8(1.3) for NSVR studies with no significant difference between groups (P=0.86). SVR studies did not share one common principle. However, 8/15 principles were present in 50% or more of the SVR studies: goal-oriented practice (90%), explicit feedback (80%), variable practice (80%), increasing difficulty (80%), spaced practice (60%), task-specific practice (60%), social interaction (60%) and implicit feedback (50%). All NSVR studies shared 3 common principles: multisensory stimulation, explicit feedback and goal-oriented practice. Among the other principles, 3 were shared by ≥50% of the NSVR studies: implicit feedback (92%), variable practice (85%) and social interaction (62%). The SVR studies were more characterized by the implementation of task-oriented practice, increasing difficulty, spaced practice and, to a lesser extent, massed practice than NSVR studies. On the other hand, the NSVR studies proposed more explicit feedback, implicit feedback and multisensory stimulation. Six of the fifteen principles were present in ≤50% of both SVR and NSVR studies: massed practice (SVR 40%; NSVR 15%), rhythmic cueing (SVR 30%; NSVR 38%), action observation (SVR 10%; NSVR 8%), dosage (SVR 0%; NSVR 15%), modulate effector selection (SVR 10%; NSVR 0%) and mental imagery (SVR 0%; NSVR 8%).

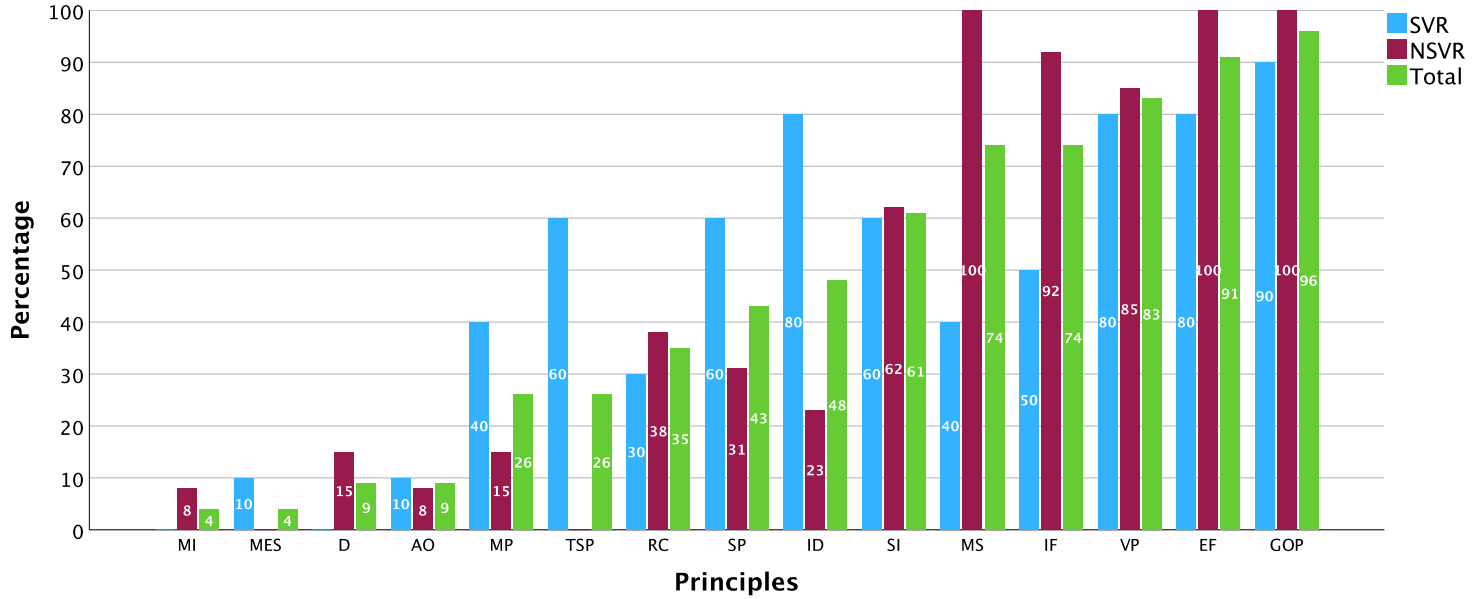

Figure 4.9. *Percentages of neurorehabilitation principles included in SVR, NSVR and all studies.*
Blue indicates SVR studies, red NSVR studies and green Total.
Abbreviations: AO, Action Observation; D, Dosage; EF, Explicit Feedback; GOP, Goal-Oriented Practice; ID, Increased Difficulty; IF, Implicit Feedback; MES, Modulate Effector Selection; MI, Motor Imagery; MP, Massed Practice; MS, Multisensory Stimulation; RC, Rhythmic Cueing; SI, Social Interaction; SP, Spaced Practice; TSP, Task-Specific Practice; VP, Variable Practice.

Discussion

The aim of this study was to review and summarize the effect of VR rehabilitation over CT in relation to different outcomes classified in the ICF-WHO activity and participation categories (balance, functional mobility, quality of life), to subgroup the results between SVR and NSVR rehabilitation, disease severity and treatment duration and to determine their neurorehabilitation principles fulfilment.

Balance Outcomes

In the light of our results, VR rehabilitation appears to be superior to CT in improving patients' balance, with a low certainty of evidence, confirming the results of previous meta-analyses.[162,167,197] The improvement in balance can be explained by the fact that most VR exercises include movements and position changes within a small area imposed by VR systems. VR exergames therefore train the balance tasks typically assessed by BBS and SOT scales.[167]

Concerning VR types, subgroup analyses revealed that SVR and NSVR provided similar results for this outcome which is not in line with our hypothesis. Indeed, Maier et al (2019)[164] and Sarasso et al (2022)[167] found SVR to be superior to NSVR for balance outcomes for stroke and PD respectively. This difference may be due to our slightly different selection criteria, which also included two recent studies.[190,194] In addition, our results showed a greater effect of VR on balance for more severely affected patients, confirming our hypothesis that these patients would benefit more from this treatment. This was expected, since the most affected patients are those with the greatest balance disorders in need of improvement.[198] Balance is also influenced by patients' cognitive and visual impairments[199,200], which are

greater in the most severely affected patients.[201] Since VR exergames include dual-task exercises combining cognitive and balance training while stimulating patients with different visuals, VR training could be all the more effective for patients requiring the most attention in this area. Also, VR rehabilitation was even more effective in studies proposing longer total treatment duration with large effect size for ≥15 hours treatment which is in line with recommendation from existing guidelines.[202,203] To our knowledge, this study is the first to highlight the importance of longer treatment in VR to potentiate its effect on balance.

Functional Mobility Outcomes

On the other hand, VR rehabilitation did not lead to benefits over CT in terms of functional mobility, with a moderate certainty of evidence. This could be explained by the fact that VR exercises do not include walking even on short distances. Then most VR exergames do not train functional mobility and locomotion tasks typically assessed by the TUG and DGI scales. However, these results are different from previous meta-analyses[162,167] that found superiority of VR over CT to improve TUG. This difference could stem from our choice to combine results concerning TUG and DGI to assess functional mobility and also adding more studies to the analysis (10 in our study versus 8[167] and 7[162]). To our knowledge, this study is the first to perform a subgroup analysis to distinguish SVR from NSVR results on functional mobility outcome. However, no superiority of one VR type over the other could be demonstrated. A possible explanation could be that both SVR and NSVR methods offered static exercises which were far from the dynamic gait and transfer tasks required by the TUG and DGI. In the future, VR rehabilitation

methods should offer both static and dynamic exercises involving locomotion to improve functional mobility.

Quality of Life Outcomes

Regarding quality of life, VR did not lead to benefits over CT with low certainty of evidence, which confirms previous results.[167] The results could be explained by the eminently subjective nature of patients' responses to quality of life questionnaires, and by the diversity of areas covered by these scales. They may also be explained by the fact that VR exercises did not improve functional mobility, which is a determining factor for independence in daily life and quality of life.[204] Unfortunately, a subgroup analysis based on VR type was not possible due to the lack of SVR studies investigating these outcomes.

Adherence to Neurorehabilitation Principles

In total, SVR studies did not significantly fulfil more neurorehabilitation principles than NSVR ones. This invalidates our initial hypotheses and may partly explain the similarity of results between the SVR and NSVR studies regarding balance and functional mobility.

Nevertheless, SVR studies fulfiled principles relevant to PD patients' rehabilitation. In particular, the "Task Oriented Practice" principle refers to training in situations that are relevant to the activities of daily living. Interestingly, 60% of SVR studies fulfiled this principle versus 0% of NSVR studies. An explanation is that most NSVR games do not aim to reproduce everyday situations. Also interesting is the "Spaced Practice" principle, which was more often fulfiled in SVR, where NSVR tried to produce fun situations that follow one another with little downtime.

By design, NSVR offers a great deal of explicit feedback via multisensory stimuli to maximize the feeling of winning. Similarly, game manufacturers spend a great deal of effort to ensure that the movements of the avatars follow the patient's movements as closely as possible, to emotionally involve the player. In our view, this emotional engagement could be one of the keys to enabling VR to surpass CT in terms of patient adherence and motivation.[161] Furthermore, although not statistically significant, a recent meta-analysis[205] suggested a lower drop-out rate in studies including PD patients treated with VR rehabilitation versus CT. Future SVR studies should focus on producing high-quality explicit and implicit feedbacks using multisensory stimulations to the level offered by NSVR games to optimally engage patients emotionally.

Importantly, 6/15 of these principles were fulfiled in less than 50% of SVR and NSVR studies. Massed practice could be fulfiled by offering treadmill treatment combined with VR. Indeed, treadmill walking allows the patient to walk for extended periods of time, providing a large number of movement repetitions. Furthermore, treadmill therapy has demonstrated its effectiveness in PD.[206] Finally, the combination of VR and treadmill is feasible in PD.[122,185,207] Regarding rhythmic cueing, it is surprising to find so few VR methods that incorporated this principle. Additionally, there were more NSVR than SVR studies fulfiling this principle. The rehabilitative value of rhythmic cueing is widely recognized in PD[60] and should be an integral part of VR rehabilitation. Action observation and motor imagery are relatively lesser-known rehabilitation techniques in PD and few studies fulfiled these principles. Nevertheless, a recent systematic review evaluating the effectiveness of both techniques provides promising results.[208] To implement action observation, instructions can be simply explained through videos

showing a real or virtual model performing the exercise before the patient carries it out. To modulate effector selection, constraint-induced movement therapy is widely used in the context of stroke but less so in PD. Given the asymmetric nature of motor impairment in PD, this type of therapy, which promotes massed practice on the more severely affected side, seems interesting. The use of split belt treadmills can enable this modulation, as demonstrated in the study by Lau et al. (2022).[185] Ultimately, treatment dosage appears to be largely insufficient in the various proposed treatment protocols (mean of 2.2 hours a week) compared to the 5 hours a week suggested in the neurorehabilitation principles and the higher dosage recommended in a previous meta-analysis.[197] Furthermore, our results highlighted a large effect size for longer VR treatment durations.

Although interesting, these neurorehabilitation principles deserve to be nuanced in the light of guidelines concerning PD patients rehabilitation.[202,203] Some principles come close to the guidelines: rhythmic cueing / external cueing, social interaction / community-based exercise, task specific practice / task specific training, explicit and implicit feedbacks plus goal-oriented practice / behavior-change approach.[203] Conversely, other guidelines are not included or are implicitly present in the exergames studied: aerobic training, resistance training, gait training, balance training, flexibility exercises.[203] These neurorehabilitation principles should therefore be fleshed out by the addition of certain guidelines elements, and a weighting of the importance of each of these principles should be carried out in the future.

Clinical Implication

This meta-analysis further supports the use of VR in balance rehabilitation for PD patients with a low certainty of evidence. Therefore, we recommend the use of VR as a complementary approach to CT. In light of our findings, it would be all the more advisable to offer VR rehabilitation to patients more severely affected by the disease (Hoehn & Yahr ≥2), and for longer treatment durations (>15 hours). Subsequently, we recommend assessing whether the VR exergames under consideration fulfil relevant neurorehabilitation principles and integrate existing guidelines. Nevertheless, the cheaper NSVR solutions appear to be effective to improve static balance, are easy to use and could be recommended if available.

Recommendations for Future Research

In light of current technological advancements, the VR equipment used in even recent studies appeared outdated and were sometimes no longer available. Future research should rely on cutting-edge technologies such as immersive VR headsets. This technology is promising because it offers complete immersion while being cheap. The importance of immersion in VR rehabilitation has been emphasized in previous studies[161] but it was not present in any of the methods included in the studies reviewed. These technologies provide a large play area to work on dynamic balance, and immersion allows for greater emotional engagement through enhanced implicit feedback felt from a first-person perspective. Furthermore, the use of VR headsets is feasible and well-supported by PD patients.[122,207] One downside of these technologies is the increased social isolation that could be overcome by a multiplayer mode.

Few studies have evaluated participants after a post-treatment follow-up period. More clinical studies evaluating the effects of VR rehabilitation over the longer term need to be carried out.

The neurorehabilitation principles should be refined to the specific context of PD by implementing elements taken from existing guidelines. At the same time, it would be advisable to weight the importance of each of these principles.

More RCTs with superior methodological quality and less risk of bias are needed in the future to further increase our knowledge of the use of VR in PD rehabilitation.

Strength and Limitations

This meta-analysis was rigorously conducted in accordance with PRISMA guidelines. In addition, several original analyses were carried out: SVR vs NSVR for functional mobility outcomes, influence of VR treatment duration, completion of neurorehabilitation principles.

However, some results should be interpreted with caution due to the low methodological quality and limited number of studies included. Moreover, this limited number of studies did not allow for subgroup analysis for quality of life outcomes.

Regarding neurorehabilitation principles, while we could verify outside of the study protocols whether certain principles were fulfiled for NSVR games, this was not the case for most of the SVR solutions due to their homemade nature. Future studies using VR exergames should explicitly give as much details as possible about their content.

Conclusion

VR rehabilitation seems to be superior to CT in improving balance in PD patients with low certainty of evidence. Conversely, VR rehabilitation did not lead to a significant benefit over CT to improve functional mobility and quality of life with moderate and low certainty of evidence respectively. The subgroup analysis conducted for balance and functional mobility did not show a superiority of SVR over NSVR. Conversely, VR rehabilitation seems to be even more effective on balance outcome for more severely affected individuals and if treatment is given for longer periods. SVR studies did not significantly fulfiled more neurorehabilitation principles than NSVR studies, but future studies should aim to comply with even more principles.

Acknowledgment

No conflict of interests to disclose.

Table 4.1. Characteristics of studies included in the qualitative analysis*.

Author	Intervention	n	Age	YSD (years since diagnostic)	H&Y	VR design	PEDro
SVR studies							
Carpinella et al. 2017[183]	VR vs CT (6x3x45) +(1x2x45) =15 hours	17/37	VR =73.0(7.1) CT =75.6(8.2)	VR =7.5(3.2) CT =10.3(5.7)	VR =2.7(0.7) CT =2.9(0.5)	VR environment on a computer screen and motion tracking through wearable sensors	6
Feng et al. 2019[209]†	VR vs CT 12x5x45 =45 hours	14/28	VR =67.5(4.7) CT =66.9(4.6)	VR =7.1(1.4) CT =6.6(1.5)	VR =3.0(0.6) CT =3.0(0.6)	VR environment on a computer screen and motion tracking system not specified	7
Lau et al. 2022[185]	VR vs NI 4x3x30 =6 hours	9/18	VR =64(9) NI =71(5)		VR =2.0(0.6) NI =1.9(0.7)	VR environment on a screen using a projector and data of the treadmill for motion tracking	4

(Continued)

Pazzaglia et al. 2019[210]†	VR vs CT 6x3x40 =12 hours	25/51	71(8.5)	6.1(6.3)		VR environment using NIRVANA projector system and infrared camera for motion tracking	7
vShih et al. 2016[211]†	VR vs BT 8x2x50 =13.3 hours	10/20	VR =67.5(10.0) BT =68.8(9.7)	VR =4.0(3.7) BT =5.2(4.9)	VR =1.6(0.8) BT =1.4(0.5)	VR environment on a screen homemade exergames and motion tracking through Microsoft Xbox Kinect	6
Song et al. 2018[189]†	VR vs NI 12x3x15 =9 hours	28/53	VR =68(7) NI =65(7)	VR =7(4) NI =9(6)		VR environment on a screen using a modified homemade version of "Dance Dance Revolution Stepmania" game and motion tracking through a custom-made step mat	8

(Continued)

van den Heuvel et al. 2014[188]	VR vs CT 5x2x60 =10 hours	15/32	VR =66.3(6.4) CT =68.8(9.7)	VR =9.0[4.0-13.3] CT =8.8[2.5-11.5]	VR =2.5[2.0-2.5] CT =2.5[2.0-3.0]	VR environment on a screen and motion tracking through a force plate and inertial sensors	8
Yang et al. 2016[212]†	VR vs CT 6x2x50 =10 hours	11/23	VR =72.5(8.4) CT =75.4(6.3)	VR =9.4(3.6) CT =8.3(4.1)	VR =3[3-3] CT =3[3-3]	VR environment on a screen and motion tracking through a balance board	7
Yen et al. 2011[184]	VR vs BT vs NI 6x2x30 =6 hours	13/38	VR =70.4(6.5) BT =70.1(6.9) NI =71.6(5.8)	VR =6.0(2.9) BT =6.1(3.3) NI =7.8(4.2)	VR =2.6(0.5) BT =2.4(0.5) NI =2.6(0.4)	VR environment on a screen and motion tracking through a balance board	7
Yuan et al. 2020[186]	VR vs NI Crossover design 6x3x30 =9 hours	12/24	Group A =67.8(5.5) Group B =66.5(8.8)		Group A =2[1-3] Group B =2[1-3]	VR environment on a screen and motion tracking through a step mat	7

(Continued)

