Gait in Parkinson's Disease

Lead Guest Editor: Daniel Martinez-Ramirez
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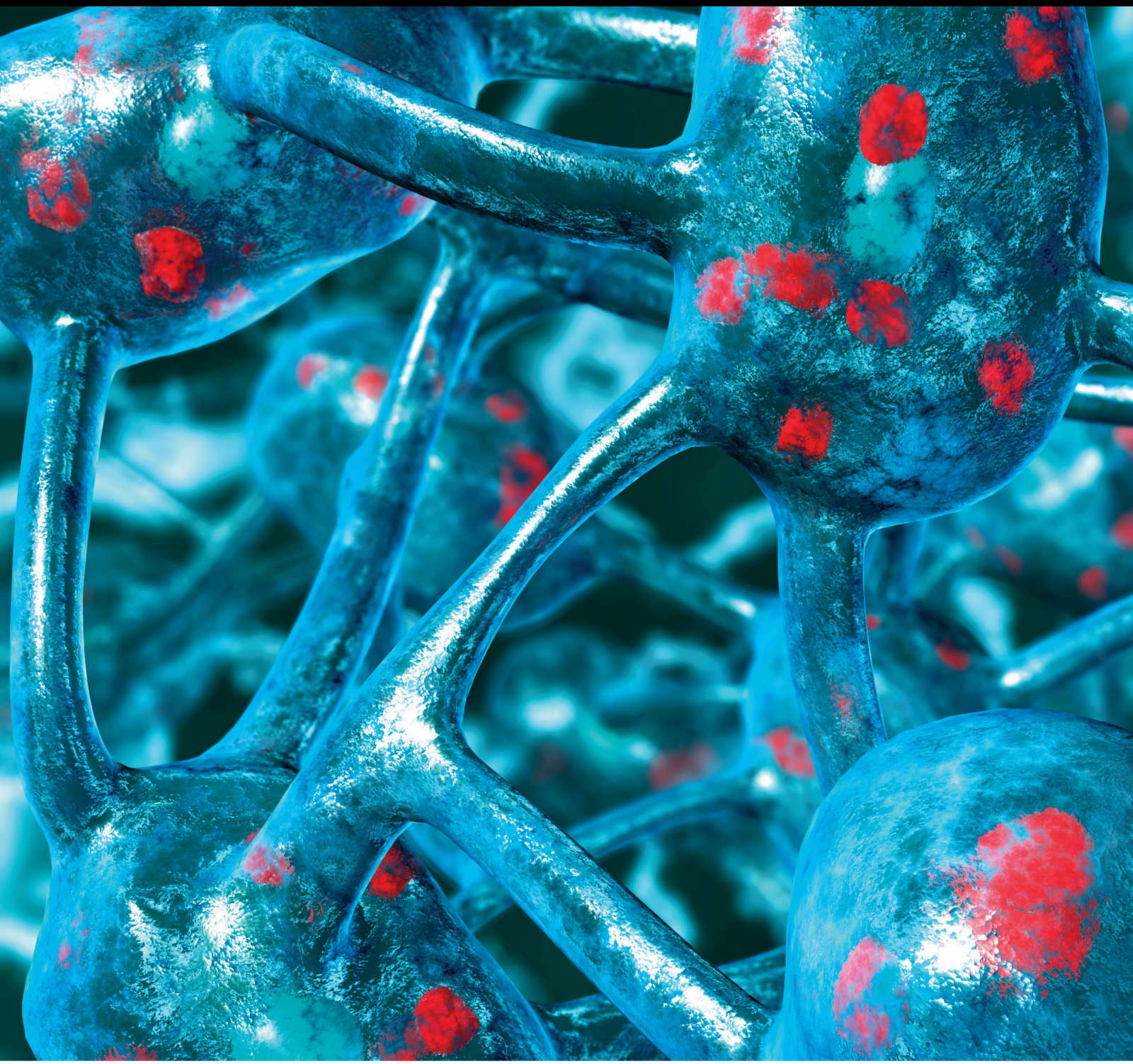

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Editorial Board

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Editorial
Gait in Parkinson's Disease

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Parkinson's disease (PD) is the second most common neurodegenerative disorder and its incidence is expected to double by 2030 worldwide. PD is characterized by a variety of motor and nonmotor symptoms caused by dysfunction of multiple interconnected brain circuits. As the disease progresses, gait and balance symptoms become increasingly problematic, greatly affecting patient's quality of life. These symptoms increase patient's risk of falls and related complications such as hospitalizations and fractures. Gait difficulties in PD are one of the most difficult symptoms to manage. While optimization of dopaminergic drugs and physical therapies are currently the main treatments, additional therapeutic interventions are needed to help patients and prevent complications. Increasing understanding of gait difficulties in PD patients is one of the greatest needs in the field.

In this special issue titled "Gait in Parkinson's Disease," a total of 13 manuscripts were submitted, from which 5 were accepted for publication (3 experimental and 2 observational studies). The topic attracted original articles investigating a broad range of topics from clinical research to technological advances and therapies for gait difficulties in PD patients.

J. Ma and colleagues examined the working mechanism of repetitive transcranial magnetic stimulation (rTMS) on freezing of gait (FoG) by studying the sequence effect in 28 PD patients in an experimental, controlled, randomized study. The sequence effect was defined as the progressive decrease in amplitude of the sequential movements characteristic in PD patients. Patients received either real or sham 10-Hz rTMS over the supplementary motor area for ten sessions over two successive weeks. Results of the primary outcome showed that rTMS did not improve the sequence effect. However, a transient beneficial effect was observed on FoG and other gait parameters including ambulation time, cadence, step count, and velocity gait. The authors conclude that other mechanisms of how rTMS works, besides improving the sequence effect, should be explored. This study has in the experimental design its most important strength. In addition, this is the first study investigating the role of rTMS on sequence effect. Still, several important limitations must be considered including the study sample size. Research investigating the effects of rTMS in FoG began over a decade ago and continues to be an active field in neuromodulation [1]. A recent meta-analysis by Y. W. Kim et al. reported significant improvement in the freezing of gait questionnaire (FOG-Q) scores, but no differences in the Unified Parkinson's Disease Rating Scale (UPDRS) scores with rTMS when compared with placebo [2]. Evidence supports the role of rTMS in the treatment of PD, but further studies are required to elucidate and determine its mechanism of action, the optimal stimulation site, stimulation parameters, and duration and number of stimulation sessions [3–7].

R. Marsh and colleagues studied the benefits of visual cueing on FoG in an experimental uncontrolled study of 20 PD patients. During a two-minute walk and an obstacle course, results showed an improvement in distance walked during the two-minute walk test when a cueing device was on phasic and tonic modes. The tonic visual cueing demonstrated superiority over the phasic visual cueing.

However, this benefit was not observed during the obstacle course. Although different wearable visual cueing devices have shown improvement on FoG episodes in PD patients [8], few studies have studied the effect of different modes of visual cueing. The strength of the study is the novel approach used to experiment with two patterns of visual cueing, phasic and tonic patterns. However, not having a control group and sample size are important limitations to consider. Further studies are required to clarify the role of different visual cueing modes on FoG.

K. Sato and colleagues studied the clinical benefits of rehabilitation after DBS surgery. An experimental uncontrolled study was planned to examine the effect of two weeks of rehabilitation on gait and postural instability of PD patients following STN-DBS surgery. Sixteen patients were analyzed retrospectively. Rehabilitation was focused on muscle strengthening with stretching and balance training. Results showed an improvement in balance measured by Mini-BESTest and gait measured by Timed "Up and Go" (TUG) test when compared to baseline evaluations. The role of rehabilitation therapies shortly after deep brain stimulation (DBS) surgery is unknown, since most evidence focuses on longer term management. This study adds to a better understanding and timing of the role of PT after DBS for PD or other movement disorders. However, the uncontrolled design of the study and sample size are important limitations to consider. Recently, N. Allert et al. discussed and highlighted the importance of a coordinated therapy within a multidisciplinary team to achieve maximal results after DBS therapy. Still, guidelines in the postoperative rehabilitation management of these patients are required [9].

B. Muñoz-Ospina and colleagues studied the effects of aging in gait in an observational cross-sectional comparative study using the Microsoft Kinect sensor camera in 30 PD patients compared with 30 age-matched controls. Results demonstrated that PD patients exhibited prolonged swing and stance times and lower speed values compared to controls. However, this was not observed in the group of 76–88 years old. The authors concluded that the consequences of age in gait of PD patients should also be considered when approaching these patients. The strength of the study is the use of 3D gait analysis in patients compared to controls; however, the cross-sectional design of the study is a limitation to consider since a cause-effect relationship is not possible to consider. Despite the study design, the authors provide reasons to be optimistic in the use of technology to better analyze gait in PD patients. This can increase our understanding and knowledge on how to focus therapy [10].

Finally, C. Geroin and colleagues assessed the effects of axial deformities such as camptocormia on gait. The authors conducted an observational, cross-sectional comparative study to compare gait parameters, gait variability, and asymmetry and postural control of 46 PD patients with and without camptocormia. The study demonstrated that lower trunk camptocormia was associated with more severe gait and postural impairment. PD deformities are important to consider when analyzing and providing therapy for gait problems. Recent studies using 3D gait analysis have shown reduced movements in the hip and knee joints of patients with camptocormia [11]. The present study provides important information with regards to postural deformities of the lower trunk and its possible negative impact on gait. However, studies with better design are required to establish a more direct cause-effect relationship. Despite these limitations, results suggest that technology can be used to better define camptocormia in order to provide individualized therapies.

In summary, we hope that this special issue brings new insights into the latest advances in the diagnosis, treatment, and pathophysiology of gait difficulties in PD. We hope this new information will help other researchers pave the way for the development of strategies to help PD sufferers.

Conflicts of Interest

Guest Editors report no conflicts of interest.

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Research Article

Music and Metronomes Differentially Impact Motor Timing in People with and without Parkinson's Disease: Effects of Slow, Medium, and Fast Tempi on Entrainment and Synchronization Performances in Finger Tapping, Toe Tapping, and Stepping on the Spot Tasks

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Introduction. Rhythmic auditory stimulation (RAS) has successfully helped regulate gait for people with Parkinson's disease. However, the way in which different auditory cues and types of movements affect entrainment, synchronization, and pacing stability has not been directly compared in different aged people with and without Parkinson's. Therefore, this study compared music and metronomes (cue types) in finger tapping, toe tapping, and stepping on the spot tasks to explore the potential of RAS training for general use. *Methods*. Participants (aged 18–78 years) included people with Parkinson's ($n = 30$, Hoehn and Yahr mean = 1.78), older ($n = 26$), and younger adult controls ($n = 36$), as age may effect motor timing. Timed motor production was assessed using an extended *synchronization-continuation* task in cue type and movement conditions for slow, medium, and fast tempi (81, 116, and 140 mean beats per minute, respectively). *Results*. Analyses revealed main effects of cue and movement type but no between-group interactions, suggesting no differences in motor timing between people with Parkinson's and controls. Music supported entrainment better than metronomes in medium and fast tempi, and stepping on the spot enabled better entrainment and less asynchrony, as well as more stable pacing compared to tapping in medium and fast tempi. Age was not confirmed as a factor, and no differences were observed in slow tempo. *Conclusion*. This is the first study to directly compare how different external auditory cues and movement types affect motor timing. The music and the stepping enabled participants to maintain entrainment once the external pacing cue ceased, suggesting endogenous mechanisms continued to regulate the movements. The superior performance of stepping on the spot suggests embodied entrainment can occur during continuous movement, and this may be related to emergent timing in tempi above 600 ms. These findings can be applied therapeutically to manage and improve adaptive behaviours for people with Parkinson's.