NSVR studies							
Alagumoorthi et al. 2022[194]†	VR+CT vs BT+CT 12x3x30-40(30) =36-42 hours	96/192	VR+CT =69.7(10.0) BT+CT =68.5(9.8)	VR+CT =5.4(3.6) BT+CT =5.3(3.0)	VR+CT =3.4(0.6) BT+CT =3.4(0.6)	Wii Sports on Nintendo Wii	8
Anwar et al. 2021[196]	VR vs BT 4x3x45 =9 hours	12/24	VR =55.0(6.8) BT =52.3(6.8)			Wii Sports and Balance Board games on Nintendo Wii	6
de Melo et al. 2018[213]†	VR vs TT vs CT 4x3x20 =4 hours	12/37	VR =60.3(9.3) TT =61.0(10.7) CT =65.6(13.0)		VR =1.4(0.5) TT =1.5(0.7) CT =2.1(0.9)	Your Shape – Fitness Evolved 2012 – Run the World game on Microsoft Xbox Kinect	7
Ferraz et al. 2018[214]†	VR vs BE vs CT 8x3x50 =20 hours	20/62	VR =67[66-68] BE =67[64-71] CT =71[66-75]	VR =4[4-7] BE =6[4-9] CT =4[3-7]	VR =2.5[2.0-2.5] BE =2.5[2.0-3.0] CT =2.5[2.5-3.0]	Kinect Adventure games on Microsoft Xbox Kinect	7

(Continued)

Gandolfi et al. 2017[215]†	VR vs SIBT 7x3x50 =17.5 hours	36/70	VR =67.5(7.2) SIBT =69.8(9.4)	VR =6.2(3.8) SIBT =7.5(3.9)	VR =2.5[2.5-2.5] SIBT =2.5[2.5-3.0]	Wii Fit Plus games on Nintendo Wii	7
Kashif et al. 2022[190]†	VR+MI+PT vs PT+WE+BE 12x3x 10-15(45-50) =36 hours	20/41	VR+MI+PT =63.9(4.6) PT+WE+BE =62.3(4.6)	VR+MI+PT =6.2(1.9) PT+WE+BE =6.6(1.7)	VR+MI+PT =2.1(0.7) PT+WE+BE =2.3(0.7)	Wii Fit Plus and Wii Sports games on Nintendo Wii	7
Kashif et al. 2022[191]†	VR+MI+PT vs PT+WE+BE 12x3x 10-15(45-50) =36 hours	20/41	VR+MI+PT =63.9(4.6) PT+WE+BE =62.3(4.6)	VR+MI+PT =6.2(1.9) PT+WE+BE =6.6(1.7)	VR+MI+PT =2.1(0.7) PT+WE+BE =2.3(0.7)	Wii Fit Plus and Wii Sports games on Nintendo Wii	7
Lee et al. 2015[216]†	VR+NDT +FES vs NDT+FES 6x5x30(45) =37.5 hours	10/20	VR+NDT+FES =68.4(2.9) NDT+FES =70.1(3.3)			K-Pop Dance Festival game on Nintendo Wii	4

(Continued)

Liao et al. 2015[193]†	VR+TT vs CT+TT vs NI 6x2x45(15) =12 hours	12/36	VR+TE =67.3(7.1) CT+TE =65.1(6.7) NI =64.6(8.6)	VR+TE =7.9(2.7) CT+TE =6.9(2.8) NI =6.4(3.0)	VR+TE =2.0(0.7) CT+TE =2.0(0.8) NI =1.9(0.8)	Wii Fit Plus games on Nintendo Wii	7
Liao et al. 2015[192]†	VR+TT vs CT+TT vs NI 6x2x45(15) =12 hours	12/36	VR+TE =67.3(7.1) CT+TE =65.1(6.7) NI =64.6(8.6)	VR+TE =7.9(2.7) CT+TE =6.9(2.8) NI =6.4(3.0)	VR+TE =2.0(0.7) CT+TE =2.0(0.8) NI =1.9(0.8)	Wii Fit Plus games on Nintendo Wii	7
Pedreira et al. 2013[182]	VR vs CT 4x3x40 =8 hours	16/32	VR =61.1(8.2) CT =66.2(8.5)	VR =8.6(4.6) CT =7.3(6.6)	VR =2.5(0.6) CT =2.4(0.7)	Wii Sports games on Nintendo Wii	4
Pompeu et al. 2012[195]†	VR+CT vs BT+CT 7x2x30(30) =14 hours	16/32	67.4(8.1)	5.0(4.5)		Wii Fit games on Nintendo Wii	5
Ribas et al. 2017[217]†	VR vs CT 12x2x30 =12 hours	10/20	VR =61.7(6.8) CT =60.2(11.3)	VR =6.5(4.0) CT =7.0(2.8)	VR =1.25[1.0-2.0] CT =1.5 [1.0-2.0]	Wii Fit games on Nintendo Wii	7

(Continued)

Santos et al. 2019[218]†	VR vs CT vs VR+CT 8x2x50 =13.3 hours	15/45	VR =61.7(7.3) CT =64.5(9.8) VR+CT =66.6(8.2)	VR =7.0(2.8) CT =6.5(2.0) VR+CT =7.8(3.7)	VR =1.4(0.6) CT =1.3(0.3) VR+CT =1.5(0.4)	Wii Fit and Wii Sports games on Nintendo Wii	7
Tollár et al. 2018[187]	VR vs BE vs NI 5x5x60 =25 hours	25/74	VR =70.0(4.7) BE =70.6(4.1) NI =67.5(4.3)	VR =7.5(1.8) BE =7.5(2.2) NI =7.3(2.2)	VR =2.3(0.5) BE =2.4(0.5) NI =2.4(0.5)	Kinect Adventures and Just Dance games on Microsoft Xbox Kinect	6

Abbreviations: BE, Bicycle Exercise; BT, Balance Training; CT, Conventional Therapy; FES, Functional Electrical Stimulation; H&Y, Hoehn & Yahr scale; MI, Mental Imagery; NDT, NeuroDevelopmental Treatment; NI, No Intervention; NSVR, Non-Specific Virtual Reality; PEDro, Physiotherapy Evidence Database scale. SIBT, Sensory Integration Balance Therapy; SVR, Specific Virtual Reality; TT, Treadmill Training; VR, Virtual Reality intervention; WE, Walking Exercise; YSD, Years Since Diagnostic.

*Intervention : intervention (VR ± other(s)) vs control group (CT, BE, BT, TT, WE, NI, NDT, FES, PT, SIBT), Weeks × Sessions per week × Minutes (if additional other treatment was given) = Total amount of intervention in hours; n = number of patients in the VR group / Total number of patients after treatment; Age : mean age of the patients (SD or range); Mean H&Y: mean or median stage on the Hoehn & Yahr scale (SD or range); Type of VR: short description of the VR set up used; PEDRo : score of the study on the PEDro scale.

†Studied included in the quantitative analysis.

Table 4.2. Aim, ICF-WHO outcomes, main finding, and fulfiled neurorehabilitation principles in included studies.

		ICF-WHO category						
Author	Aim	BF	AC	PP	Other Scales	Follo w-up	Main Finding	Principles
SVR studies								
Carpinella et al. 2017[183]	Feasibility and effects of VR vs CT on balance and gait	Stabilome-tric assessment	BBS 10MWT UPDRS-III TUG ABC FOGQ	PDQ39		1 month	BBS significantly improved in VR compared to CT after treatment	-Variable Practice -Increasing Difficulty -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Social Interaction
Feng et al. 2019[209]†	Effects of VR vs CT on gait and balance		BBS TUG UPDRS-III FGA			No	Improvement in all outcomes for both groups and significantly higher in the VR group	-Spaced Practice -Task-Specific Practice -Variable Practice -Goal-Oriented Practice

(Continued)

Lau et al. 2022[185]†	Feasibility and effects of treadmill VR on gait	6MWT TUG TUG-Cognitive		SDMT MoCA TVF-F TVF-V TVF-A	No	Feasible, no significant difference between groups except for TUG Cognitive	-Massed Practice -Spaces Practice -Task-Specific Practice -Increasing Difficulty -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Modulate Effector Selection -Goal-Oriented Practice -Rhythmic Cueing
Pazzaglia et al. 2019[210]†	Efficacy of VR vs CT on balance, gait and quality of life	BBS DGI	SF-36	DASH	No	BBS, DGI and SF-36 significantly improved with VR	-Massed Practice -Spaced Practice -Variable Practice -Multisensory Stimulation -Explicit Feedback -Goal-Oriented Practice -Social Interaction

(Continued)

Shih et al. 2016[211]†	Therapeutic application test of VR vs BT on balance	LOS OLS	BBS TUG			No	LOS (directional control) significantly improved in VR compared to CT after treatment	-Massed Practice -Spaced Practice -Task-Specific Practice -Variable Practice -Increasing Difficulty -Explicit Feedback -Implicit Feedback -Rhythmic Cueing
Song et al. 2018[189]†	Efficacy of VR on stepping performance and gait.	Muscle Power, Hand reaction time	FGA CSRT TUG GAT NFOGQ	FES-I	MoCA TMT A&B N° of falls	No	No significant difference or improvement in FGA or CSRT after treatment	-Increasing Difficulty -Explicit Feedback -Goal-Oriented Practice -Rhythmic Cueing

(Continued)

van den Heuvel et al. 2014[188]	Feasibility of VR and effects of VR vs CT on balance	H&Y HAS	FRT BBS OLS 10MWT	PDQ39 FES-I	UPDRS MFI	6 weeks	No significant difference or improvement in any outcomes after treatment	-Massed Practice -Spaced Practice -Task-Specific Practice -Variable Practice -Increasing Difficulty -Explicit Feedback -Implicit Feedback -Action Observation -Goal-Oriented Practice -Social Interaction
Yang et al. 2016[212]†	Efficacy of VR vs CT on balance		BBS DGI TUG UPDRSIII	PDQ39		2 weeks	Improvement in all outcomes in both groups	-Spaced Practice -Task-Specific Practice -Variable Practice -Increasing Difficulty -Explicit Feedback -Goal-Oriented Practice -Social Interaction

(Continued)

Yen et al. 2011[184]	Effects of VR vs BT on sensory integration		SOT		VRT	4 weeks	Improvement in SOT in VR and BT after treatment	-Task-Specific Practice -Variable Practice -Increasing Difficulty -Goal-Oriented Practice -Social Interaction
Yuan et al. 2020[186]	Efficacy of VR on balance	MSL MDRT	BBS	SF-36	MFES	No	BBS and MFES significantly improved with VR	-Variable Practice -Increasing Difficulty -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Social Interaction

(Continued)

NSVR studies								
Alagumoorthi et al. 2022 †	Efficacy of VR vs BT on the number of fallers		BBS TUG	PDQ39	N° of falls, Fall history	24 weeks	Significantly less falls after VR treatment and at follow up	-Massed Practice -Variable Practice -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Social Interaction
Anwar et al. 2021	Efficacy of VR vs CT on balance		BBS TUG			No	BBS significantly improved in VR compared to CT	-Variable Practice -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Social Interaction
de Melo et al. 2018[213]†	Efficacy of VR vs TT vs CT on walking distance and physical fitness	Gait symmetry index, gait speed, SpO2, Heart rate, Blood pressure, Borg scale	6MWT			30 days	Improvement of 6MWT in VR and TT after treatment	-Increasing Difficulty -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice

(Continued)

Ferraz et al. 2018[214]†	Efficacy of VR vs BE vs CT on gait capacity	Body Mass Index, Abdominal circumference	6MWT 10MWT SRT	WHODAS -2.0 PDQ39 EQ-5D		No	Improvement of 6MWT, SRT and WHODAS 2.0 in all groups after treatment	-Spaced Practice -Variable Practice -Increasing Difficulty -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Social Interaction
Gandolfi et al. 2017[215]†	Efficacy of VR vs SIBT on postural stability		BBS ABC 10MWT DGI	PDQ8	N° of falls, Satisfa-ction question-naire, Costs of rehabili-tation	1 month	BBS significantly improved in VR compared to SIBT	-Variable Practice -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Rhythmic Cueing -Social Interaction

(Continued)

Kashif et al. 2022[190]†	Effects of VR+MI+PT vs PT+WE+BE on balance, motor function and activities of daily living	UPDRSII UPDRSIII BBS ABC	4 weeks	Clinically significant improvement in all outcomes in VR vs PT after treatment and at follow-up	-Massed Practice -Variable Practice -Increasing Difficulty -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Motor Imagery -Social Interaction
Kashif et al. 2022[191]†	Effects of VR+MI+PT vs PT+WE+BE on UPDRSIII	UPDRSIII	4 weeks	Significant improvement in certain domains of UPDRSIII	-Massed Practice -Variable Practice -Increasing Difficulty -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Motor Imagery -Social Interaction

(Continued)

Lee et al. 2015[216]†	Efficacy of VR+NDT+ FES vs NDT+FES on balance, activities of daily living, depression		BBS MBI		BDI	No	Improvement in all outcomes in VR after treatment	-Dosage -Multisensory Stimulation -Explicit Feedback -Action Observation -Goal-Oriented Practice -Rhythmic Cueing
Liao et al. 2015[193]†	Effects of VR+TT vs CT+TT vs NI on obstacle crossing and balance	Gait speed, Stride length, Toe obstacle clearance	LOS SOT TUG	PDQ39 FES-I		30 days	No significant difference in obstacle crossing between VR and CT	-Variable Practice -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice
Liao et al. 2015[192]†	Effects of VR+TT vs CT+TT vs NI on strength, gait and sensory integration	Gait speed, Stride length, Muscles strength	FGA SOT			30 days	Improvement in all outcomes in VR and CT	-Variable Practice -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice

(Continued)

Pedreira et al. 2013[182]	Effects of VR vs CT on quality of life		PDQ39	No	Significant improvement in VR vs CT after treatment	-Spaced Practice -Variable Practice -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice
Pompeu et al. 2012[195]†	Efficacy of VR vs BT on UPDRSII	UPDRSII BBS		60 days	Improvement in UPDRSII in both groups after treatment	-Variable Practice -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Rhythmic Cueing -Social Interaction
Ribas et al. 2017[217]†	Efficacy of VR vs CT on functional balance, fatigue, functional exercise capacity and quality of life	BBS 6MWT	FSS PDQ39	60 days	Improvement in balance and fatigue in VR after treatment	-Variable Practice -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Rhythmic Cueing

(Continued)

Santos et al. 2019[218]†	Efficacy of VR+CT vs VR vs CT on balance, gait, functional mobility and quality of life	BBS DGI TUG	PDQ39		No	Improvement in all outcomes in all groups after treatment	-Spaced Practice -Variable Practice -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Social Interaction
Tollár et al. 2018[187]	Effects of VR vs BE vs NI on mobility	UPDRSII SE-ADL TAT BESTest BBS DGI 6MWT Postural stability	EQ-5D PDQ39	BDI	No	Improvement in UPDRSII in VR and BE after treatment	-Spaced Practice -Dosage -Variable Practice -Multisensory Stimulation -Explicit Feedback -Implicit Feedback -Goal-Oriented Practice -Rhythmic Cueing -Social Interaction

Abbreviations: 6MWT, 6 Minutes Walking Test; 10MWT, 10 Meters Walk Test; ABC, Activities-Specific Confidence scale; AC, Activity; BBS, Berg Balance Scale; BDI, Beck Depression Inventory; BE, Bicycle Exercise; BF, Body Function. BT, Balance Training; CSRT, Choice Stepping Reaction Time test; CT, Conventional Therapy; DASH, Disabilities of the Arm, Shoulder and Hand; DGI, Dynamic Gait Index; EQ-5D, Euro-Quality of Life 5 Dimensions questionnaire; FES-I, Fall Efficacy Scale-International Questionnaire; FES, Functional Electrical Stimulation; FGA, Functional Gait Assessment; FOGQ, Freezing Of Gait Questionnaire; FRT, Functional Reach Test; FSS, Fatigue Severity Scale; GAT, Gait Adaptability Test; H&Y, Hoehn & Yahr scale; ICF-WHO, International Classification of Functioning – World Health Organization. LOS, Limit of Stability test; MBI, Modified Barthel Index; MDRT, MultiDirectional Reach Test; MFES, Modified Falls Efficacy Scale; MFI, Multidimensional Fatigue Inventory; MoCA, Montreal Cognitive Assessment; MSL, Maximum Step Length; NDT, Neurodevelopmental Treatment; NFOGQ, New Freezing of Gait Questionnaire; NI, No intervention; NSVR, Non-Specific Virtual Reality; OLS, One-Leg Stance test; PDQ39, Parkinson's Disease Questionnaire 39; PDQ8, Parkinson's Disease Questionnaire 8; PP, Participation; SDMT, Symbol Digit Modalities Test; SE-ADL, Schwab and England Activities of Daily Living scale; SF-36, Medical Outcomes Study Short Form 36; SIBT, Sensory Integration Balance Therapy; SOT, Sensory Organization Test; SRT, Sitting-Rising Test; SVR, Specific Virtual Reality; TAT, Tinetti Assessment Tool; TMT, Trail Making Test; TT, Treadmill Training; TUG, Timed Up and Go; TVF-F/TVF-V/TVF-A, Tests of Verbal Fluency Fruits, Vegetables, and Animals; UPDRS(II/III), Unified Parkinson's Disease Rating Scale (part II/III); VR, Virtual Reality; VRT, Verbal Reaction Time; WE, Walking Exercise; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0.

†Studied included in the quantitative analysis

Table 4.3. GRADE approach regarding the outcomes.

Outcome	Study design	N	Global Risk of Bias	Inconsistency	Indirectness	Imprecision	n	Certainty of Evidence
Balance	RCT	13	Serious[a]	Serious[b]	Not serious	Not Serious	567	Low
Functional mobility	RCT	10	Not serious	Not serious	Not serious	Serious[c]	531	Moderate
Quality of life	RCT	8	Serious[a]	Not serious	Not serious	Serious[c]	453	Low

RCT= Randomized Controlled Trial ; N= number of studies included in the statistical analysis ; n= number of observations ; [a]= The overall risk of bias of some studies included in this analysis was found to be unclear ; [b]= Heterogeneity may be important ($I^2 > 30\%$) ; [c]= low to moderate magnitude of effect (SMD < 0.5).