1. Introduction

Studies comparing people with and without Parkinson's disease suggest it is the loss of the dopamine-producing cells in the substantia nigra in the basal ganglia that results in the impairment of time perception and internally generated timed motor production abilities [1–7]. Although medication regimens help manage symptoms, they are not necessarily effective for improving deficits in gait, such as shuffling, step irregularity, freezing, and postural instability,

for example [8, 9]. Such difficulties with walking are detrimental to the quality of life experienced by people with Parkinson's, not least because the deficits often lead to falls, which can in turn contribute to further physical and psychological health problems [10, 11]. Consequently, finding adjunct therapies to improve gait is a priority for Parkinson's-related research [12–14].

One avenue of investigation, based on findings from neuroimaging studies, has focused on how external sounds can prime the movement areas in the brain for action [15–18]. Researchers in neurologic music therapy have operationalized this as rhythmic auditory stimulation (RAS [19]). The therapeutic strategy involves recruiting the connections between the auditory and motor systems by using metronomes or rhythmically enhanced familiar music (commonly a metronome embedded into the music) to provide the external cues to improve gait. These improvements are manifested in observable positive outcomes such as regulating cadence and increasing gait velocity and stride length (e.g., [20] and see [13, 17, 21, 22] for reviews). The phenomena enabling these beneficial changes include *entrainment*, *synchronization*, and *pace stabilization*.

Entrainment is the general phenomenon of moving the body to the pace of regular cue (such as metronome or music in the auditory sense) without specifically synchronizing each motor element to a discrete beat. This has been described as the "propensity to latch on to an [even] pulse ... making human music and allied arts of dance and drill a privileged form for the exercise of our entrainment capacity" ([23], p. 7).

Entrainment is a skill that infants gradually learn. Up to the age of two, infants do not tend to adjust their movement to tempo of music with which they are engaged [24, 25]. Children then steadily improve their entrainment capacity until the age of puberty [23]. In adults, although gait characteristics are known to differ in older and younger people [26, 27], and that age-related conditions such as dementia affect entrainment ability [28], researchers have not yet directly compared entrainment in healthy younger and older adults and/or with people with Parkinson's for whom dementia as well as gait deficits are a concern as the disease progresses [29]. To recap, rhythmic entrainment is the ability of the motor system to couple with the auditory system and drive movement patterns [30]. This phenomenon can be measured using a percentage error calculation between interresponse intervals (*IRI % Error*), which compares mean sequential pacing frequencies between the cue and the movement [31, 32].

Synchronization is different to entrainment because it only occurs when the timing of self-initiated movements is simultaneously aligned to a specific point with the pacing source, a particular skill requiring the adjustment of sensorimotor reaction times using predictive timing (i.e., error correction), which enables the intentionally accurate coordination of such rhythmic behaviour in temporal synchrony (rather than intermittent or relative coordination [31]). As such, the accuracy of synchronization ability can be measured using Absolute Asynchrony, a direct comparison of the difference between the pacing event and the timed movement [33]. This skill can be trained [34], to a level of expertise (for example, in musicians [35] and dancers [36]). However, sensorimotor synchronization can also occur spontaneously; for example, when a person taps their toe or moves their head or body in time with music [37, 38]. Walking in time to the underlying beat of music does not necessarily occur as a natural phenomenon but can and does occur through explicit training [39].

In contrast to either entrainment or synchronization, *pace stability* reflects how similar each movement cycle is without direct reference to a cue source. It specifically measures within-subject movement variability using the *IRI coefficient of variance* (*IRI CoV* [40]). Compared to controls, people with basal ganglia dysfunction are sometimes more variable in their movements (e.g., [41–43]) though not always [44].

These distinctions are important as although RAS has primarily been used for gait rehabilitation, it is possible that understanding how the underlying mechanisms of these phenomena work in Parkinson's (and other pathologies) may help us extend the principles of RAS therapy to other paced movements [45, 46]. For example, metronome RAS has also been used to decrease variability in rhythmic timing of arm and finger movements [47, 48]. However, Grahn and Rowe [49] have suggested the richness of the cue may provide better guidance for movement. Furthermore, de Dreu et al. [50] and Overy [51] have suggested that there may be an additional advantage of engaging in group synchrony, in which locomotor movements are performed "in place," i.e., as a form of dancing (or "footfall stomping" according to [23], p. 7). Dancing has been shown to ameliorate some motor (and nonmotor) symptoms for people with Parkinson's [52–54]. Dancing generally encompasses some organized rhythmic relationship between sound and movement, and understanding whether the mechanism of RAS is present (i.e., measurable in terms of entrainment and synchronization), at least at a basic level would further support these findings.

However, entrainment, synchronization, and pace stability are tested experimentally using a finger tapping synchronization-continuation task (for a review, see [31, 55]). The synchronization-continuation task begins with paced sensorimotor synchronization (i.e., tapping in time to stimuli usually for 30 secs) directly followed by a similar duration of continuous finger tapping without the stimuli (i.e., unpaced, see [40] for full theoretical description). The optimal rate for spontaneous human movement occurs in cycles between 500 and 600 ms [56], a phenomenon described as the 2 Hz human resonance theory [57] observed in various movements such as walking and clapping and also associated with a preferred tempo in music [58]. Although in general sensorimotor synchronization performance is better when the tempo of the stimuli is within this specific range, research has shown that pathology affects performance related to both the perception and production of timing [59, 60].

In Parkinson's studies specifically, Jones and Jahanshahi [6] reviewed research related to perceptual and motor timing tasks and found mixed results. The performance of people

with Parkinson's was compromised in 60% of the nine perceptual timing studies analysed, 50% of time estimation tasks (two of the four studies analysed), and 67% of the time production tasks (i.e., eight of the twelve finger-tapping studies). Furthermore, tempo was an influencing factor in the studies they compared, with performance only impaired in people with Parkinson's at tapping rates faster than 500 ms. In addition to behavioural studies, Grahn and Brett [3] conducted a neuroimaging study which showed that beat perception is impaired in people with Parkinson's when comparing nonmusical beat-based stimuli to nonbeat stimuli in a discrimination task. However, Grahn [61] suggested that music may provide additional dynamic properties that may ameliorate this deficit. A further study confirmed that when the beat is embedded in musical excerpts, people with Parkinson's perform the same as controls (when ON (ON and OFF are terms commonly used to describe when a person with Parkinson's is dopaminergically medicated or not) medication [62]).

Music and metronomes offer different properties as auditory cues. Metronomes are repetitive regular nonmusical sound events experienced as a continuous stream [63]. However, they are not memorable, even by trained musicians [64]. In contrast, the underlying beat of music is memorable [65, 66]. Interestingly, in an early RAS study, Thaut et al. ([20], p. 199) reported that some people with Parkinson's reported "pacing themselves by singing the music silently" suggesting the ability to endogenously generate pacing cues in the absence of external auditory cueing. Additionally, music is known to have an effect of affective states [67], and when experienced as having "groove," it is able to induce the urge to move [38, 68]. These properties on music may affect RAS in different ways, for example, by increasing the ability to synchronize, by helping maintain entrainment, by increasing the intention or motivation to move, by reducing perceived fatigue, or potentially by improving adherence to interventions by making "permanent cueing regimens more pleasant" [69–71]. Although music and metronomes have yet to be directly compared as pacing cues in people with Parkinson's, Leow et al. [71] did compare music with high and low groove (a subjective percept related to connection between hearing the music and wanting to move [68]), and metronomes as pacing cues for walking in neurotypical adults. The findings suggested that metronomes supported synchronization accuracy better than high-groove music, with the most asynchrony associated with low-groove music. As music has been found to be distracting in Parkinson's studies due to additional cognitive demand effects [1, 72], it would be useful to compare the effect of cue types on measures of RAS directly in people with and without Parkinson's disease.

McPherson and colleagues [73] have suggested more research is needed to understand which components (which sound cues, which types of movements, and at which tempi) produce the therapeutic effects in terms of motor rehabilitation. Therefore, the first aim of this study was to directly compare metronomes and ecologically valid music in terms of entrainment capacity (*IRI % Error*), synchronization accuracy (Absolute Asynchrony), and pacing stability (*IRI CoV*). The second aim was to compare the different types of movements in order to explore the potential for RAS beyond gait training and/or the experimental paradigm of finger tapping. To undertake this research, we devised a study in which we could compare the effect of cue types (music and metronomes in slow, medium, and fast tempi) on entrainment, synchronization, and pacing abilities in finger tapping, toe tapping, and stepping on the spot in older and younger healthy adults and people with Parkinson's. Our hypothesis were as follows:

H_1: music will support entrainment better than metronomes for people with Parkinson's as measured using IRI % Error across the synchronization-continuation task, particularly in the medium tempo

H_2: Absolute Asynchrony will be affected by tempi, and people with Parkinson's will perform significantly worse than control groups in the slow tempo metronome condition due to the deficits in their predictive timing abilities

H_3: people with Parkinson's will perform better when stepping on the spot in comparison with finger and toe tapping (i.e., not significantly different from controls, less IRI % Error, Absolute Asynchrony, and IRI CoV)

2. Methods

This study investigated the effect of cue type (music and metronome) and movement modality (finger tapping, toe tapping, and stepping on the spot) on entrainment capacity, synchronization ability, and pacing stability using a synchronization-continuation task. The synchronization-continuation task was extended with a "re-synchronization" section to provide a second set of synchronization data, thereby reducing the demand on participants with Parkinson's and also to provide an enjoyable "game-like" task with positive feedback for participants with Parkinson's in terms of their ability to engage with the different types of movements and auditory cues.

The between-subject factor was a group including people with Parkinson's (Parkinson's) and two healthy adult control groups (younger and older) with age as a potential factor based on equivocal findings in the literature. The older participants were age matched to the Parkinson's group (Section 2.1). The choice of ecologically valid music as cue types was included to differentiate from the auditory cues typically used in RAS therapy (i.e., metronomes and "rhythmically enhanced music") so as to investigate the general use of music for people with Parkinson's as this may be more accessible in general and helpful to practitioners. The three movement modalities were chosen to enable comparison between strike-based type data from finger-tapping studies during which there is no forward motion in that type of nonspatial "tapping." In order to find common ground between finger tapping and RAS gait studies, "stepping in the spot" represented the type of "in place" locomotion or footfall stomping previously suggested [23, 73]. The "stepping in the spot" action requires whole body movement similar to drill and incorporates that aspect

of "dancing," though with reduced degrees of freedom in movement. Tempo was an independent variable nested within stimuli (range 779–417 ms). The range of tempi was chosen to reflect the typical range of music that people move to [58, 74] but was partially constrained by choice of using only instrumental naturalistic music with a strong beat perceived in agreement through pilot testing (Section 2.2.2). This study was approved by the Health, Sciences, Engineering and Technology ECDA (Ethics Committee with Delegated Authority; Protocol Reference aLMS/SF/UH/02547) at the University of Hertfordshire. All participants provided written informed consent prior to the beginning of the study in accordance with the recommendations of the Helsinki Declaration.