Chapter 4

Vision: Optic flow manipulation

Immersive Virtual Reality to Restore Natural Long-Range Autocorrelations in Parkinson's Disease Patients' Gait During Treadmill Walking

Chapter 4

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Immersive Virtual Reality to Restore Natural Long-Range Autocorrelations in Parkinson's Disease Patients' Gait During Treadmill Walking

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Abstract

Effects of treadmill walking on Parkinson's disease (PD) patients' spatiotemporal gait parameters and stride duration variability, in terms of magnitude [coefficient of variation (CV)] and temporal organization [long range autocorrelations (LRA)], are known. Conversely, effects on PD gait of adding an optic flow during treadmill walking using a virtual reality headset, to get closer to an ecological walk, is unknown. This pilot study aimed to compare PD gait during three conditions: Overground Walking (OW), Treadmill Walking (TW), and immersive Virtual Reality on Treadmill Walking (iVRTW). Ten PD patients completed the three conditions at a comfortable speed. iVRTW consisted in walking at the same speed as TW while wearing a virtual reality headset reproducing an optic flow. Gait parameters assessed were: speed, step length, cadence, magnitude (CV) and temporal organization (evenly spaced averaged Detrended Fluctuation Analysis, α exponent) of stride duration variability. Motion sickness was assessed after TW and iVRTW using the Simulator Sickness Questionnaire (SSQ). Step length was greater (p = 0.008) and cadence lower (p = 0.009) during iVRTW compared to TW while CV was similar (p = 0.177). α exponent was similar during OW (0.77 ± 0.07) and iVRTW (0.76 ± 0.09) (p = 0.553). During TW, α exponent (0.85 ± 0.07) was higher than during OW (p = 0.039) and iVRTW (p = 0.016). SSQ was similar between TW and iVRTW (p = 0.809). iVRTW is tolerable, could optimize TW effects on spatiotemporal parameters while not increasing CV in PD. Furthermore, iVRTW could help to capture the natural LRA of PD gait in laboratory settings and could potentially be a challenging second step in PD gait rehabilitation.

Keywords: Parkinson's disease, gait disorders, gait assessment, virtual reality, gait variability, fractals, long range autocorrelations, treadmill walking

Introduction

Parkinson's disease (PD) results from dopamine-producing neurons degeneration in the basal ganglia and is clinically characterized by classical motor triad combining rest tremor, plastic rigidity, and bradykinesia.[116] Postural instability and gait disorders including reduced gait speed and step length, increased cadence and altered stride duration variability in terms of magnitude [increased coefficient of variation (CV)] and temporal organization constitute hallmarks of PD gait.[35,118] Regarding temporal organization of gait, stride duration is known to fluctuate in a complex structured manner over many consecutive strides and this can be quantified with non-linear analysis such as long-range autocorrelations (LRA) computation.[24] Indeed, stride duration variability presents with a fractal pattern[30,119] that is somehow a sign of a long- term memory in the locomotor system[27] and would be representative of adaptative abilities of healthy systems.[29,31,119] On the contrary, a breakdown in LRA would be the signature of a pathological state.[28,29,31] Such a breakdown is present in PD[35,46] with diminished fractal scaling exponent α that would be linked to the degeneration of the basal ganglia[27,29,40,41] which are an important part of the central nervous system notably involved in the regulation of posture and gait.[144] Interestingly, strong correlations between breakdown of LRA and balance impairments but also with disease progression were recently highlighted in PD patients.[35,46,118] The more the disease progresses, the greater the neurodegeneration, the lower the α exponent and the greater the risk of falls and their consequences. Therefore, LRA computation was proposed as an objective and quantitative biomarker of postural instability as well as disease progression that highly condition the higher fall risk inherently associated to PD.[35,37]

Given the impact of these gait disorders on the risk of falling, researchers and clinicians are looking for innovative ways to assess and rehabilitate PD patients' gait. Among others, treadmill walking is one of the most widely used tools to both assess and treat gait disorders in this population. Indeed, treadmill walking improves spatiotemporal gait parameters on the long term[206] and is known to modify LRA in PD gait.[56,74] In addition, this allows patients to walk long distances in a safe manner. However, treadmill walking lacks ecological visual inputs encountered when walking overground in daily-life situations. Indeed, combined with vestibular and proprioceptive information, visual inputs encountered during an ecological walk such as an optic flow (movement of the environment perceived while walking) are of essential importance to control gait. Previous studies stressed the unique importance of vision and especially optic flow during healthy subjects' gait compared to the other sensory inputs concerning positional information[110,219] and correct adjustments of gait parameters during locomotion.[109] Likewise, visual disturbances lead to a higher variability of spatiotemporal parameters which may supposedly increase the risk of falling.[110] If visual inputs are important for healthy subjects, it seems to be even more so for PD patients during walking[90] and obstacle crossing.[92] This observation leads to think that it would be possible to further improve treadmill training by adding an optic flow. The most appropriate way to create a realistic optic flow during treadmill walking is to use high-end technologies such as immersive virtual reality (iVR) headsets.

In previous studies, 2D displays and projection systems were used to study the impact of optic flow during treadmill walking on healthy subjects' gait[106–111] and PD gait.[86,112] Although these devices are still used in recent studies,

some of their technical characteristics do not make it possible to realistically produce an optic flow. Among others, these are: narrow vertical and horizontal field of view, no stereoscopic 3D rendering that gives the necessary depth of field essential to the optical flow, low rendering framerate limiting image fluidity, low immersion and feeling of presence in the virtual environment limiting the forgetting of the laboratory context in which the patient is located.[161] On the contrary, iVR headsets make it possible to reproduce this ecological visual information better than these older devices and seem to solve almost all their technical limitations.

Although only one previous study[207] showed both feasibility and tolerability of the iVR on treadmill in PD, no study has evaluated the impact on PD patients' spatiotemporal gait parameters of an optic flow reproduced in an iVR headset during treadmill walking. Furthermore, no study has to date investigated the impact of this combination on gait variability measures (CV and LRA computation) of these patients, even with older devices. Thus, this pilot study aims to compare PD gait during three conditions: on overground and on a treadmill with and without iVR. Considering visual dependence of PD gait, the lack of optic flow on TW and recent technological advances, we put forward the hypothesis that the addition of an optic flow in iVR during treadmill walking will allow to more ecologically and accurately capture PD patients' natural LRA in stride duration variability, similar to overground walking.

Methods

This pilot study had approval from the local ethics committee (B403201837458/Clinicaltrial.gov registration: NCT04019158). Participants gave written informed consent in accordance with the Declaration of Helsinki prior to data collection. Testing took place in Cliniques universitaires Saint-Luc (Brussels, Belgium).

Participants

Ten PD patients were recruited for this pilot study according to the following inclusion criteria: idiopathic PD according to the UK Brain Bank Criteria[128], modified Hoehn & Yahr scale[129] ≤ 3, Mini-Mental State Examination[130] > 24/30, no other pathology interacting with gait or causing dizziness, no uncorrected visual deficiency and ability to walk 512 consecutive strides (± 10– 15 min)[**]. Patients were also evaluated using the Movement Disorders Society – Unified Parkinson's Disease Rating Scale[133], the Mini Balance Evaluation Systems Test[220] and the Activities specific Balance Confidence scale.[131]

Clinical characteristics and anthropometrics of the 10 PD patients are displayed in Table 5.1.

[**]Absence of freezing of gait was asked by phone at the inclusion, asked via item 2.13 of the part II of MDS-UPDRS and checked clinically with item 3.11 of the part III of MDS-UPDRS.

Table 5.1. Characteristics of the PD patients

Women/men ratio	4/6
Age (y)	63.7 (±10.6)
Modified H&Y scale (0-5)	1.75 [1-2]
MMSE (/30)	27.5 (±1.8)
MDS-UPDRS total (/260)	44.7 (±16.8)
MDS-UPDRS part III (/132)	24.9 (±15)
Mini-BESTest (/28)	23.6 (±1.9)
ABC-scale (%)	82.3 (±14.6)

Mean (±SD) ; Median [interquartile range].

ABC-scale, Activities specific Balance Confidence scale; H&Y, Hoehn & Yahr; MDS-UPDRS, Movement Disorder Society – Unified Parkinson's Disease Rating Scale; Mini-BESTest, Mini Balance Evaluation Systems Test; MMSE, Mini Mental State Examination.

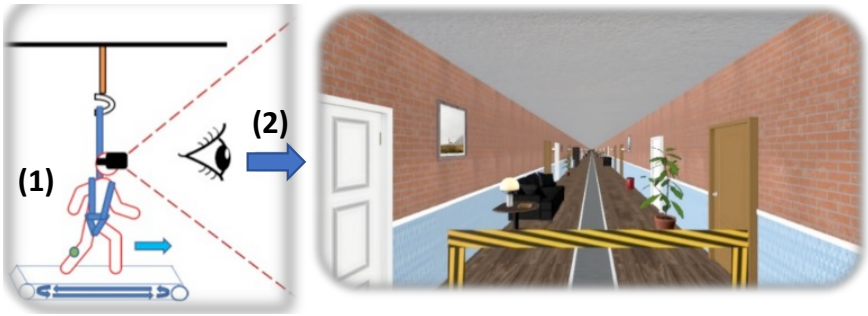
Procedure

Participants were asked to walk in a randomized order in three conditions: Overground Walking (OW), Treadmill Walking (TW), and immersive Virtual Reality on Treadmill Walking (iVRTW). Each condition lasted 10–15 min in order to get a minimum of 512 strides necessary to determine the presence of LRA during gait with a high level of evidence.[80,81] During OW, patients walked on a 63.2 m rectangular track with smooth rounded corners at their comfortable speed. Prior to data collection, all patients performed one lap to get used to the terrain. In addition, patients were instructed to walk right in the middle of the track. During TW, patients walked on a treadmill at their comfortable speed assessed before with a 10 m walking test, were secured by a non-weight bearing harness and had no handrails that could have been grabbed so as not to interfere with the swinging of the arms. During iVRTW, patients walked on the treadmill at the same speed as during TW, wearing the harness, still without handrails, while wearing an iVR headset. Through the iVR headset (HTC, Vive, Taiwan), patients were immersed in a homemade environment created with Unity software (USA) and written in C# (Visual Studio, Microsoft, United States). The iVR headset weighed 470 grams and provided patients with a horizontal field of view of 110 degrees, a resolution of 1080 × 1200 pixels per eye and a refresh rate of 90 Hz. Also, this system allows to create depth of field by rendering stereoscopic 3D. To provide a complete visual immersion, the headset was designed to occlude peripheral vision in all directions. In this way, patients could not see the real environment around them and therefore only saw the virtual environment. The virtual environment consisted in a straight realistic endless hallway with some unevenly placed furniture on the sides in order to look real but to still avoid a rhythmic visual cueing to isolate optic flow effect. The goal was therefore to

have a realistic ecological environment with fewer potentially distracting elements than an outside environment. Choosing a closed and restricted environment also saves computing power to ensure a fluid image without loss of framerate that could have given a jerky image. While walking on the treadmill, patients perceived an optic flow within the virtual environment moving at the same speed as the treadmill and creating the illusion of walking in an actual hallway (see Supplementary material 5.1).

During each condition, two Inertial Measurement Units (IMeasureU Research, VICON, United Kingdom) were taped on patients' lateral malleoli to record ankle accelerations at a sample of 500 Hz in antero-posterior direction. During OW, the recording was started after the warm-up lap. Regarding TW and iVRTW, recordings took place after a 3-min session of habituation to each condition and were initiated while patients walked on the treadmill while performing each condition. Data was then transferred onto a computer and stride durations were determined using a peak detection method.[135,152]

(A)



(B)

(C)

(D)

(E)

Supplementary material 5.1. *iVRTW setting and safety rules.* ***(A)*** *Patient walking on the treadmill wearing a non-weight bearing security harness (Volt, Petzl, France) attached to the ceiling and an immersive virtual reality (iVR) headset (Vive, HTC, Taïwan) (1). The patient sees a long hallway moving forward at the same speed as the speed of the treadmill (2).* ***(B)*** *What the patient sees if the security rules are followed. To walk in the middle of the treadmill, the patient must walk on the grey carpet between the two white lines on the floor representing the left and right limits of the treadmill.* ***(C)*** *If the patient is walking too much on one side (on the left in the example), the line corresponding to this side turns red. The line turns back to white if the patient recenters himself in the middle. The yellow and black lined fence always represents the front end of the treadmill and is moving forward as fast as the optic flow.* ***(D)*** *If the patient is walking too fast on the treadmill and is too close to the fence, a blue panel with a "-" sign appears and a voice urges the patient to walk slower.* ***(E)*** *If the patient is walking too slowly and is too far from the fence, a red panel with a "+" sign appears and a voice urges the patient to walk faster. The panels disappear if the patient walks back to the right speed. The width between the white lines and the width of the grey carpet, the height of the fence and the distance between the front and the back limits can be modulated according to any treadmill dimensions using an option interface. The speed of the optic flow and the fence can also be changed using this option interface.*

Gait was assessed in terms of spatiotemporal gait parameters and variability in terms of magnitude and temporal organization.

Spatiotemporal gait parameters were assessed as follow:

$$Gait\ speed\ (m.s^{-1}) =$$

$$-\ During\ OW: \frac{Total\ walking\ distance\ (m)}{Total\ acquisition\ time\ (s)};$$

$$-\ During\ TW\ and\ iVRTW: Preset\ speed\ of\ the\ treadmill\ (m.s^{-1});$$

$$Cadence\ (\#steps.min^{-1}) = \frac{Total\ number\ of\ steps\ (\#)}{Total\ acquisition\ time\ (min)};$$

$$Step\ length\ (m) = \frac{Gait\ speed\ (\mathrm{m.s^{-1}})}{Cadence\ (Hz)};$$

$$Mean\ stride\ duration\ (s) = \frac{Total\ acquisition\ time\ (s)}{Total\ number\ of\ strides\ (\#)}.$$

To assess magnitude of stride duration variability, CV was calculated using the mean stride duration and SD: $CV\ (\%) = \left[\frac{SD}{mean}\right].100$.

Temporal organization of stride duration variability was assessed by LRA computation using the evenly spaced averaged version of the detrended fluctuation analysis (DFA)[155] to obtain α exponent. This method was chosen given its robustness regarding stationary and non- stationary processes.[28,137] LRA are present when α exponent values are between 0.5 and 1 meaning that large stride duration fluctuations tend to be followed by other large fluctuations, and vice- versa. An α exponent of 0.5 indicates the absence of LRA and a fully random organization (i.e., white noise). Also, α exponent values below 0.5 is the signature of anti-persistence. Finally, an α exponent of 1 (i.e., 1/f noise) is the boundary between stationarity and non-stationarity.[32] Peng et al. (1995) interpreted 1/f noise as "a "compromise"

between the complete unpredictability of white noise (α = 0.5) (very rough "landscape") and the very smooth "landscape" of Brownian noise (α = 1.5)".[33] Then, 1/f noise is interpreted in the context of the theoretical framework of optimal movement variability[28,34,119] as the optimal state of variability characterizing healthy gait.

When using iVR, some studies reported the occurrence of what is known as "motion sickness." This phenomenon is defined as the occurrence of adverse symptoms when using iVR headsets such as dizziness, nausea, headaches, and others.[221] Indeed, in some cases iVR can induce a mismatch between visual, proprioceptive, and vestibular inputs creating a sensory conflict.[222] As such, patients of this study completed the Simulator Sickness Questionnaire (SSQ) after TW and iVRTW conditions to assess the presence of motion sickness based on a cut-off score of 15 out of 235.6 on the total score.[223] Three sub-scores (i.e., Nausea, Oculomotor, and Disorientation) were also assessed.[223]

Statistical Analysis

A power analysis was computed using the data of Warlop et al. (2018).[56] Authors compared PD patients' temporal organization of stride duration variability using α exponent calculated with the DFA during two conditions: overground walking and treadmill walking. The power analysis was made using PASS software, in the idea of performing a one-way repeated measures ANOVA. Total sample of 10 participants achieved 80% power to detect differences among the means versus the alternative of equal means using an *F*-test with a 0.05 significance level. The size of the variation in the means

was represented by their standard deviation which is 0.08. The common standard deviation within a condition was assumed to be 0.2.

Sigmaplot 13.0 software (Systat, Richmond, CA, United States) was used to analyze data. Normal distribution of the data was verified for all variables using the Shapiro–Wilk normality test. A paired *t*-test showed a difference between gait speed during OW and TW/iVRTW ($p = 0.003$). Given that gait speed influences spatiotemporal parameters and CV[35,56,224], OW could not be compared with TW and iVRTW. Since gait speed is not expected to modify the LRA[224], a one way repeated measures ANOVA comparing the three conditions was performed only for the results of the evenly spaced averaged DFA and a Holm–Sidak *post hoc* test was performed. Regarding SSQ and the other gait outcomes, paired *t*-tests were performed to compare TW and iVRTW only. Cohen's *d* was used to express the effect size between conditions for all outcomes if a significant difference was found.

Results

First, the added optic flow during iVRTW induced a positive effect on the spatiotemporal gait parameters with higher step length and reduced cadence compared to TW. Indeed, step length was higher (Cohen's d = 0.392, p = 0.008) and cadence lower (Cohen's d = 0.712, p = 0.009) during iVRTW than during TW for the same walking speed (Table 5.2 and Figure 5.1).

Regarding magnitude of stride duration variability, the CV was similar between TW and iVRTW (p = 0.177) which shows that the added optic flow had no significant effect on this parameter (Table 5.2 and Figure 5.1).

As expected, patients presented with a similar temporal organization of stride duration variability during OW and iVRTW. Conversely, α exponents were higher during TW. Indeed, even though all patients presented LRA during all conditions, α exponent was different between the three conditions [F(2,9): 5.633; p = 0.013]. While no difference was found between OW and iVRTW (p = 0.553), the α exponent during TW was higher than during OW (p = 0.039) and higher than during iVRTW (p = 0.016). The effect size was large for both comparisons: Cohen's d = 1.030 when comparing TW to OW and 1.141 when comparing TW to iVRTW (Table 5.2 and Figure 5.1).