2.1. Participants. In total, 92 participants between 18 and 80 years completed the study. The sample was split into three groups: Parkinson's: $n = 30$, 20 females, mean age = 62.23 (SD = 10.48), range 34–77 years, and the two healthy adult control groups: younger: $n = 36$, 29 females, mean age = 20.75, SD = 3.18, range 18–32 years and older (age matched to the Parkinson's group), $n = 26$, 12 females, mean age = 64.35, SD = 13.02, range 32–78 years. Participants were recruited through Parkinson's UK research network as well as through connections with the institution's Parkinson's Advisory Group and Dance for Parkinson's class. The younger group was recruited through the institution and received course credits for participation. The exclusion criteria included cognitive impairment assessed using the Mini Mental State Examination (<24 score, [75]). Participants were also asked whether they had any hearing difficulties. No participants were excluded on any of these bases.

Parkinson's group were tested during the "ON" state of their stabilized medication, and all Parkinson's participants confirmed they were diagnosed by a neurologist. The Unified Parkinson's Disease Rating Scale (UPDRS [76]) was used to evaluate their current status. The group UPDRS mean was 25.57 (SD = 10.15, range = 1–50 (max = 176)). Scores for the three factors that make up to overall scores were as follows: mentation, behaviour, and mood (mean = 3.5, SD = 1.68, range = 1–8 (max = 16)); activities of daily living (mean = 10.43, SD = 4.68, range = 0–21 (max = 52)); and motor examination (mean = 11.63, SD = 5.64, range = 0–25 (max = 108)). The range for this sample for the Schwab and England Activities of Daily Living Scale [77] was 50–100% and mean = 82.33% (SD = 11.94). The Hoehn and Yahr Scale [78] mean was 1.78 (SD = 0.83), ranging from 0 to 4 (max = 5). Time since diagnosis ranged from 5 months to 21 years, averaging just over 5.6 years (SD = 59.19 months). Participants were asked to report their current medication regimens. Though these data were not used in analyses, a summary of these can be found in Supplementary Table 1.

2.2. Equipment, Stimuli, Procedure, and Measures

2.2.1. Equipment. A stomp box (used by musicians to provide bass drum sounds, generally in acoustic music) (Acoustim8, Series 100 Foot Drum, UK) was used to collect finger- and toe-tapping data in order to provide an ergonomically appropriate way of collecting tapping data and enable quick and easy transition between finger (table) and toe (floor) tapping, thereby reducing experimental demand for people with Parkinson's.

BioPac heel and toe strike transducers (Model RX111) attached to BioNomadix ankle sensors (Model BN-TX STRK2-T) gathered press and release data for stepping "on the spot" (Figure 1). The experiment was ran on Superlab software (Version 5, Cedrus Corporation, San Pedro, CA) connected to an MP150 (Biopac Systems Inc., CA) unit running an STP100C Solid State Relay Drive, a UIM100C (for the StompBox), and two BioNomadix STRK2-R units (for stepping). Two mixing desks were used to split and connect the stimuli (Peavey PV6 and Behringer Xenyx502). Participants self-adjusted volume levels on headphones (Studiospares Model 448740).

2.2.2. Stimuli. For the auditory cues, two types of stimuli, music and metronomes, were compared.

As dual task processing can be difficult for people with Parkinson's [1, 72], the musical stimuli chosen were instrumental excerpts (i.e., did not include any words, spoken or sung) of naturalistic music (Table 1). The metrical structure of all music was in common time (i.e., four beats in a musical bar). The aim of the music selection was to include songs that would be both familiar and unfamiliar across the participant ages (the effects of familiarity and likeability, alongside the dynamic acoustic features of the musical stimuli, are presented in a separate paper, Rose et al. [79], under review) but which also had a strong beat and included 30 second instrumental sections. To this end, 28 music excerpts were pilot tested for "ease of entrainment" prior to data collection for this study. On the basis that >60% of participants ($N = 50$) agreed that the song excerpts were "easy to tap along with," nine songs were chosen for this study. The stimuli (including metronome beep tracks which were matched to each of the musical excerpts) were created in Logic Pro (Apple Inc., CA). In common with other timing studies, for all stimuli, an eight-beat "count in" section was provided (with an accented beep on the first and fifth beats) to reduce data loss caused by initial listening and movement adjustment by participants [31]. Stimuli were divided into slow, medium, and fast (Table 1) and analysed separately as various studies of timing in general and in Parkinson's have suggested tempo may be a mediating factor in motor abilities [6].

2.2.3. Procedure. The synchronization-continuation task consisted of three consecutive sections: Sync A, Continuation Task, and Sync B (i.e., resynchronization). Participants were explicitly asked to synchronize their movements to the beat of the stimuli (i.e., either finger or toe tapping or stepping on the spot) and to try to continue that same movement when the auditory stimuli stopped, and then to resynchronize (if necessary) when the stimuli restarted. Each participant completed 18 trials (9 music and 9 metronomes), three in each movement modality. Two practice examples

Figure 1: Stepping on the spot and finger- and toe-tapping equipment and actions.

Table 1: Naturalistic musical stimuli.

Song code	Tempo	Beats per minute	Interbeat interval (ms)	Song	Artist	Year of release
	Slow[a]	69	870	Moments in Love	Art of Noise	1984
Song 1	Slow	77	779	Teardrop	Massive Attack	1998
Song 2	Slow	81	741	El Condor Pasa	Leo Rojas	2012
Song 3	Slow	85	706	Bitter Sweet symphony	The Verve	1997
	Medium[a]	120	500	España Cañí	Pascual Marquina Narro	1923 (recording 2010)
Song 4	Medium	112	536	Robot Rock	Daft Punk	2005
Song 5	Medium	117	513	Axel F	Harold Faltermeyer	1984
Song 6	Medium	120	500	March of Toreadors from Carmen	Georges Bizet	1875 (recording 2011)
	Fast[a]	125	480	Get Ready for This	2 unlimited	1991
Song 7	Fast	136	441	Material Girl	Madonna	1984
Song 8	Fast	139	432	Beat It	Michael Jackson	1983
Song 9	Fast	144	417	The Beautiful People	Marilyn Manson	1996

[a]Used for practice trials only.