Regarding motion sickness, the SSQ total score as well as sub-scores were low and similar between TW and iVRTW (Table 5.3). Interestingly, 7/10 patients did not reach the cut- off score after TW and 5/10 after iVRTW while surprisingly no patient complained orally of motion sickness symptoms or discomfort linked to the headset during and after these two conditions. Note that two patients reached the cut-off score both after TW and after iVRTW,

one patient who reached the cut-off after TW but not after iVRTW and three patients did not reach the cut-off after TW but did after iVRTW.

Table 5.2. Absolute mean values of the spatiotemporal gait parameters and stride duration variability assessed during Overground Walking (OW), Treadmill Walking (TW) and immersive Virtual Reality on Treadmill Walking (iVRTW) conditions and comparison between TW and iVRTW conditions.

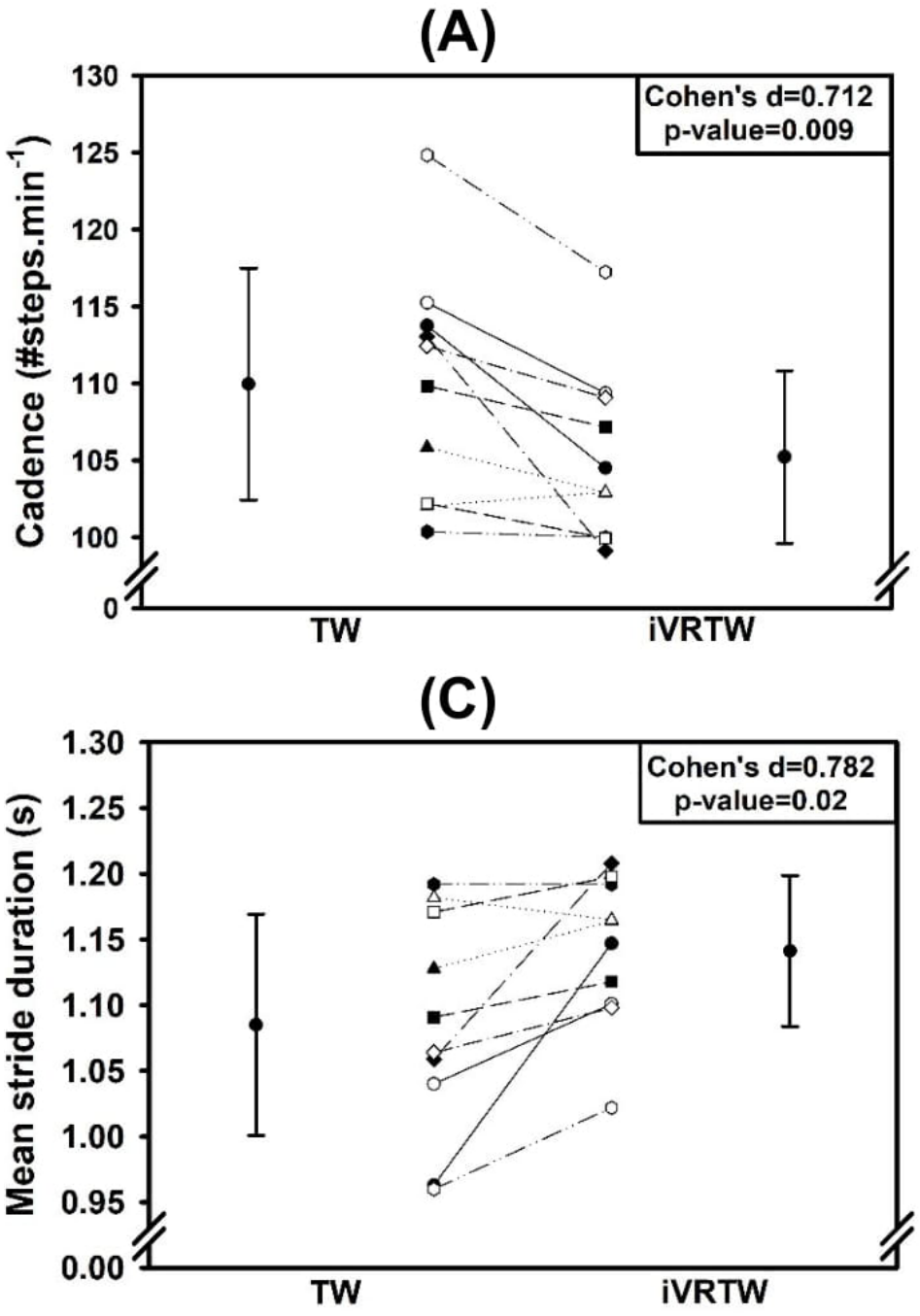
	OW	**TW**	**iVRTW**	**p-value**
Speed ($m.s^{-1}$)	1.31 (±0.10)	1.14 (±0.13)	1.14 (±0.13)	1.000
Cadence ($\#steps.min^{-1}$)	110.3 (±6.4)	109.9 (±7.5)	105.2 (±5.6)	**0.009**
Step length (m)	0.71 (±0.05)	0.62 (±0.07)	0.65 (±0.06)	**0.008**
Mean stride duration (s)	1.09 (±0.06	1.08 (±0.08)	1.14 (±0.06)	**0.020**
Coefficient of Variation (%)	1.95 (±0.53)	2.98 (±1.34)	2.46 (±0.72)	0.177
α exponent	0.77 (±0.07)	0.85 (±0.07)	0.76 (±0.09)	**0.016**

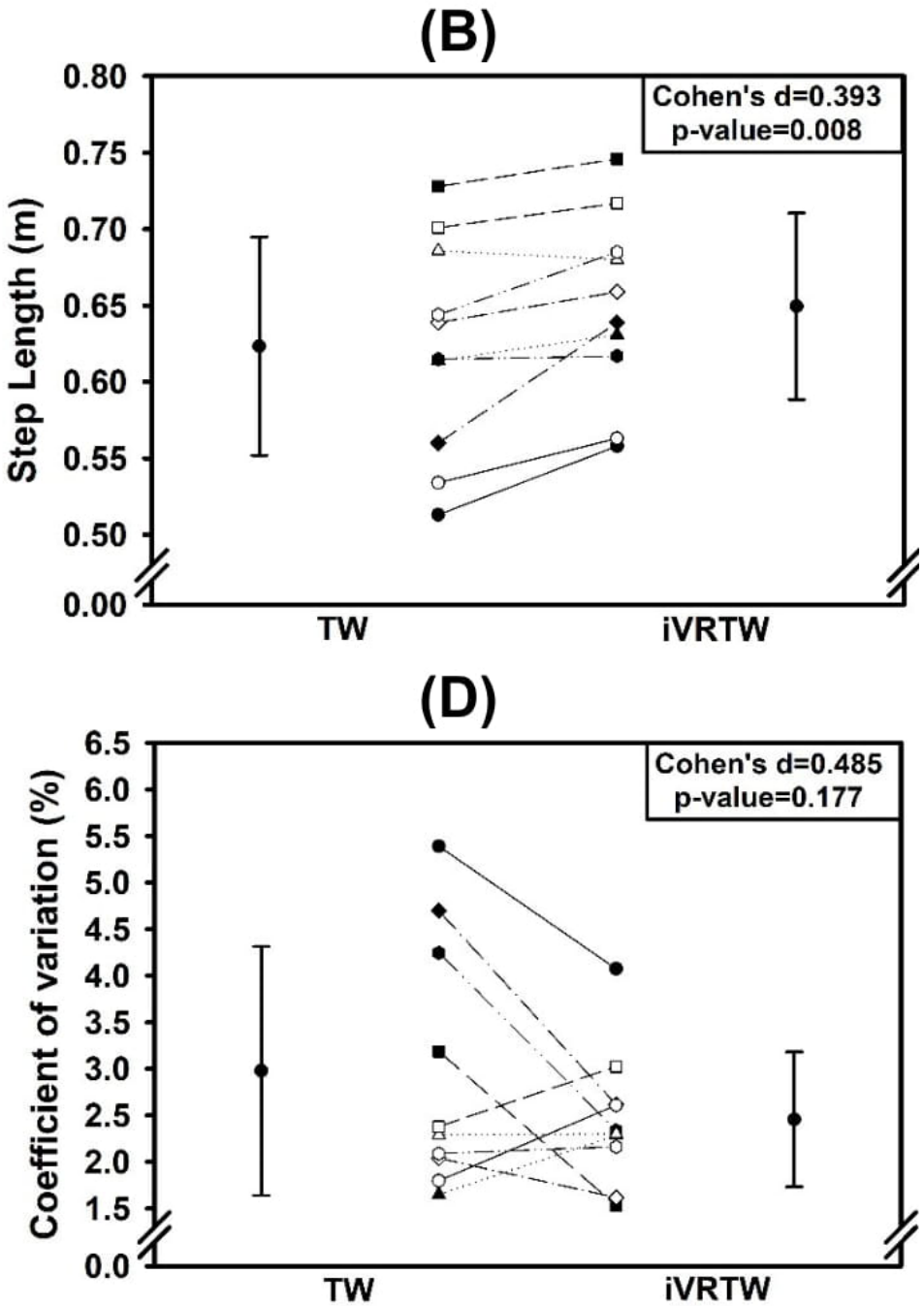
Absolute value is expressed as mean (±SD). Bold data indicates if the comparison between TW and iVRTW (paired t-test) was significant ($p < 0.05$).

Table 5.3. Absolute mean values of the Simulator Sickness Questionnaire (SSQ) total and sub scores for the comparison between Treadmill Walking (TW) and immersive Virtual Reality on Treadmill Walking (iVRTW) conditions.

	TW	**iVRTW**	**p-value**
SSQ Total (/235.6)	15.0 (±19.7)	16.8 (±14.8)	0.809
SSQ Nausea (/200.3)	11.5 (±12.6)	17.2 (±11.7)	0.370
SSQ Oculomotor (/159.2)	12.1 (±15.7)	15.9 (±17.7)	0.563
SSQ Disorientation (/292.3)	16.7 (±29.2)	8.4 (±9.7)	0.379

Absolute value is expressed as mean (±SD)


(A)
Cohen's d=0.712
p-value=0.009
Cadence (#steps.min-1)
130
125
120
115
110
105
100
0
TW
iVRTW
(C)
Cohen's d=0.782
p-value=0.02
Mean stride duration (s)
1.30
1.25
1.20
1.15
1.10
1.05
1.00
0.95
0.00
TW
iVRTW


(B)
Step Length (m)
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.00
Cohen's d=0.393
p-value=0.008
TW
iVRTW
(D)
Coefficient of variation (%)
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
0.0
Cohen's d=0.485
p-value=0.177
TW
iVRTW

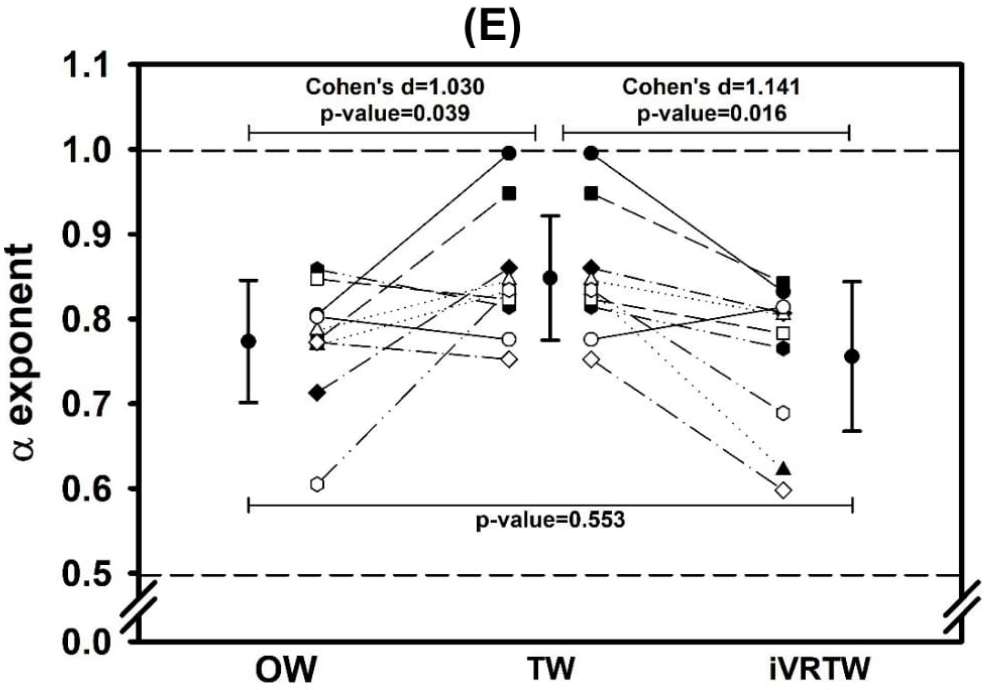


Figure 5.1. *Graphs showing mean (±1SD) and individual gait parameters values assessed during Overground Walking (OW, only graph (E)), Treadmill Walking (TW) and immersive Virtual Reality on Treadmill Walking (iVRTW) conditions.* ***(A)*** *Cadence graph.* ***(B)*** *Step length graph.* ***(C)*** *Mean stride duration graph.* ***(D)*** *Coefficient of variation graph.* ***(E)*** *α exponent graph (dashed lines corresponding to the limits between which there are LRA).*

Discussion

Purposes of this pilot study were to assess the effects of adding an optic flow displayed through an iVR headset during treadmill walking on gait and verify its feasibility and tolerability in PD population. The added optic flow during iVRTW improved step length and reduced gait cadence in comparison to TW at the same gait speed. Regarding magnitude of stride duration variability, CV was similar between iVRTW and TW. On the contrary, optic flow affected temporal organization of stride duration variability. Indeed, LRA were similar when the optic flow was present (during OW and iVRTW) but different when it was absent (during TW). Finally, this study confirmed that iVRTW is feasible and tolerable in PD.

Spatiotemporal gait parameters were influenced by iVRTW. Reduced step length is a well-known PD gait feature[225], one of the components of cautions gait associated with fear of falling[226] and TW is known to be an effective rehabilitative approach to improve it.[206] However, it is also known that frail[226,227] and PD[56] patients adopt a more precautious gait on the treadmill with decreased step length and increased cadence to maintain speed. This may have been due to the newness and the lack of "naturalness" of the task perceived by the patients. With the same gait speed as TW, patients increased step length and reduced cadence during iVRTW perhaps indicating a less cautious and a more natural gait adopted during this condition. The optic flow added with the iVR headset could then be an additional way to improve the well-known effect of TW on spatiotemporal parameters potentially leading to less cautious gait.

As described in the introduction, magnitude of stride duration variability (i.e., CV) is increased in PD[118] and is associated with the presence of a postural reflex disorder.[46] Also, usually considered as a marker of attentional load allocated to the task, CV was not different between TW and iVRTW. On one hand, some authors[113] hypothesized that the absence of optic flow during TW would decrease the attentional load on PD patients. With fewer environmental factors to consider while walking, PD patients would then more easily focus on walking on the treadmill allowing to overcome damaged automaticity in PD gait.[228] If this hypothesis was accurate, CV would have been higher during iVRTW than during TW since iVRTW can be disturbing at first glance for patients (newness of the task, safety instructions to follow, potential anxiety of not seeing the real environment). On the other hand, recent studies showed that walking speed has the greatest influence on CV in both healthy and PD populations and, for the latter, for both OW and TW.[56,224] Since CV was similar between TW and iVRTW for the same gait speed, it could be concluded that the magnitude of stride duration variability does not seem to be influenced by the presumed attentional load induced by the added optic flow in iVR. Note that such results are also in line with a similar study conducted on young healthy subjects using older equipment.[108]

In contrast to the magnitude of stride duration variability, the temporal organization of gait variability was significantly modulated by the addition of optic flow during iVRTW. Such results brought two lines of thought. On one hand, this study confirmed that TW would improve the temporal organization of gait variability among PD.[56,74] On the other hand, by adding an optic flow, iVRTW would be a controlled and safe alternative to assess and maybe rehabilitate PD patients' gait in a more ecological way.

All patients exhibited α exponents between 0.5 and 1 in all conditions, indicating the presence of LRA in the temporal organization of stride duration variability. Interestingly, α exponent during TW was closer to 1, approaching 1/f noise considered as an optimal state of variability[28,33,34] and indicating strong coordination among the multiple sub-systems that regulate locomotion.[20,31] Attempting to get closer to 1/f noise seems clinically significant given the results of previous studies. Indeed, Hausdorff (2007) stated that it was possible to discriminate between elderly fallers (α close to 0.5) and non-fallers (α close to 1) based on LRA computation and that this could even have a prognostic value on the risk of falling.[27] Similarly, a positive correlation was shown between low α exponent and poor balance test scores in PD patients.[35,46] So, getting closer to 1 seems to be an interesting goal in PD patients' gait rehabilitation. On the other hand, α exponent was lower and similar between OW and iVRTW. Optic flow could be an explanatory factor since PD patients can overreact to visual information for maintaining balance.[86,229] By increasing degrees of freedom, the added optic flow could thus increase the regulatory load on the locomotor system during iVRTW in a similar way to OW, decreasing α exponent compared to TW.[108] On the contrary, the absence of optic flow during TW reduces the amount of information to be managed by the patients, allowing them to focus on the motor task. In addition to previous studies[56,74], this study highlights that, by reducing the degrees of freedom on the PD deficient locomotor system, absence of optic flow combined with the constant rolling of the treadmill could provide a framework for PD patients to regulate the temporal organization of their gait. The treadmill would provide external cues to patients allowing to bypass defective internal pallidocortical projections responsible for rhythm control impairments in PD.[55,228] It is therefore

interesting to notice that during iVRTW, the rolling of the belt was kept as well as the constant speed imposed. Therefore, patients should somehow have kept this framework and this cueing effect, but these seemed to be lost by the addition of the optic flow. This may further underscore the fact that PD patients take into account and rely predominantly on visual information and optic flow to regulate their gait[90,92] compared to proprioceptive information, whose acuity is diminished in PD.[230,231] From a PD gait rehabilitation point of view, TW could be conceived as a first step and iVRTW could have the potential to be a second stage in a challenging, safe and ecological rehabilitation approach, perhaps allowing a smoother progression between what has been worked on during rehabilitation and everyday walking.