(first a metronome at 500 ms and then a musical example randomly assigned as either slow, medium, or fast tempo) were provided in each movement modality to ensure participants understood the task and were physically comfortable. The presentation of stimuli and movement modality were counterbalanced within-subject for each participant and between-subjects. Analysis confirmed there were no significant order effects between groups ($p > 0.8$).

2.2.4. Measures. Participants were tested for beat perception ability (beat alignment test; BAT) and musical sophistication using the Goldsmiths Musical Sophistication Index (Gold MSI, [80]), both of which are freely available as research tools. The Gold MSI is a self-report scale which was developed to investigate "musical sophistication" in the general population. This term was chosen to reflect the many ways in which people can and do engage in musical activities without necessarily becoming professional musicians and therefore enable a less hierarchical, more fine-grained approach to studying the psychological effects of music and musical behaviours. The measure has been validated on 147,636 people (see Cronbach's alpha statistics in Table 2 in Section 3). The Gold BAT is presented as an online listening task during which participants state whether the click track (i.e., isochronous tone sequence) overlayed onto naturalistic instrumental music is "on" the beat (i.e., "in time with the underlying beat of the music") or "off" the beat (i.e., asynchronous to the beat of the music). This measure has been used previously in

Table 2: Goldsmiths Beat Alignment Test and Musical Sophistication Index by group.

	Younger			Older			Parkinson's			Gold MSI Population Norms			
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Cronbach's alpha
Beat Alignment Test Scores	10.66	1.43	8–14	11.31	2.59	6–16	11.03	2.59	7–16	11.98	2.80	Chance = 8.5/17	0.67
Music Sophistication Index													
General	69.78	15.58	35–99	68.96	22.57	31–114	59.70	15.55	33–95	81.58	20.62	18–126	0.93
Musical Training Subscale	19.75	8.27	7–36	21.54	12.37	7–43	16.13	9.75	7–39	26.52	11.44	7–49	0.90
Active Engagement Subscale	36.50	9.41	18–53	34.38	11.85	15–57	31.77	7.80	16–44	41.52	10.36	9–63	0.87

Parkinson's research [61] and see Table 2 (Section 3) for previously unpublished score norms obtained in personal communication with Professor Müllensiefen, 2019 [81]. In this study, the general factor and the subscales of musical training and active engagement with music of the Gold MSI and the BAT scores were compared between groups in order to establish any group differences that might warrant including these factors as covariants.

2.3. Motor Timing Parameters. The interonset interval (IOI) refers to an audible pacing event (metronome beeps or musical beat). The interresponse interval (IRI) refers to the time interval between the onsets of two successive strikes produced by a participant. The mean IRI is commonly used to reflect the participants' capacity to accurately produce a timed motor interval [31]. The mean IOI of the stimuli classified by tempo and the mean IRI for each group are provided in Table 3.

In this study, data from the central ten bars in each of the three twelve-bar sections (Sync A, Continuation Task, and Sync B) were used in analyses. The concept of entrainment is operationalized in terms of how the auditory stimuli has been internalized by the participant, evidenced by being able to maintain their motor timing across the three consecutive sections, characterized by calculating the IRI % Error, a dependent variable demonstrating the percentage of absolute difference between each IRI and the reference IOI of a given trial (IRI % Error = (mean IRI − mean IOI)/mean IOI ∗ 100). Asynchrony is the measure of the ability to produce a rhythm that synchronizes with an expected rhythm in terms of accuracy. A second dependent variable, Absolute Asynchrony, was calculated for each strike as the time interval (in ms) between the start of the nearest sound event and the closest detected point of contact between the effectors and the tapping surface: $\text{Strike}_{\text{Start}} - \text{Pulse}_{\text{Start}}$ (see [31, 32] for similar calculations). The third dependent variable the IRI coefficient of variation (*IRICoV*) measured within-subject performance variability (i.e., pacing stability) was calculated as IRI standard deviation/IRI mean ∗ 100) (full documentation of the data extraction can be found in Rose et al. (under review)) [79].

2.4. Data Preparation. During preprocessing, trials were removed from analyses if less than 18 and more than 44 strikes were recorded in all movement modalities (i.e., 10% above or below the required number of strikes). These anomalies were due to either participant error and/or equipment failure. Table 4 shows the missing databy group, tempi, cue type, and movement modality.

Finally, a 40% criterion (deviation from interonset interval in the stimuli) was calculated to remove outliers from the *IRI* mean based on [31]. Similarly, for the Absolute Asynchrony, a 25% criterion was calculated to remove outlying data points based on [82]. This final process amounted to the loss of 7.65% data points, 7.18% for metronome stimuli, and 8.19% for music stimuli.

2.5. Statistical Analyses. Multifactorial repeated measures ANOVA were conducted by group (Parkinson's, older, and younger controls), across the three sections of the experimental paradigm for entrainment (measured using *IRI % Error*) and pace stability (measured using *IRI CoV*), and for Absolute Asynchrony using the data from Sync A and Sync B sections only in terms of comparing the strikes against the reference points in the auditory stimuli. Factors included cue type (metronomes and music) and movement modality (finger tapping, toe tapping, and stepping on the spot). Where significant main effects and interactions were observed, post hoc pairwise comparisons (Tukey HSD) further explore these data where the findings are considered meaningful in application for practitioners, although it is indicated when findings do not withstand Bonferroni adjustment for multiple comparisons (alpha $p < 0.001$). Where assumptions for sphericity were not met with these data, the Greenhouse–Geisser adjusted statistic is reported. The sample size required for the critical statistical test of each research hypothesis was calculated using $G*$ Power. Required sample size was computed for paired-samples t tests. In the estimation of effect size, the results of Dalla Bella et al. [12] were used as group parameters. The power analysis indicated that 18 participants minimum would be required per group ($dz = 0.50$; $\alpha = 0.05$; $1 - \beta = 0.80$). Furthermore, our sample size is similar to that used in other Parkinson's studies (e.g., [12] ($N = 21$), [44] ($N = 15$), [83] ($N = 18$), [20] ($N = 15$), and [84] ($N = 22$)). Effect sizes are

Table 3: Mean interonset interval of the stimuli and interresponse intervals by group for each tempo.