Likewise, a previous study questioned the adequate gait assessment of gait variability during TW in PD participants.[56] As the study of LRA has to be done over a long period of time, much research has relied on treadmill walking in laboratory setting to assess PD patients' temporal organization of gait in a controlled and safe manner. However, the results of the present study and of previous ones[56,74] highlight that the assessment of LRA on a treadmill does not adequately capture the natural temporal organization of gait in PD patients. Conversely, iVRTW could be an interesting way since α exponent during iVRTW was similar to that of OW.

Results regarding motion sickness are in line with those of the sole previous study conducted on PD population.[207] Indeed, five patients out of 10 reached the cut-off point at which motion sickness is considered significant after iVRTW. However, this cut-off was already reached by three patients after TW. The fact that motion sickness symptoms appeared even without iVR for some PD patients was expected because it is well-known that these patients

have impairments in sensory processing and integration.[232] These impairments coupled with medication[233] could then be explanatory factors. Likewise, no significant differences were found regarding the SSQ total score and sub-scores between the two conditions meaning that iVRTW did not induce more motion sickness than TW. The hypothesis behind this result is that the mismatch between the visual, proprioceptive and vestibular inputs perceived by the patients was minor during iVRTW. Given that motion sickness is induced by a sensory conflict[222], it could be concluded that the iVR method of displaying an optic flow during treadmill walking used in this study would be efficient enough to limit this conflict. Another explanatory factor could be the technological upgrade seen regarding iVR in the last 10 years: better image framerate, higher display resolution, higher field of view. Furthermore, this present study reinforces the results of the sole previous study[207] who had shown tolerability over 5 min sessions while the present results showed tolerability over a ± 15 min session.

Some limitations of the present study should be addressed. First, although significant results were found only 10 PD patients were included. This study should be considered as a pilot study and it could be used to make sample calculations for future studies on the subject. Second, included patients were clinically mildly affected by PD with a fairly low Hoehn & Yahr score. More transversal and longitudinal studies including more patients at different stages of the disease are then required to confirm our findings regarding spatiotemporal gait parameters and on magnitude and temporal organization of stride duration variability. Third, one of the safety instructions during iVRTW was to follow a virtual security fence in iVR ensuring the patients walked at the right speed on the treadmill. This may have caused a cueing

effect that may have had consequences on patients' gait. Fourth, this study only investigated the direct adaptation of patients during TW and iVRTW but did not investigate potential after-effects when walking overground directly after these two conditions. Future studies should therefore focus on the acute effects potentially present after these particular walking conditions. Fifth, despite the impressive technological advancement of iVR headsets, the 2 years old headset used in this study only proposes a horizontal field of view of 110 degrees. Although it is superior to the devices used in previous studies, it is still below the natural field of view of the human eye. This loss of peripheral vision could have a significant impact on the correct perception of the optic flow during iVRTW. Newer headsets already offer a significant improvement in display resolution and a larger field of view. It is then likely that iVR headsets with a natural field of view will be available in a few years' time. Finally, this study focused solely on a single method to analyze gait dynamics. Future studies similar to this one could add other methods to analyze gait dynamics (ARFIMA, Lyapunov exponent, entropy).[234,235]

In conclusion, this pilot study highlighted that iVRTW could enhance the effectiveness of TW in improving step length while not increasing magnitude of stride duration variability. Also, TW could be perceived as a first step in PD gait rehabilitation to regulate temporal organization of gait and iVRTW as a second one within a challenging, safe and ecological gait rehabilitative approach. In addition, iVRTW may be a more adequate way to safely assess LRA in PD gait over a long period of time than TW. Future transversal and longitudinal studies including more PD patients presenting with a broader spectrum of disease severity need to be conducted in order to confirm these findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Comité d'Ethique Hospitalo-Facultaire of Cliniques universitaires Saint-Luc. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AL handled the creation of the iVR environment and of the study protocol, managed patient recruitment, data collection and analysis, interpretation of the results, and wrote the manuscript. JL provided methodological inputs to the study, participated in the interpretation of the results, and revised the manuscript. CF and CS helped with patient recruitment, data collection, data analysis, and interpretation of the results. GS helped with patient recruitment, participated in the interpretation of the results, and revised the manuscript. TW participated in the interpretation of the results and revised the manuscript. CD provided methodological and statistical inputs to the study, helped to the application of mathematical methods, participated in the interpretation of the results, and revised the manuscript. TL provided methodological inputs to the study, participated in the interpretation of the results, greatly assisted in writing the manuscript, and revised the final manuscript. Lastly, all authors approved the final manuscript.

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General discussion

Preamble

Gait disorders in PD patients have been studied for decades now. Treatments already exist to improve PD patients' gait in terms of spatiotemporal parameters. On the other hand, the study of variability in terms of temporal organization is more recent. This temporal organization is altered in PD patients with a clinical significance that was previously only assumed.[29–31,39] Recently, this significance has been reinforced by studies establishing strong correlations between impaired temporal organization of gait and impaired balance in PD patients.[35,46] Warlop et al (2016)[35] therefore suggested that measuring this temporal organization by LRA computation could be an objective biomarker to assess patients' potential risk of falling. Based on these findings, it was suggested that these non-linear measures could be of particular importance in the study of PD patients' gait, in addition to linear measures.

The origin of LRA is debated, but the main hypothesis suggests significant control via the central nervous system.[32,35,36] The basal ganglia, brain structures known to be degraded in PD and involved in the generation of temporally organized rhythmic movements and the regulation of gait and posture[11,12,37,38,41], could be partly to blame. Given the internal rhythm generation disorders induced at least in part by the degeneration of the basal ganglia, it is natural to attempt to re-imprint a rhythm via external stimuli to

influence the temporal organization in patients' gait. The use of cueing to manipulate the patient's senses (touch, hearing, vision) was already widely implemented with known effectiveness on linear measures such as spatiotemporal parameters. Although a few studies had investigated the effects of this sense manipulation on non-linear measures, questions remained to be addressed in PD for each of these three main senses. The aim of this thesis was to increase knowledge about the effects of manipulating PD patient’s three main senses (touch, hearing, vision) on linear and non-linear gait measurements.

Touch

Reminders and results

In Chapter 1, the purpose was to study the impact of isochronous rhythmic vibrotactile cueing on patients' gait in terms of spatiotemporal parameters, but above all variability in terms of magnitude and temporal organization. The effects of this type of cueing on PD patients' LRA had never been studied before, whereas those of auditory and visual cues are attested in a more extensive literature. This study presented with similar effects between auditory and vibrotactile isochronous cueing on spatiotemporal parameters, as well as on stride duration variability in terms of both magnitude (CV) and temporal organization (LRA), confirming our initial hypothesis. With regard to LRA, a wide variability of results was found between participants, underlining that some patients may be more receptive to one type of cueing than another.

Strength lies in diversity: Same cueing category, different mechanisms of action

Vibrotactile cues can be placed in a broader category of haptic/somatosensory cues. This category includes treadmill walking.[56,113,236] The treadmill provides a constant rolling motion under the patient's feet, depending on the chosen speed. Although these two types of cueing share the same category, it is clear that these do not have the same effects on PD patients' gait. Where the treadmill increases LRA[56,122] when PD patients walk on it, it was not the case when using vibrotactile cueing. Part of the explanation may lie in the neural pathways employed by these two techniques. On the one hand, the constant rolling of the treadmill belt induces consecutive hip extensions

generating automation and potentially stimulating the Central Pattern Generators (CPGs) at spine level[113,237–239] (Figure 6.1). On the other hand, vibrotactile cueing involves tact sensitivity, the peripheral sensory nervous system sending afferents to the sensory areas of the cerebral cortex. This underlines all the more the extent to which gait is a complex system influenced by internal and external elements of different sorts. Another part of the explanation could come from the location where the vibrating units were placed. Where a treadmill provides somatosensory stimulation to the feet, anatomical areas intimately linked to gait, our method stimulated the wrists.

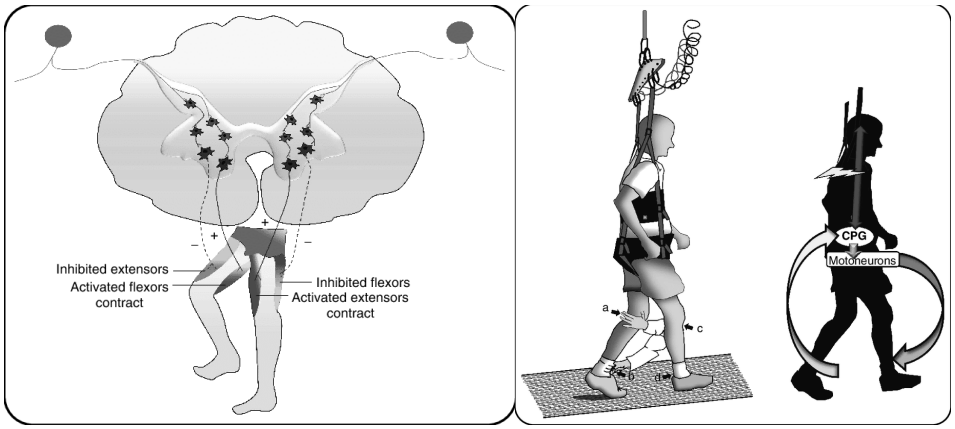

Figure 6.1. *Schematic illustration of Central Pattern Generators. Adapted from Reier et al (2009).*[240]

Skin: a wide playground

The total area of skin covering our body is as many possible locations to use vibrotactile cueing. This observation also raises questions about the number of stimulation sites to be considered. A previous study[241] indicated that the number of vibrating units to be used should be reduced, as too many would increase cognitive load, with repercussions on gait. Another found that a vibrating unit placed at the ankle was more effective to reduce freezing of gait events, but that a unit placed at the waist would be more effective for balance.[242] In the past, other studies have evaluated the effects on gait if the vibrating unit was placed on the wrist, as in our study (Figure 6.2). It was already known that at this location, step length could be increased and cadence decreased.[55,126] Moreover, as the stimulation is performed at the wrist, this location seems ideal for improving patients' impaired arm swing, which was confirmed in the study by Thompson et al (2017).[126] Unlike auditory cues, whose sound waves can reach the patient's ear canals from a variety of locations, and visual cues, which can only occur in the patient's field of vision, vibrotactile cues can operate at different anatomical locations, with different potential effects on gait depending on the location. The question therefore remains as to where the vibrating unit is most effective in improving both spatiotemporal parameters and, potentially, PD patients' LRA. Future studies should investigate the optimal number and locations to use when applying this type of cueing.

Figure 6.2. *Vibrotactile unit used in Chapter 1 (Pulse, Soundbrenner, China/Germany).*

Not one size fits all

With regard to LRA, there was considerable heterogeneity of results from one patient to another in our study. In fact, although the results were not significant at group level, some patients responded better to auditory cueing and vice versa regarding LRA. Although this has never been studied before, our results concur with the findings of a previous study, this time concerning the occurrence of freezing of gait.[243] Therefore, it would seem that there is inter-personal variability in the efficacy of different types of cueing. It remains to be determined what accounts for these inter-personal differences, in order to apply the best cueing type to each patient and individualize the management of gait disorders. This is in line with previous works stressing that 'not one size fits all' when talking about gait rehabilitation for PD patients[244,245], which is applicable to cueing. A previous clinical study[62] gave patients the choice of being treated with the type of cueing of their choice

(haptic, auditory, visual) and showed that of their 153 patients, 67% chose auditory cueing, 33% chose haptic cueing and 0% chose visual cueing. These results give an idea of patients' preferences, but do not give a clue of the possible importance of this preference on gait parameters. Future studies should evaluate PD patients' preference for cueing type (haptic, auditory, visual) and determine the potential influence of this preference on their gait in terms of spatiotemporal parameters and LRA.

Our results, although obtained on a small number of patients, suggest that vibrotactile cueing could replace auditory cueing, depending on whether a patient is more receptive to this type of stimuli. With the idea of proposing individualized tailored treatment, somatosensory deficits should be assessed before vibrotactile cueing is applied. Obviously, well-conducted clinical studies are needed to truly compare these two types of cueing and their real effects on LRA over the long term.

Practical use and perspectives

From a purely practical point of view, vibrotactile cueing seems far more convenient for daily use. Cueing can be seen as a treatment, but also as a method that can be used on a day-to-day basis, especially given that there seems to be little retention of post-treatment benefits if cueing is discontinued at follow-up.[62] Furthermore, and this is in line with previous studies[55,126], auditory cues interfere with the patient's ability to listen to what is going on around them, and visual cues potentially distract the patient from seeing their environment. Vibrotactile cues have the advantage of not presenting these problems, making them ideal for everyday use. Similarly, this type of

stimulus would appear to require little attention and cognitive resources from the people to whom these are presented.[246]

With the advent of smartwatches linked wirelessly to headphones, it is now possible to combine vibrotactile cues from the watch with auditory cues from the headphones. Patients would then be able to control the cueing of their choice via an app on their smartwatch. It is also conceivable that this type of advanced device could incorporate an artificial intelligence that would study the individuals' gait parameters in real time via the on-board inertial sensors, to provide relevant, personalized cues.

Finally, it is possible that, as with auditory cueing[57,79,124], isochronous vibrotactile cueing does not present the optimal temporal structure to apply. Future studies should evaluate the effects of vibrotactile cues with different temporal organizations on PD patients' gait parameters.

Hearing

Reminders and results

Auditory cues are the most widely studied cues in PD. The effects of isochronous auditory cueing are well known, both on spatiotemporal parameters[60] and on the temporal organization of stride duration variability in PD patients.[57,150] Indeed, although it improves spatiotemporal parameters, isochronous auditory cueing significantly alters LRA.[57,150,247] Therefore, the question arose as to whether inducing variability in the temporal organization of the cueing rhythm would have an impact on patients' gait. Two previous studies had already partly addressed this question.[57,79] Nevertheless, confirmation was needed. Indeed, on the one hand[57], a too short acquisition time for robust LRA computation[28,80–83] was used. On the other hand, music was used[79], a very different auditory cueing compared to the metronome classically used. In Chapter 2, it was therefore decided to compare four walking conditions: no cueing, isochronous cueing, random cueing and autocorrelated cueing. Our results showed that the different cues used had no different effects on the spatiotemporal parameters, but all cues significantly reduced the α exponent compared with the condition without cueing. As a reminder, an α exponent close to 0.5 means a reduced temporal organization approaching complete randomness, and according to the theory of optimal variability[28,33,34], an α exponent close to 1 would be a goal to aim for. The greatest breakdown of LRA (α exponent close to 0.5) occurred with isochronous metronome and the least with autocorrelated metronome. From the results and discussion of Chapter 2, it remains clear that a significant number of issues deserve further elaboration.

Speed of Sound: Cueing frequency matter

One of the first fundamental and simple questions to ask is what frequency to set the cues at. Current guidelines recommend the use of auditory cueing[202], but do not specify the beat frequency to be used. While some studies set the metronome beat frequency 10% faster than the patient's comfort cadence, others like ours chose to match the two.

This consideration seems to be important, since a number of previous studies have shown the superiority of a higher 10% RAS frequency for improving PD patients' spatiotemporal parameters.[60,120] In Chapter 1, we also chose to set a RAS frequency 10% faster than patients' comfort cadence and the spatiotemporal parameters were indeed significantly increased compared to the control condition. Conversely, no significant difference was found between conditions in Chapter 2 for spatiotemporal parameters with RAS frequency matched to patient cadence.

Regarding the magnitude of stride duration variability, Dotov et al (2017)[57] used RAS frequency 10% higher than patients' comfort cadence and found an increased CV while other studies showed the opposite.[120,248] Similarly, no difference was found in our study for CV.

With regard to LRA, Dotov et al (2017)[57] found no difference between their control condition and their 10% faster autocorrelated RAS condition, whereas the autocorrelated RAS used in our study induced a significant decrease in LRA compared to our control condition. On the basis of these results, it does possibly seem that a rhythm frequency set 10% higher than the patient's comfort cadence could be recommended to both improve spatiotemporal parameters but also allow less degradation of LRA when using RAS. Future

transversal and longitudinal studies comparing the effects of autocorrelated RAS presenting with different frequency speeds on PD patients' LRA are still needed to confirm these assumptions. Likewise, sufficient acquisition times are mandatory to draw adequate conclusions.

You'll Never Walk Alone: The closed-loop method

While, most of the time, the RAS used are determined in advance according to the patient's gait cadence measured during a test, others have turned their attention to the use of RAS that adapt in real time.[249] This type of cueing, called "closed-loop" cueing (Figure 6.3), has the advantage of being activated only when the patient moves, making it more practical for everyday use. At first glance, it may not seem worthwhile to use this type of cueing if it follows the gait rhythm of patients with impaired LRA. What would be the point of applying cueing with a pathological temporal organization of its variability? Since the temporal organization of stride duration variability in PD patients is close to randomness[35], this type of closed-loop cues could be close to the RRAS condition of Chapter 2, with possibly negative effects on PD individuals' LRA while using it.

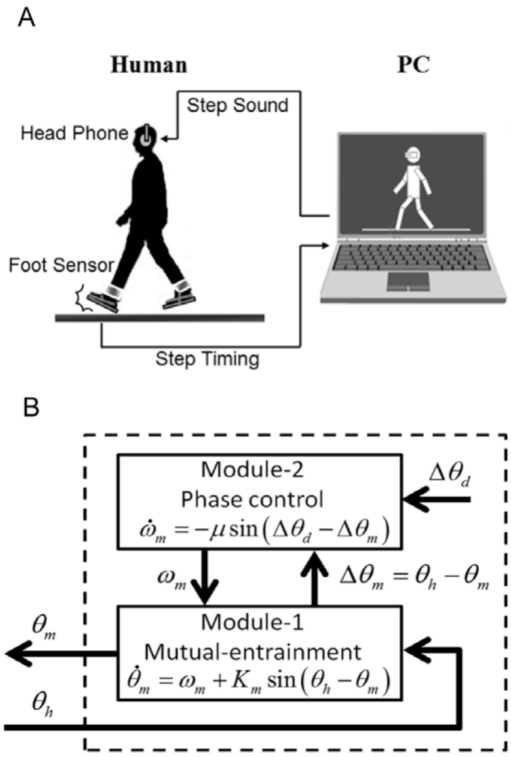

Figure 6.3. *Schematic representation of a closed-loop auditory cueing, "WalkMate". Adapted from Hove et al (2012).*[150]

Although the above reasoning may seem logical, studies have found that, on the contrary, PD patients with breakdown of LRA improved their LRA using closed-loop RAS.[139,150] The mechanism invoked by the authors is that this interactive system keeps the beats constantly close to the motor output time, thus promoting the integration of these beats directly into the motor input timing.[150] As the internal elements governing rhythm generation (basal ganglia) are defective in PD with influence on LRA, this external element, modelled on the patient's own motor outputs, would enable reintegration of

the natural timing of the gait rhythm. Cortical activation would therefore depend on linkages between sensory inputs and motor outputs.

For Uchitomi et al (2013)[139] the effectiveness of closed-loop cueing is similar to what happens when two people walk side by side. In such situation, interpersonal synchronization occurs with gait rhythms synchronization[250] which may neurally stem from perception-action linkages[251] and mirror neuron systems.[252] With closed-loop cueing, synchronization is no longer interpersonal, but intrapersonal. Somehow, closed-loop cueing mimics interpersonal synchronization, but is based on the patient's own rhythm. This would enable intrapersonal gait relearning, with an increase in the audio-motor linkage neural connection to control intrapersonal gait rhythms.

However, these results need to be tempered by the short acquisition times used. Likewise, this type of cueing is more complicated to implement due to the multitude of sensors to be placed. Future studies could compare closed-loop cueing either matching the patient's cadence without any correction, and cueing matching the patient's mean cadence in real time but applying a correction involving normative autocorrelated temporal organization.

To go back briefly to somatosensory cueing, a simple and low-cost way of applying closed-loop cueing is to use Nordic walking poles. As the patient lands the poles on the ground at each step, a tactile stimulus is produced in the hands, in line with the patient's own gait cadence. The results of Warlop et al (2017)[173] demonstrate an improvement in PD individuals' LRA while using Nordic walking poles (Figure 6.4), which is in line with the results on closed-loop auditory cueing. In addition, Nordic walking stimulates an active lifestyle as well as arm swing, which is impaired in PD.[254]

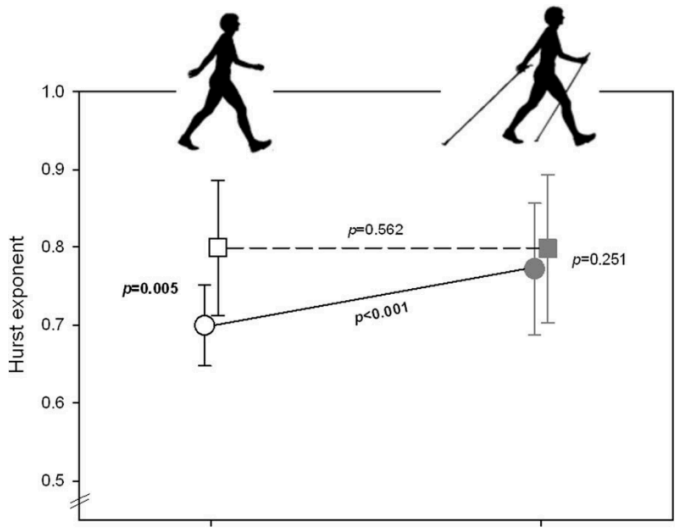

Figure 6.4. *Influence of pathological and walking conditions on LRA exponent (Hurst exponent = variation of α exponent) in PD and healthy participants. Post-hoc analysis for the (Pathological x Walking) interaction for LRA exponent in PD (white and grey circles for usual and Nordic walking sessions, respectively; black solid line) and healthy controls (white and grey squares for usual and Nordic walking sessions, respectively; black dashed line). Adapted from Warlop et al (2017).*[253]

Give Life Back to Music: Music as auditory cueing

Auditory cueing using a metronome, while effective on certain gait parameters in PD patients, can be tedious to use. For some years now, research has been focusing on the effects of music on PD gait. Quite simply and logically, the more familiar the individual is with the type of music used, the greater the pleasure of using auditory cueing.[58,255] Also, the greater the familiarity, the more positive the effects on spatiotemporal parameters.[58,256]

Conversely, the use of dissonant music creates negative feelings in patients, accompanied by altered spatiotemporal parameters.[257] This could be due to the cognitive overload implied by dissonant music[257] whereas familiar music would reduce this load, with positive effects on gait.[258] It is therefore important to take the patient's preferences into account when proposing music-based auditory cueing. Where cognitive overload can degrade LRA in PD patients, no study has evaluated the influence of patient's familiarity with music on LRA.

At first sight, there does not seem to be any advantage of music over a simple metronome in improving PD individuals' spatiotemporal gait parameters.[259] It would appear that PD patients have impaired ability to identify the presence of a rhythmic beat in the music they listen to[260], which would be directly linked to damage to the basal ganglia.[261] Some authors therefore emphasize the importance of beat salience ("groove"), which improves rhythmic synchronization, gait[262], arousal and affective state[263], and can increase the vigour of movement (velocity and amplitude) in PD patients.[264]

Marmelat et al (2020)[79] evaluated the effects of music on PD individuals' LRA. Note that their music used an autocorrelated rhythm that could be compared to the autocorrelated RAS used in Chapter 2. Contrary to our results, they showed an increase in LRA exponent compared to control condition. Music is composed of multiple layers making it a more complex auditory cue which could have an impact on LRA by proposing more degrees of freedom and then being less "strict" than a simple metronome. The emotions evoked by music[158,159] could also improve patient's implication to the task which could impact gait parameters such as the temporal organization of gait variability. Interestingly, Marmelat et al (2020)[79] also reported that it

was the PD patients most severely affected by the disease who exhibited the greatest increase in LRA exponent while listening to music. This observation was also made in the context of the magnitude of stride duration variability (CV).[265]

Music represents a continuous sound that differs from the discrete sounds delivered by a metronome, and this could be significant. Indeed, whereas discrete sounds allow greater precision of coincidence between each step and the beats, music seems to allow greater consistency in movement durations and smoother movement trajectories.[266] The explanation could lie in the increased flexibility affordance produced by music and continuous sounds, facilitating adaptation of the gait pattern to the different sounds making up a piece of music without the strict rigidity imposed by a simple metronome. As gait is a continuous event involving a series of movements of different parts of the body and not just heel strike itself, the use of continuous auditory cues such as music makes sense for guiding the entire gait and its complex temporal organization.

Music therefore appears to be a valid alternative to classic metronome, with positive effects on spatiotemporal parameters and gait variability while potentially improving PD patients' adherence to the therapy if familiar with it. Future longitudinal studies should compare the effects of simple metronome versus music based auditory cueing on spatiotemporal gait parameters and most of all on LRA in PD patients.

Rhythm in the Blood: Importance of synchronization abilities

As a rhythm is imposed to the patients, it seems interesting to look at the PD patients' abilities to synchronize to these rhythms and the impact of these

abilities on gait. Previous researches have shown that PD individuals have difficulty synchronizing to rhythms, the more so if they are severely affected by the disease[267] and/or if they present with freezing of gait.[268] Moreover, PD patients with good residual synchronization skills are the ones who will benefit from auditory cueing, whereas those who have lost these skills will find their gait altered by cueing in terms of spatiotemporal parameters[257,267,269] (Figure 6.5). Following this logic, the least severely affected PD individuals would be those benefiting most from auditory cueing. This seems to be true for spatiotemporal parameters, but the opposite could be true for LRA. Indeed, as discussed above, Marmelat et al (2020)[79] found with their autocorrelated music cueing a better effect on LRA for patients with a higher degree of severity and therefore those potentially synchronizing least well to the cues. It would therefore be possible that patients' synchronization abilities are not important for observing an improvement in LRA following the use of autocorrelated auditory cueing. However, we can observe a disparity in the results of studies evaluating LRA in PD gait depending on whether or not patients were specifically asked to synchronize to the cues.

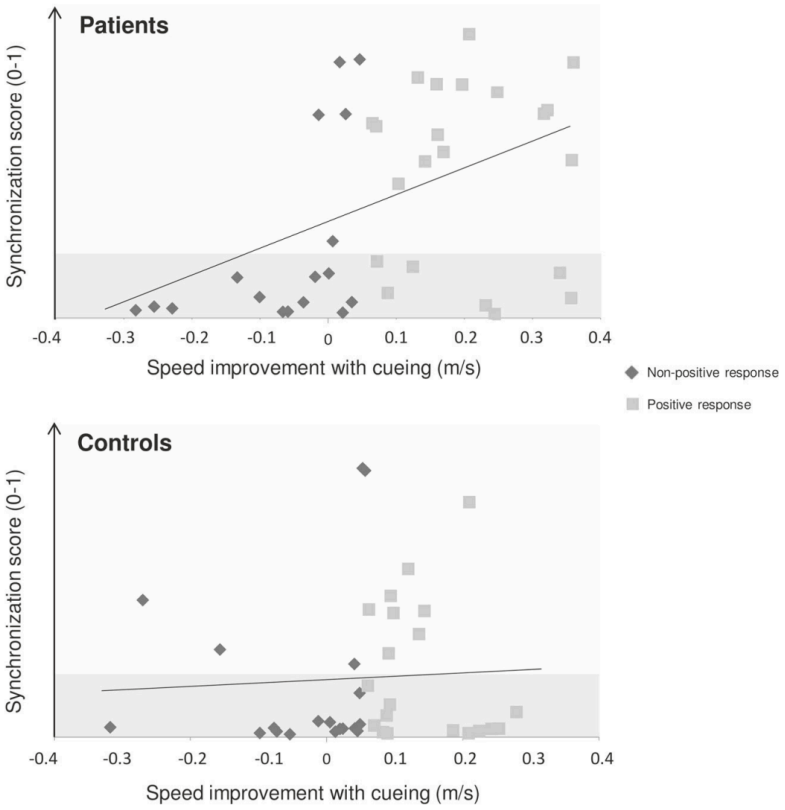

Figure 6.5. *Individual responses to auditory cueing expressed as the difference in gait speed between cueing and the baseline, in PD patients (graph above) and healthy controls (bottom graph). PD patients who aligned their steps to the beat also increased their speed; this is not the case of controls. Light-coloured squares represent subjects with positive response (increased speed); dark-coloured squares represent subjects with non-positive response. Adapted from Cochen De Cock et al (2018).*[269]

As the devil is in the detail, should patients be explicitly instructed to synchronize with auditory cueing or not? Indeed, while some authors did not ask patients to synchronize, others, as in our study in Chapter 2, explicitly asked them to do so. This may seem trivial, but it could explain some of the disparities in results between studies. Indeed, while LRA were altered by our autocorrelated RAS, this was not the case in the study by Dotov et al (2017)[57] where no synchronization instruction was given. This ties in with the discussion in Chapter 2 explaining that this instruction gives a framework that reduces degrees of freedom and would have a negative impact on LRA by constraining gait to a stereotyped pattern. This instruction could increase cognitive load, which has an impact on the gait of PD patients who are known to have difficulty managing dual-tasking.[270–273]

To temper this hypothesis that this strict RAS framework would have a negative impact on LRA in PD gait, treadmill walking, on the other hand, seems to improve LRA[56,122] despite proposing an even stricter framework. Although PD individuals have somatosensory deficits[75,76], it is possible that this difference in stimulated senses could explain the disparity in results. Whereas auditory cueing involves supraspinal neuronal circuitry[59,62,65–70], treadmill walking involves constant hip extension, which stimulates CPGs at spine level.[237–239] As a result of this stimulation at spine level, the haptic cueing produced by the treadmill tends to automate gait. This, together with the absence of optic flow, could considerably reduce the cognitive load and hence the dual-tasking of this type of cueing compared with auditory cueing, potentially explaining these results.

Studies specifically evaluating the impact of the instruction to synchronize to RAS on LRA but also research assessing the direct impact of PD patients' synchronization abilities to RAS on LRA need to be conducted.

Cracks or beeps: Action-relevant cues

Another complementary way of proposing auditory cueing is to provide rhythmic sounds that seem to come from real life, called action-relevant sounds (e.g. the crunching of footsteps on gravel, falling drops, etc.). This richer, more complex type of sound allows the patient to be emotionally involved in the auditory cueing.[266] Notably, while listening the sound of footsteps in gravel, both healthy subjects[274] and PD individuals[275] are able to guess the step length of an individual and thus attempt to emulate them. This seems to have the same effect on spatiotemporal parameters than a simple metronome, while reducing the magnitude of stride duration variability in PD patients, which could mean less cognitive load.[275]

In the context of PD, there are to our knowledge no studies that have evaluated the effects of action-relevant auditory cueing on LRA. Future studies comparing the effects on PD individuals' LRA of a simple metronome with those of action-relevant auditory cues should be conducted.

Vision: VR exergames as a rehabilitative approach in PD

Reminders

VR based rehabilitation has been studied for years for its effects on PD patients' gait and balance. Although essentially non immersive, VR rehabilitation across longitudinal studies could be divided between pathology-specific VR solutions created by research teams and commercial VR video games. Attempting to determine which of specific and non-specific VR is more effective in improving balance and functional mobility in PD patients is of interest.

The aim of our meta-analysis was not only to study the effects of VR rehabilitation on balance, functional mobility and quality of life, but also to sub-group results according to: VR type (specific (SVR) vs non-specific (NSVR) virtual reality), disease severity and treatment duration. The originality of this work was also to determine the fulfilment of neurorehabilitation principles in the included studies. These principles, initially determined in the context of stroke[164,165], also seemed relevant to PD rehabilitation. Regarding results, VR appeared superior to conventional therapies in improving patients' balance, but these results were not found for functional mobility and quality of life. Contrary to our hypotheses, SVR was not superior to NSVR for all outcomes, and did not appear to fulfil more neurorehabilitation principles than NSVR on average. Nevertheless, our results suggest that VR may be more effective for patients with more severe disease progression, and if treatment is given for longer periods. Lastly, even though these neurorehabilitation principles seem relevant, these could be improved in the light of existing guidelines for PD.

Playing rules: Towards refining the neurorehabilitation principles to be applied to VR exergames in the context of PD

Maier et al (2019)[165] made a great deal in determining the neurorehabilitation principles to be applied to VR exergames in the context of stroke. After slight modifications, we decided to retain these principles, but this time in the context of PD. This decision responds to the hypothesis of Maier et al (2019)[165] that these principles would also be applicable to PD. In PD, these principles share elements that are already an integral part of the rehabilitation guidelines[202,203], but add some of their own.

Some of these principles seem to us to be essential in the context of PD: massed practice, dosage (confirmed by our results), task-specific practice, rhythmic cueing. Other principles are important components of VR exergames: increasing difficulty, variable practice, explicit feedback, implicit feedback, multisensory stimulation. These features of VR exergames are essential both to offer patients tailored challenges and to give them incentives to continue their treatment, and thus to try to increase their adherence.[161] In our view, some of the treatment bases listed in existing guidelines should be explicitly included in the proposed VR exergames. Indeed, these guidelines have been selected for their proven positive effects in clinically improving PD patients.[202,203] It therefore seems logical to implement them in the VR exergames.

Although most of the time implicitly included in both SVR and NSVR games, balance training in the broadest sense must be specifically included.[202,203] Furthermore, since games are mainly played in front of a screen, VR balance training is often static rather than dynamic (e.g. balance training during

locomotion). VR exergames should add dynamic components and train balance during dual-tasks as PD patients present with difficulties in dealing with it.[270–273] One way of doing this is to offer a combination of treadmill walking with an exergame as in the study of Lau et al (2022)[185], or to use immersive VR headsets allowing a large play area in which the patient can move freely while walking.

In NSVR solutions more than in SVR ones, games sometimes require you to perform fast actions to beat either another player or a character managed by the game itself. This probably sometimes leads to an increase in heart and respiratory rate, but the aim never seems to be to follow aerobic training recommendations for PD patients. However, there are strong recommendations for the implementation of aerobic training for PD patients with high quality evidence.[203] Future VR exergames should explicitly aim to offer moderate-to-high intensity aerobic training (60%-85% maximum heart rate, 3 days a week, 30-40 minutes each session). This could be achieved by monitoring patients' heart rates using devices directly linked to VR exergames, which would adapt the difficulty of the games in real time to match aerobic training recommendations.

This finding is all the more important in the case of resistance training, since no studies have applied this type of training to the VR exergames used. However, as with aerobic training, resistance training is strongly recommended for PD patients with high quality evidence. Indeed, this type of training increases strength, reduces the frequency of falls and improves patients' balance, mobility and quality of life.[203] Resistance training should be offered three times a week, for 45 minutes each session, and large muscle groups should be exercised before small ones. Resistance training could be

implemented in VR exergames via weight machines directly connected to the VR hardware.

Gait training is also strongly recommended with high quality evidence.[203] Although some SVR exergames are played in combination with treadmill walking, most of the exercises are static and do not work specifically on gait, which is strongly impacted in PD. VR exergames should expressly include gait training, either via large play areas allowing for locomotion or via treadmill walking.

A new version of these neurorehabilitation principles, including guidelines specific to PD, should be drawn up in the future. It seems difficult to create the perfect VR exergame fulfiling all these principles. In our opinion, it would therefore be appropriate in the future to weight the importance of each of these principles, in order to prioritize the fulfilment of certain principles over others. This weighting should be accompanied by guidelines for the development of exergames in the context of PD, defining the strength of recommendations for each principle retained: quality of evidence, risk-benefit balance, inclusion of patient opinion, expert consensus.