Tempo	Beats per minute	IOI	IRI younger mean[a] (SD)	IRI older mean[a] (SD)	IRI Parkinson's mean[a] (SD)
Slow	81.02	741.87	740.35 (31.77)	735.86 (36.14)	735.15 (52.89)
Medium	116.25	516.71	515.56 (17.10)	516.63 (19.46)	514.10 (19.33)
Fast	139.68	429.95	430.12 (10.79)	430.21 (9.89)	428.35 (14.98)

IOI, interonset interval; IRI, interresponse interval; SD, standard deviation; [a]milliseconds.

Table 4: Missing data by group, tempi, cue type and movement modality.

	Metronome			Music		
	Finger tapping	Toe tapping	Stepping on the spot	Finger tapping	Toe tapping	Stepping on the spot
Slow tempo						
Younger	0	2	1	0	2	3
Older	0	6	4	0	6	4
Parkinson's	1	2	5	1	1	3
Total *N* missing	1	10	10	1	9	10
% missing	1.09	10.87	10.87	1.09	9.78	10.87
Medium tempo						
Younger	0	2	1	0	2	2
Older	0	1	3	0	1	4
Parkinson's	0	5	7	1	4	5
Total *N* missing	0	8	11	1	7	11
% missing	0.00	8.70	11.96	1.09	7.61	11.96
Fast tempo						
Younger	1	2	3	0	1	1
Older	0	1	2	0	1	7
Parkinson's	0	4	9	1	8	5
Total *N* missing	1	7	14	1	10	13
% missing	1.09	7.61	15.22	1.09	10.87	14.13
Overall *N* missing	2	25	35	3	26	34
Overall % missing	0.72	9.06	12.68	1.09	9.42	12.32

reported as partial eta squared (interpreted as small = 0.01, medium = 0.06, and large = 0.14 according to [85, 86]). Analyses were conducted with SPSS software (v23, IBM Inc.).

3. Results

3.1. Goldsmiths Beat Alignment Test (BAT) and Musical Sophistication Index (MSI). No significant between-group differences were found for the Gold MSI general measure ($p > 0.05$), or for the subscales of musical training ($p > 0.1$), and active engagement with music ($p > 0.1$), or for the Gold BAT ($p > 0.5$) (Table 2). As the range of scores was similar to the published population norms, these data were not included in further analyses for this study.

3.2. Entrainment, Synchronization, and Pacing Stability. Table 5 presents the results for the multifactorial repeated measures ANOVA for the dependent variables (IRI % Error, *IRICoV*, and Absolute Asynchrony).

3.2.1. Entrainment: IRI % Error

(1) Cue Type. In slow tempo, no main effect or group interactions were revealed. In medium tempo, a significant main effect showed that overall participants performed with less error (i.e., closest to 0, $p = 0.002$) with music (mean IRI % Error = −0.003, SE = 0.233) compared to metronome (mean IRI % Error = −0.799, SE = 0.152). The mean difference between cue types was ±0.796, ms, $p = 0.002$, and CI ± 0.315–1.276. The effect size of this result was large, and as Figure 2 shows the direction of error differed for metronome (negative) and music (positive). No interaction between groups was revealed in this tempo. In fast tempo, a significant main effect showed that overall participants performed with less error with metronome than with music. Pairwise comparisons showed the mean difference between cue types in the fast tempo was ±0.793 ms, $p = 0.001$, and CI ± 0.361–1.225. The metronome mean was negative at −-0.352 ms and SE = 0.198, whereas the music was positive, 0.441 ms and SE = 0.347. Figure 2 illustrates how the effect of auditory cueing is most observable during the continuation task section of the experimental paradigm.

Repeated measures ANOVA results revealed the following:

For slow tempo, no effect main effect ($p > 0.1$) or group interaction ($p > 0.3$)

For medium tempo, a main effect $F(1, 62) = 10.966$, $p = 0.002$, and $\eta_\rho^2 = 0.150$, and no group interaction ($p > 0.2$)

Table 5: Repeated measures ANOVA results for modality and cue type by tempi.