Bonus stage: VR as a complement to conventional treatments

Our meta-analysis confirms the results of previous studies[162,166–169] on the effectiveness of VR rehabilitation in improving PD patients' balance. Although these results are interesting, it should be remembered that the quality of evidence was assessed as low according to the GRADE approach. We also confirmed that the results for VR treatments did not lead to a significant difference over conventional therapies with regard to functional mobility and quality of life, with moderate and low quality of evidence

respectively according to the GRADE approach. The non-superiority of VR regarding these outcomes, and the low quality of evidence concerning balance outcome, do not allow us to recommend the use of VR over other conventional treatments. Nevertheless, we feel that VR exergames are a welcome addition to the treatment of PD patients, as long as the following conditions are met: VR exergames that take account of neurorehabilitation principles and guidelines, a patient willing to accept this type of treatment, and a staff trained and enthusiastic about using this type of technology.

Although VR rehabilitation seems to us to be a good complement to existing approaches and guidelines, a number of barriers need to be taken into account before we can hope for its widespread use[276]:

1) Heterogeneity and proliferation of existing hard- and softwares
2) Cost of equipment
3) Space required to use the equipment
4) Data collection and protection
5) Proof of cost-effectiveness in the context of PD rehabilitation
6) Barriers specific to therapists
7) Barriers specific to PD patients

Regarding therapist- and patient-related barriers, no studies were found specifically in the context of PD and/or VR, but we believe that the literature concerning other neurological pathologies and new technologies in general may be broadly applicable. Barriers include therapists' insufficient knowledge and ability to assess the usefulness of new technologies and a lack of means and opportunities to try out technologies such as VR.[277] Also, when this type of technology is implemented in clinics, there is a lack of time devoted by

technical support to teach therapists how to use the equipment.[277] Therapists seem to have difficulty coping with the time required to find the right equipment, learn how to use it and set it up for their patients.[277] Other barriers include the belief that the equipment will be too expensive or too complicated for their patients to use, and the difficulty of keeping up to date with rapidly evolving technology.[277] The general barriers that PD patients face to involvement in a rehabilitation program are: little hope of treatment outcome given the progressive nature of the disease, lack of time and fear of falling.[278] A potential barrier that may limit patients' acceptance of new technologies, and therefore of VR, is their known lack of cognitive flexibility.[279]

Finally, although it is not mentioned in the studies, we think that two specific obstacles to the use of VR concern both therapists and patients. The first is the generation from which some therapists and the patients come, most of whom are elderly. Indeed, they have not grown up with the rapid advance of new technologies and may present difficulties in adapting. This ties in with the general concept of the "digital divide".[280] Indeed, lack of familiarity seems to be a major obstacle to the use of technology by PD patients, in addition to the cost and technical problems encountered with the equipment.[281] The second barrier concerns the negative prejudices associated with video games and conveyed by the general press and politicians. We believe that in the future, these two barriers will no longer exist.

The implementation of VR in everyday practice will only be possible if these barriers are removed. So, even if research is making great strides in this field, there still seems to be a long way to go before we can easily offer this type of treatment to our patients.

Final boss: Thoughts about a transition to immersive VR

The next lines of this chapter will take a look at VR in general and its use in research and clinical practice.

Our research team is composed of some VR enthusiasts and a technology-lovers in general. We are particularly interested in keeping up to date with technological advances in a variety of fields on a daily basis. In the context of VR, we were especially interested in the SVR and NSVR methods used in the studies included in the meta-analysis. Until very recently, a significant number of studies have evaluated the effectiveness of the Nintendo Wii in treating PD patients. Without calling into question the intrinsic qualities of this gaming console, it is far from being at the cutting edge of what can be offered in terms of VR, and all the more so as this hardware has no longer been produced by Nintendo since October 2013. We know that the general pace of research is inherently slow, but we do not think this justifies the fact that 10 years after a piece of hardware has ceased production, studies continue to investigate its effectiveness, to the point of recommending its use in everyday practice. We agree that it is difficult to keep up with the frenetic pace of hardware and software releases, but precisely at a time when one day's technological truths are no longer the same the next, so fast are things moving, we cannot accept continuing studies on a 17-year-old hardware (Figure 6.6).

Figure 6.6. *Individual playing Nintendo Wii, non-immersive VR (photo credits: New York Times).*

At a time when the quality of immersion offered by VR is acclaimed as an integral part of its appeal and potential effectiveness[161,276], the use of immersive VR by means of virtual reality headsets (Figure 6.7) seems to be gaining ground. In particular, the "Sense of Presence" provided by immersive VR enables patients to respond to virtual stimuli in a natural way, as they would if they were physically present in the real world[282,283], thus increasing its ecological validity against non-immersive methods. This sense of presence is measurable via physiological measurements (heart rate, skin conductance, skin temperature)[284] and makes it possible to involve the patient all the more emotionally in in-game actions[283] which is particularly important in the context of PD.[285] This mental state could have a positive impact on the efficiency of VR treatments[286], as well as facilitating the transition between actions performed in VR and those performed in the real world. Last but not least, immersive VR enables advanced manipulation of the patient's senses to create situations that are impossible to reproduce in real life (changing size of body parts, changing body shape, exaggerating the range of virtual movement compared to what is effectively achieved by the patient, highly controlled virtual environment that can be modulable at will, changing the point of view from which the patient sees himself). It is also possible to recreate real-life but dangerous situations (crossing the road, avoiding obstacles, etc.).

Figure 6.7. *Individual using an immersive VR headset (Meta Quest 2, Meta) on the right and what she sees in real time on the left (photo credits: Wall Street Journal).*

For the purposes of the study of Chapter 4, I learned how to code my own VR game compatible with a VR headset. Nowadays, if you are even remotely interested in IT and computers, it is easy to learn how to create immersive VR games. Moreover, free graphics engines such as Unity or Unreal Engine make it easy to create games with out-of-the-box solutions. As the game creation community is also very active, it is fairly easy to solve problems linked to a lack of experience. Once the basics are understood, the possibilities seem endless, whereas non-immersive solutions are more limited. Furthermore, with competition raging between video game manufacturers, it is becoming cheaper and cheaper to buy VR hardware.

To place the use of immersive VR in the context of Parkinson's disease, no randomized controlled trial to our knowledge has used immersive VR to treat

patients' gait or balance disorders. At best, a recent cohort study gave encouraging results regarding balance.[289] Yet the feasibility of using this type of equipment with these patients has already been demonstrated in past studies[207,289] and this was confirmed in our study combining immersive VR and treadmill walking.[122] Indeed, immersive VR did not induce significantly more motion sickness than a non-VR condition. As long as there is no mismatch between the different sensory afferences[222], motion sickness seems to remain marginal and should not be a barrier to the use of immersive VR in PD patients.

Based on these findings, we truly believe that future research should open up to the use of immersive VR and gradually move away from non-immersive solutions. Clinical studies are awaited to finally appreciate the potential of these technologies in PD gait and balance rehabilitation.

Vision: Optic flow to ecologically enhance treadmill walking

Reminders

Among the visual information influencing balance regulation during gait, optic flow is of particular importance in general[103–105], and even more so for PD individuals.[59,86,90,91] Optic flow acts as a hint, indicating a person's progress in the surrounding space. To study its influence on healthy and PD gait, previous studies have attempted to reproduce the illusion of a modulable optic flow when walking on a treadmill.[86,106–112] Indeed, there is classically no optic flow during treadmill walking, which removes an essential ecological component that can disturb PD individuals. This lack of optic flow could partly explain why not only PD patients' spatiotemporal parameters[113,114] but also LRA[56,74] are different from overground walking during treadmill walking. This means that gait analysis during treadmill walking does not represent the "natural" gait of PD individuals regarding these particular parameters. To recreate optic flow on a treadmill, previous studies used methods that were probably innovative in their time, but could not claim to recreate a true sensation of optic flow: screens covering few fields of vision, no sensation of depth (stereoscopic 3D rendering), black background with white dots traveling from the center to the extremities of the screen, no recreation of an ecological situation.[86,106–112]

The second study in Chapter 3 aimed to determine the influence of an artificial optic flow in immersive VR, applied during treadmill walking, on PD patients' spatiotemporal gait parameters but also, and more importantly, on LRA. Our results showed that this method could potentially enhance the already existing effects of the treadmill on spatiotemporal parameters. Also,

the addition of optic flow captured LRA similar to those computed during overground walking, perhaps increasing the validity of the study of PD patients' gait during treadmill walking, at least regarding this outcome. On the other hand, where we confirmed that treadmill walking significantly increased PD patient LRA[56], the addition of optic flow significantly altered them. Consequently, treadmill walking without VR optic flow would seem to be more appropriate to improve the temporal organization of stride duration variability in PD patients.

Open Your Eyes: Vision in PD, pathophysiological substrate, and clinical implications

To discuss the results of this study further, we need to determine the importance of visual information in regulating PD patients' gait, why and how this information is important, and what this implies clinically.

Generally speaking, as mentioned in the introduction of this thesis, gait is regulated by the constant interaction between internal elements (central and peripheral nervous system, musculoskeletal system) and external elements (terrain, external auditory/haptic/visual stimuli). In this study, we focused on external visual stimuli by recreating an optic flow. From a subject's point of view, visual information can be roughly divided into two parts: exteroceptive information and exproprioceptive information.[290]

Exteroceptive information is made up of the environment around us, without any assessment of our body's position in relation to it, and enables us to plan ahead before negotiating obstacles. This type of information mainly involves the center of our visual field.[290] On the other hand, exproprioceptive information accounts for our body's position in relation to its direct

environment. This involves peripheral vision in particular, and is used to negotiate nearby obstacles and make fine adjustments to our movements in relation to our direct environment during locomotion.[290] These two elements can be manipulated. By influencing on the optic flow, and therefore the impression of self-motion, we manipulate exteroceptive information. On the other hand, the use of discreet visual cues, such as markings on the floor with instructions to step over them, focuses the patient's attention on exproprioceptive information.

In PD, it would appear that patients have difficulty finding their way in space.[291] This phenomenon could be directly linked to damage to the basal ganglia[84] and reduced dopamine levels in peripheral visual structures.[85] The basal ganglia play a role in kinesthesia[87], the internal sensory perception that allows an individual to perceive and comprehend the position, movement, and muscular tension of their own body. It plays a crucial role in motor coordination and proprioception, enabling an individual to sense and understand the position and movements of their limbs, even without relying on vision. As this part of the brain is preferentially affected in PD, patients experience reduced kinesthetic feedback.[86–89] As a result of these kinesthesia impairments, patients rely all the more heavily on vision to guide and modulate their movements during locomotion. With regard to the degradation of dopamine levels in the retina, patients experience difficulties in correctly capturing exteroceptive and exproprioceptive visual information.[292] To illustrate these phenomena, Schubert et al (2005)[86] reproduced an optic flow during treadmill walking while varying its speed and direction. Half of the patients included did not notice that the optic flow speeds were different, yet effects on gait were still observed. This means that even if kinesthesia is

impaired and that the patient does not consciously perceive the subtleties in the difference in optic flow speed due to changes in the retina, visual information is still registered and has an effect on gait.

These physiological considerations taken into account, vision, although abnormal, is logically clinically of crucial importance for PD patients' gait regulation in relation to the other senses, even more so than in healthy subjects.[90,91,93,95,101,102,293,294] Researches have underlined the importance of visual exploration and the patient's dependence on attention to the surrounding visual elements in controlling and planning gait.[295] This dependence seems all the more true for the most affected individuals[90], and less so for the least affected patients.[296] The downside of this dependence on visual information is that patients may overreact to visual elements.[86,101,229] This means that, on the one hand, PD patients are highly receptive to visual cues, but on the other hand, they may react disproportionately to them.[86,229] It is with this observation that Warlop et al (2018)[56] and our study explain the effectiveness of treadmill walking on LRA, providing a framework for gait while limiting visual information for which patients might overreact.

Seven Nation Army: Possible explanations for the effects of visual cueing

As with somatosensory cueing, where different modalities can be found under the same category (vibrotactile, treadmill), and the same regarding auditory cueing (discrete sound of a metronome, continuous sound of music), there are different ways of giving visual external stimulations. These can be spatial (lines on the floor, manipulation of optical flow) or temporal (rhythmic flashes of light).

The origin of the effects of visual cueing is debated. While some believe that the effectiveness comes from the patient's attention to the stepping process (attention to placing the foot on the cues)[293,297], others think it comes from the increased sensation of self-motion and therefore perception of optic flow.[59,90,230] The first hypothesis is supported by Lebold & Almeida (2011)[293] showing that if the patient's vision is cut off from the location of his body and the environment itself (darkened room, optic flow via scrolling lights), manipulating the optic flow no longer results in an increase in step length. Afterwards, the same team[59] went a step further, differentiating between exteroceptive information and exproprioceptive information. Rather than plunging the room into darkness, which cuts off both exteroceptive and exproprioceptive information, they cut off the patient only from exproprioceptive information by hiding the lower limbs using a blind (Figure 6.8). Lines were placed on the floor, which the authors believe increased the impression of self-motion.[90,230,298,299] In this way, the patient observed the lines scrolling past, increasing the impression of self-motion, but could not adjust the position of their lower limbs in relation to these lines because they could not see them. They showed that even though exproprioceptive information was missing, an improvement in step length was present, as the optic flow "augmented" by the lines on the floor would act as an exteroceptive cue. Attention to the placement of the lower limbs in relation to cueing (exproprioceptive information) would not therefore seem to be the essential element explaining the effectiveness of visual stimulations on spatiotemporal parameters, but rather optic flow (exteroceptive information). This is in line with a study by the same team showing altered spatiotemporal parameters when optic flow is removed.[296]

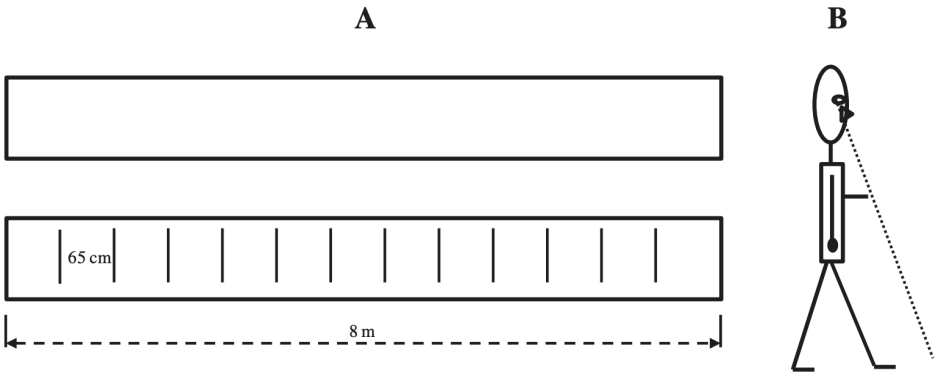

Figure 6.8. *Illustration of the pathway with and without the visual cues (A) and the blind used to remove exproprioception from lower limbs (B). Adapted from Vitório et al (2014).*[59]

Our study took this a step further and reported similar results. In fact, in the treadmill condition without VR, exteroceptive information was totally static. On the other hand, the patient saw his lower limbs on the treadmill, so exproprioceptive information was preserved. Conversely, in the VR condition, the patient received a sophisticated optic flow that faithfully reproduced the exteroceptive information actually perceived by the patient on overground (Figure 6.9). Likewise, the patient had no exproprioceptive information because the lower limbs were not digitally reproduced in the game. However, according to our results, the patient's step length was significantly higher using the VR optic flow than during standard treadmill walking, for the same walking speed. Obviously, in a real-world walking situation, it seems essential for the patient to retain exproprioceptive information in order to be able to negotiate uneven ground or obstacles. Our

study just underlined the importance of exteroceptive information in patients' gait quality with regard to spatiotemporal parameters.

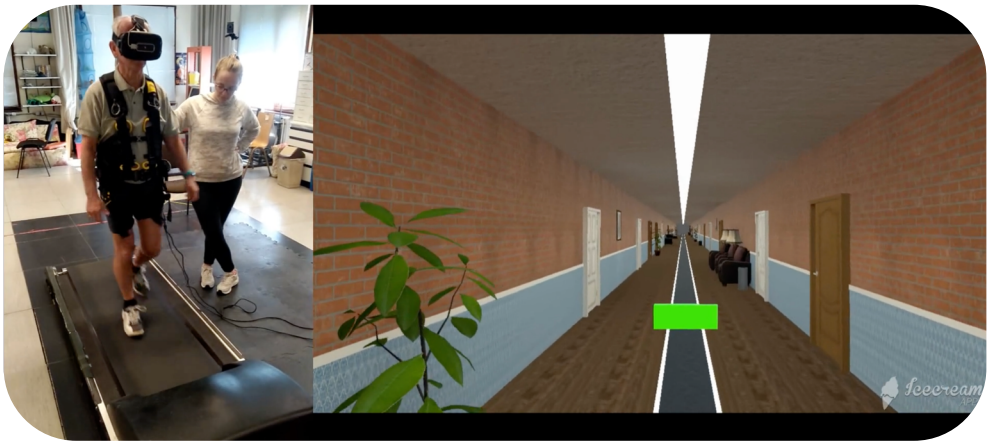

Figure 6.9. *VR set up used in the second study of Chapter 3. On the left, a PD patient using immersive VR headset while walking on the treadmill. On the right, what the patient sees in the headset, a speed matched optic flow.*

On the other hand, it is worth noting the opposite effect on LRA. Where the absence of ecological exteroceptive information on the VR-free treadmill walking condition increased LRA exponent, the addition of optic flow reduced it at the level of overground walking. This could be a sign of an increase in regulatory load on the locomotor system, caused by a higher cognitive load when visual information has to be taken into account.[108] Visual information therefore potentially modulates spatiotemporal parameters and LRA differently. Where step length would be positively regulated by manipulating exteroceptive information (addition of optic flow) to the

detriment of LRA, suppression of exteroceptive information would allow the patient to concentrate on exproprioceptive information during treadmill walking and thus on the placement of his lower limbs step by step, with a positive effect on LRA but still with a reduction in step length.

In addition to these hypotheses concerning the functioning of visual cueing, we had already mentioned the probable importance of the degree of disease severity on the way patients benefit from cueing. Indeed, Ferrarin et al (2008)[300] suggested that less-affected PD patients improve their gait parameters with augmented optic flow, whereas more-affected patients respond better to discrete rhythmic visual stimuli. This may be linked to the correlation between the progression of the disease and the deterioration of dopaminergic function in the retinal system.[85] As the patients in our study were only mildly affected (median Hoehn & Yahr scale of 1.75 [1-2]), this could explain the good effects of our VR optic flow on spatiotemporal parameters. This should be studied in more severely affected patients to see if this effect is kept. It would also be interesting to know the effects on LRA exponent of our optic flow on a cohort of more severely affected patients. Warlop et al (2018)[56] found a fairly strong positive correlation between the degree of disease severity (Hoehn & Yahr scale) and the increase in LRA exponent observed during treadmill walking without optic flow compared to overground walking. Would an inverse correlation be present between the level of disease severity and the drop in LRA exponent when the patients experience optic flow during treadmill walking or overground? Given the small number of patients included, it does not seem appropriate to make this type of correlation based on our results. Further similar studies but involving

a larger number of patients with varying degrees of disease severity are therefore required.

Here It Goes Again: Treadmill walking, an imperfect gold standard and perspectives regarding VR

In the context of PD, treadmill walking is known for its positive effects on spatiotemporal gait parameters[206], and our results confirmed the findings of a previous study[56] on its potential beneficial effects on LRA. Despite the fact that treadmill walking has become a gold standard in PD gait rehabilitation, and that this tool is widely used to perform gait assessment of PD patients, it seems to us that a number of issues remain to be explored. In particular, different types of treadmill now exist, and our study had just shown the possibility to add ecological value to treadmill walking by adding an optic flow, which may be of importance both for gait assessment and gait rehabilitation.

Our study was based on the observation that PD patients' gait assessment made on a standard treadmill does not allow for a reliable assessment of both spatiotemporal parameters and variability.[56,115,122,152,301,302] In our view, the difference between standard treadmill walking and overground walking lies in two main elements: the constant speed of the treadmill, predetermined with no variation in speed, and the non-ecological static visual information perceived during a treadmill walking task.

One way of overcoming the first issue is to use an adaptive treadmill. This type of treadmill constantly adapts its running speed to the patient's walking speed in real time. An adaptative treadmill could therefore be considered as closed-loop somatosensory cueing. The idea behind adaptative treadmill is

that, since the patient chooses his or her own pace, which is not imposed in advance, walking will be more natural. A previous study[303] compared young healthy subjects walking first during an adaptive treadmill condition and then during a speed matched standard treadmill condition. For the same walking speed, participants significantly reduced their step length during the adaptive treadmill condition. As far as spatiotemporal parameters are concerned, to our knowledge there are no studies evaluating the effects of this type of treadmill for PD patients. Conversely, a recent study evaluated the effects of an adaptive treadmill on PD patients' LRA[115] and demonstrated that this kind of treadmill also significantly increases the LRA exponent of PD patients and does not allow the measurement of patients' "natural" LRA as measured during overground walking. These results would demonstrate that the cueing effect of the treadmill on the LRA persists despite this ecological adaptation of the rolling speed.

The second issue was addressed in the final study of this thesis. The challenge was to recreate an optic flow sufficiently realistic to give the illusion of a real one. The technology embedded in immersive VR headsets makes it possible to faithfully reproduce the elements making up a realistic optic flow. Compatible computer software makes it easy to place objects, walls, floors and ceilings in a virtual space, which can be rendered photorealistically if the computer used is sufficiently powerful. The screen inside the headset, and the Fresnel lenses used to observe it, create a striking stereoscopic 3D effect. It is thanks to this technology that the sensation of depth is conveyed. This sensation is of paramount importance in promoting the sense of self-motion experienced in a real environment, with objects moving towards or away from us as we move. Only with this rendering can exteroceptive and

exproprioceptive information be offered to the patient in a realistic way. In our study, the only difference between standard treadmill walking and VR treadmill walking was the addition of optic flow. Unfortunately, our results did not allow to compare the overground condition with the VR condition for spatiotemporal parameters. It is therefore impossible to know whether this captured the patients' natural spatiotemporal parameters. On the other hand, with regard to LRA, we observed a return of LRA at a level similar from those overground. Even if our pilot study was modest, with few patients, it enables us to establish hypotheses that should be confirmed in the future.

Therefore, our conclusion is that the lack of optic flow could potentially have the greatest influence on LRA on the treadmill rather than the imposed speed of the treadmill. However, no conclusions can be drawn regarding spatiotemporal parameters at present. Future studies should seek to define the effects of adding realistic optic flow during treadmill walking on the overall gait parameters of PD patients for comparison with overground walking including kinematic, kinetic, electromyographic and energetic metrics. If our results are confirmed for other parameters, this could enable patients to be assessed ecologically and safely using quantified laboratory gait analyses to monitor the efficacy of given treatments. Another interesting subject of study would be to assess PD patients' gait during two conditions:

1) Walk on a fixed-speed treadmill with a fixed-speed optic flow in VR
2) Walk on an adaptive speed treadmill with VR optic flow whose speed also adapts in real time to the speed of the treadmill.

Perhaps this would be another step towards a more ecological treadmill walking.

While it is known that kinematic, kinetic, electromyographic and energetic metrics are similar between overground and treadmill walking for young healthy subjects[304], less is known about PD. This was not discussed in our study as it was subjective, but it seemed to us that during the experimentations, some patients visually presented with a better “quality of gait” when using VR on the treadmill (upright posture, more natural arm swing, less “tense” gait with better hip and knee flexion, etc.). Some participants also expressed this fact subjectively, explaining that it felt more natural to walk with optic flow than without. No scientific conclusions can be drawn from these observations, and it was not systematically assessed during our tests. Nevertheless, we feel that a study of gait biomechanics by means of a proper quantified gait analysis should be carried out in the future, to further investigate the effects of adding optic flow during treadmill walking.

Another research angle would be to reproduce what Schubert et al (2005)[86] have done, but with our sophisticated ecological VR optic flow. The idea would be to play with the speed of the applied optic flow (faster or slower than the patient's walking speed) or even the direction (forward or backward) and determine the effects on the patient's spatiotemporal parameters and gait variability.

With regard to the potential for rehabilitation of the combination of VR optic flow and treadmill walking, it would be interesting to offer gait retraining that would enable the patient to deal with an essential ecological element such as optic flow. The combination of treadmill and optic flow in VR would make it possible to train the patient safely by offering a high number of repetitions during long ecological walking sessions. A RCT was planned as part of this research project but could not be carried out due to the COVID-19 health

crisis. The aim of this clinical study was to compare the effects of standard treadmill treatment on spatiotemporal parameters but also - and this has never been done - on LRA with the effects of our combination of treadmill and optic flow in VR. Although LRA were increased when walking on a treadmill without optic flow, suggesting possible greater therapeutic efficacy, it seems unintuitive to retrain PD individuals to walk without the visual element on which they rely most to regulate their gait and thus their balance. Another idea would be to use our VR environment as a basis and build a genuine exergame around it to work on patients' dynamic balance, by adding dual-tasking.

One technology to rule them all: VR as the "perfect cueing machine"

Beyond the creation of an optic flow, and with a view to bringing together the concepts of the three chapters of this thesis, immersive VR has the potential to become the "perfect cueing machine". Indeed, VR hardware can provide visuals (optic flow, discrete visual cues), as well as spatialized sound in relation to the virtual environment (discrete sounds, continuous music) and finally vibratory haptic feedbacks via the gamepads provided, which can be attached to any part of the body. Staying with somatosensory cueing, we have already seen that VR can also be combined with treadmill walking. Moreover, adaptive multidirectional treadmill are currently being developed, and should enable even more ecological treadmill walking (Figure 6.10). With these observations, it is easy to imagine the creation of all kinds of cues, used in combination or not, modulable at will via a software interface designed for, and configurable in closed-loop or not via the motion detection built into the hardware itself. Similarly, to add exproprioceptive information, it is possible to model lower limbs digitally. With just a few lines of code, the possibilities

are endless. Studies have looked at the combination of several cueing types, proposing mutltisensory stimuli, with contrasting results.[100,305–309] However, to our knowledge, no study has evaluated the effect of multisensory cueing on PD patients' LRA.

The prospect of being able to modulate the types of cueing at will using immersive VR opens up the field of possibilities for evaluating the effects of various cueing combinations on spatiotemporal parameters and temporal organization of stride duration variability in PD.

Figure 6.10. *A muldirectional treadmill compatible with immersive VR headsets (Infinadeck: https://www.infinadeck.com/).*

Perspectives for future research

Although many prospects for future studies have been mentioned throughout this general discussion section, it seems appropriate to discuss here the future research we would like to carry out as a direct continuation of what has been proposed in this doctoral thesis.

First of all, it should be remembered that the results obtained in Chapters 1, 2 and 4 were obtained on patients without freezing of gait, an important and significative sub-group of patients. Similarly, most of the patients included were mildly to moderately affected by the pathology (ability to walk for at least 256 strides), so it does not seem possible to generalize our results to more severely affected patients presenting or not with freezing of gait. We therefore intend to test our different protocols on more severely affected patients, with or without freezing of gait.

We would like to evaluate the importance of LRA as a follow-up outcome alongside other parameters such as stride length and walking speed. Many transversal studies, such as ours, have looked at the direct change in LRA under specific conditions. None of them has really looked at sensitivity to change in this parameter over the long term, after rehabilitation treatment. It therefore remains complicated both to measure LRA in routine clinical practice and to recommend it as a follow-up outcome in its own right. We believe that more work is needed on this point to establish the real clinical usefulness of LRA measurement in the follow-up of PD patients.

One element that particularly caught our attention was the interpersonal difference in results in Chapter 1, with some patients benefiting more from vibrotactile cueing and others from auditory cueing concerning linear and

non-linear gait measurements. We believe it is important to find out what makes a patient benefit more from one type of cueing than another: are somatosensory/auditory/visual disorders important in deciding which type of cueing to apply? How can these deficits be rapidly assessed in routine practice, so that patients can be offered one type of cueing rather than another? Does a patient's personal preference for a particular cueing influence the effect of this cueing on their gait?

The subject of synchronization to cueing also seems to us to be important to develop. We would like to explore further the question of whether or not the patient should be asked to synchronize to the cues: does this influence the LRA? How important is the patient's preserved ability to synchronize to cueing on the LRA?

From a personal point of view, the part I enjoyed most during my thesis was learning how to develop my own VR game. The study in Chapter 3 also enabled us to see the insufficient rigor applied when creating the serious VR games used in previous studies. My wish would be to create an immersive VR exergame adapted to PD patients, accepted by them, validating neurorehabilitation criteria and meeting existing guidelines for PD rehabilitation. The aim would then be to be able to use it with patients as part of a clinical study.

With regard to the addition of optic flow during treadmill walking, we are relatively convinced that this addition enables the patient to recover a gait quality close to that observed on the ground, beyond the LRA. This would need to be objectivized by means of a quantified gait study. If we could confirm that the gait parameters assessed are indeed similar to those measured

during overground walking, this would improve the validity of PD patients' gait study during treadmill walking.

Finally, and this was initially planned as part of this thesis, we would like to compare the effects on linear and non-linear gait measures of a treadmill treatment (gold standard) with a treadmill treatment adding an optic flow via a randomized controlled trial. Through our study, we now know the direct effect of walking on a treadmill with a VR optic flow, but we do not know the medium- and long-term effects. The aim would be twofold: 1) to determine for the first time whether treadmill treatment can achieve long-term improvement of LRA and 2) to determine whether adding an important ecological element to patient walking such as optic flow could further improve a gold standard such as treadmill walking for treating PD patients' gait.

Conclusions

In this PhD thesis, we have further developed our knowledge on the effects of different types of external stimulations, including cueing, on spatiotemporal gait parameters and, more importantly, on the temporal organization of stride duration variability (LRA computation) in PD patients.

Vibrotactile cueing had never been evaluated for its potential effects on PD patients' LRA and appears to have similar effects to auditory cueing regarding this outcome.

Where the most used frequency of auditory cueing is isochronous in research and clinical practice, our work demonstrates that it degrades LRA. Likewise, applying structured variability according to LRA to the frequency of cueing could be a better way to administer this type of cueing.

Vision can be manipulated using VR headsets. We showed via our meta-analysis that VR rehabilitation improves balance in PD patients. Secondly, we knew that treadmill walking substantially altered LRA in PD patients, making its study biased in the laboratory. By adding ecological optic flow in virtual reality during treadmill walking, we were able to measure LRA similar to those measured on overground in a natural environment, increasing the validity of this measurement in a laboratory setting.

This PhD thesis provides additional information on the effects of somatosensory, auditory, visual external stimulations on temporal organization of stride duration variability (LRA computation) among PD patients. This work should stimulate future longitudinal clinical trials to study the effects of cueing rehabilitation on the LRA present in PD patients' gait.

List of abbreviations

10MWT: 10 Meters Walking Test

6MWT: 6 Minutes Walking Test

ABC-Scale: Activities-specific Balance Confidence scale

AC: Activity

ANOVA: ANalysis Of Variance

AO: Action Observation

ARAS: Autocorrelated Rhythmic Auditory Stimulations

ARFIMA: Autoregressive Fractionally Integrated Moving Average

BBS: Berg Balance Scale

BDI: Beck Depression Inventory

BE: Bicycle Exercise

(Mini-) BESTest: (Mini) Balance Evaluation Systems Test

BF: Body Function

BT: Balance Training

CC: Control Condition

CPG: Central Pattern Generators

CSRT: Choice Stepping Reaction Time test

CT: Conventional Therapy

CV: Coefficient of Variation

D: Dosage

DASH: Disabilities of the Arm, Shoulder and Hand

DFA: Detrended Fluctuation Analysis

DGI: Dynamic Gait Index

EF: Explicit Feedback

EQ-5D: Euro-Quality of life 5 Dimensions questionnaire

FES: Functional Electrical Stimulation

FES-I: Fall Efficacy Scale-International Questionnaire

FGA: Functional Gait Assessment

FOGQ: Freezing Of Gait Questionnaire

FRT: Functional Reach Test

FSS: Fatigue Severity Scale

GAT: Gait Adaptability Test

GOP: Goal-Oriented Practice

GRADE: Grading of Recommendations Assessment, Development and Evaluation

H&Y: Hoehn & Yahr scale

ICF-WHO: International Classification of Function, disability and health – World Health Organization

ID: Increased Difficulty

IF: Implicit Feedback

IRAS: Isochronous Rhythmic Auditory Stimulations

iVR: immersive Virtual Reality

iVRTW: immersive Virtual Reality on Treadmill Walking

LOS: Limit Of Stability test

LRA: Long-Range Autocorrelations

MBI: Modified Barthel Index

MDRT: MultiDirectional Reach Test

MDS-UPDRS: Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale Revision

MES: Modulate Effector Selection

MFES: Modified Falls Efficacy Scale

MFI: Multidimensional Fatigue Inventory

MI: Motor Imagery

MMSE: Mini-Mental State Examination

MoCA: Montreal Cognitive Assessment

MP: Massed Practice

MRI: Magnetic Resonance Imaging

MS: Multisensory Stimulation

MSL: Maximum Step Length

NDT: NeuroDevelopmental Treatment

NFOGQ: New Freezing Of Gait Questionnaire

NI: No Intervention

NSVR: Non-Specific Virtual Reality

OLS: One-Leg Stance test

OW: Overground Walking

PEDro: Physiotherapy Evidence Database

PD: Parkinson's Disease

PDQ-39: Parkinson's Disease Questionnaire – 39

PDQ-8: Parkinson's Disease Questionnaire – 8

PICOS: Patients/Population, Intervention, Comparator, Outcomes, Study design

PIGD: Postural Instability and Gait Disorder

PP: Participation

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

RAS: Rhythmic Auditory Stimulations

RC: Rhythmic Cueing

RCT: Randomized Controlled Trial

RoB-2: Cochrane's Risk of Bias tool 2

RRAS: Random Rhythmic Auditory Stimulations

RVS: Rhythmic Vibrotactile Stimulations

SD: Standard Deviation

SDMT: Symbol Digit Modalities Test

SE-ADL: Schwab and England Activities of Daily Living scale

SF-36: medical outcomes study Short Form - 36

SI: Social Interaction

SIBT: Sensory Integration Balance Therapy

SMD: Standard Mean Difference

SOT: Sensory Organisation Test

SP: Spaced Practice

SRT: Sitting-Rising Test

SSQ: Simulator Sickness Questionnaire

SVR: Specific Virtual Reality

TAT: Tinetti Assessment Tool

TMT: Trail Making Test

TSP: Task-Specific Practice

TT: Treatmil Training

TUG: Timed-Up and Go

TVF-A/F/V: Tests of Verbal Fluency Animals/Fruits/Vegetables

TW: Treadmill Walking

UPDRS: Unified Parkinson's Disease Rating Scale

VP: Variable Practice

VR: Virtual Reality

VRT: Verbal Reaction Time

WE: Walking Exercise

WHODAS-2.0: World Health Organization Disability Assessment Schedule 2.0

YSD: Years Since Diagnostic

Supplementary materials

Supplementary material 4.1. PRISMA Checklist.

Available here:

https://mega.nz/file/au4CwCpR#ibLFiTjF97mhnj0-y1hS-nbtAkpEVSR_AYn0BHuEPg0

Supplementary material 4.2. Search strategy.

Available here:

https://mega.nz/file/njgUTBCJ#aDmgw-ZGSKbppKNjHDbcRNmV2Q9mZArEXj-4W999ydg

Supplementary material 4.3. International Classification of Functioning – World Health Organization (ICF-WHO) categories.

Available here:

https://mega.nz/file/qvg1GQIa#U3CDFPIJ5FKVVZPw4YX-F4IfbJfES-Pcuxi0Rkwu2Dc

Supplementary material 4.4. Definition and description of the neurorehabilitation principles.

Available here:

https://mega.nz/file/H7pG2LQA#d46gz92I7y2BweioN9kq0dXGsy5fMbz1mJFVSVsumwM

Supplementary material 4.5. Sensitivity analysis.

Available here:

https://mega.nz/file/H6xihABC#iiHyH0ak1L6hvYi_nrrfqR5spGvnbG0zyeIbDDZOeQ0

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