	IRI % Error	IRICoV	Absolute Asynchrony
Cue type			
Slow			
Main effect	ns, $p > 0.1$	ns, $p > 0.7$	$F(1, 43) = 26.544$, $p < 0.001$, $\eta_p^2 = 0.382$
Group interaction	ns, $p > 0.3$	ns, $p > 0.5$	$F(2, 43) = 3.692$, $p = 0.033$, $\eta_p^2 = 0.147$
Medium			
Main effect	$F(1, 62) = 10.966$, $p = 0.002$, $\eta_p^2 = 0.150$	$F(1, 62) = 6.785$, $p = 0.011$, $\eta_p^2 = 0.099$	$p > 0.6$
Group interaction	ns, $p > 0.2$	ns, $p > 0.9$	$p > 0.5$
Fast			
Main effect	$F(1, 59) = 13.512$, $p = 0.001$, $\eta_p^2 = 0.186$	$F(1, 59) = 6.918$, $p = 0.011$, $\eta_p^2 = 0.105$	$F(1, 47) = 43.417$, $p < 0.001$, $\eta_p^2 = 0.480$
Group interaction	$F(2, 59) = 3.391$, $p = 0.040$, $\eta_p^2 = 0.103$	ns, $p > 0.1$	ns, $p = 0.068$
Modality			
Slow			
Main effect	ns, $p > 0.1$	$F(2, 128) = 37.299$, $p < 0.001$, $\eta_p^2 = 0.368$	$F(2, 86) = 22.879$, $p < 0.001$, $\eta_p^2 = 0.347$
Group interaction	ns, $p > 0.3$	ns, $p > 0.7$	ns, $p > 0.3$
Medium			
Main effect	$F(2, 124) = 7.035$, $p = 0.001$, $\eta_p^2 = 0.102$	$F(2, 124) = 61.920$, $p < 0.001$, $\eta_p^2 = 0.500$	$F(2, 66) = 31.938$, $p < 0.001$, $\eta_p^2 = 0.492$
Group interaction	$F(4, 124) = 2.629$, $p = 0.038$, $\eta_p^2 = 0.078$	ns, $p = 0.082$	$F(4, 66) = 3.089$, $p = 0.022$, $\eta_p^2 = 0.158$
Fast			
Main effect	$F(2, 118) = 5.312$, $p = 0.018$, $\eta_p^2 = 0.083$[a]	$F(2, 118) = 121.478$, $p < 0.001$, $\eta_p^2 = 0.673$	$F(2, 94) = 150.058$, $p < 0.001$, $\eta_p^2 = 0.761$
Group interaction	ns, $p > 0.2$	ns, $p > 0.5$	$F(4, 94) = 2.818$, $p = 0.038$, $\eta_p^2 = 0.107$

[a]Values reporting a Greenhouse-Geisser statistic.

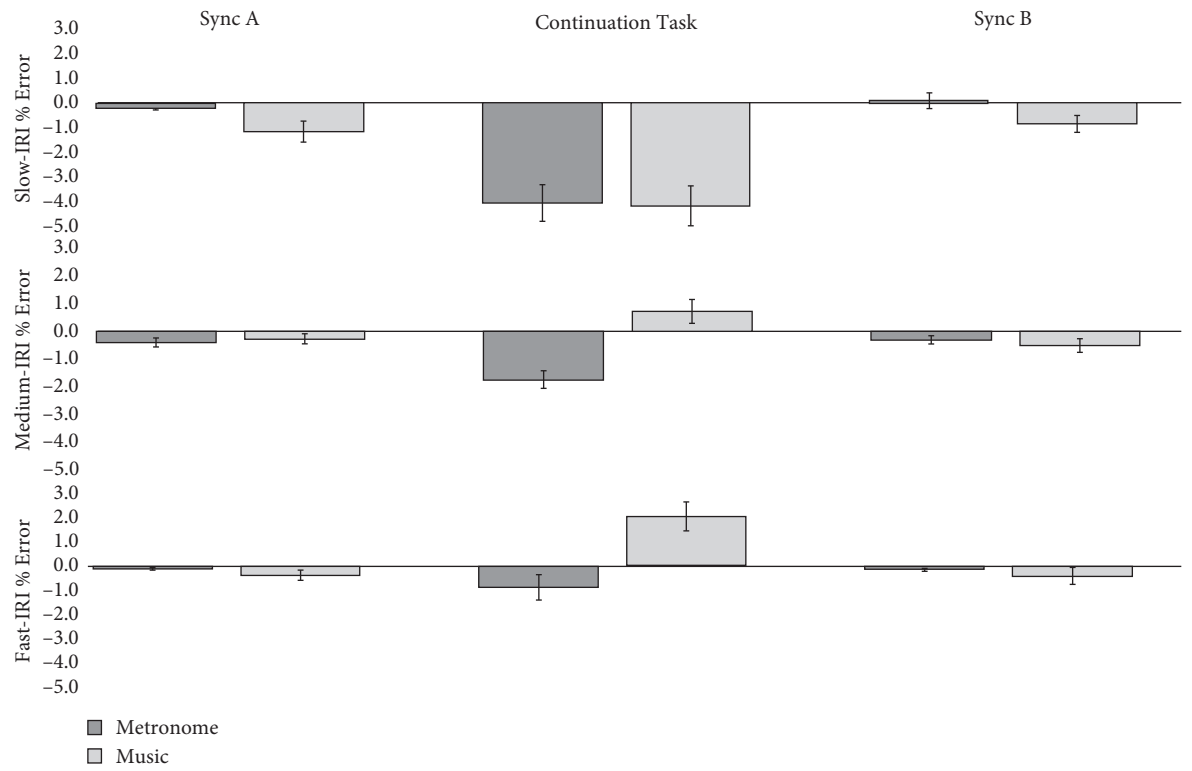

Figure 2: The main effect of cue type on entrainment ability (IRI % Error) collapsed across all groups in each tempo. *Y*-axis shows IRI % Error. *X*-axis shows the temporal nature of the experimental paradigm.

For fast tempo, a main effect $F(1, 59) = 13.512$, $p = 0.001$, and $\eta_p^2 = 0.186$ and a group interaction $F(2, 59) = 3.391$, $p = 0.040$, and $\eta_p^2 = 0.103$

Confidence intervals = standard error

Analysis of the significant interaction between groups in the fast tempo revealed a significant difference between the older and Parkinson's groups (±1.395 ms, $p = 0.050$, and CI ± 0.0–2.790) as illustrated in Figure 3. The Parkinson's and younger groups did not differ significantly ($p > 0.3$), and neither did the older and younger groups ($p > 0.1$). Although the effect size for this interaction was large, it should be noted that the result does not withstand Bonferroni adjustment for alpha p.

Repeated measures ANOVA results revealed the following:

A main effect of cue type $F(1, 59) = 13.512$, $p = 0.001$, and $\eta_p^2 = 0.186$

An interaction between groups, $F(2, 59) = 3.391$, $p = 0.040$, and $\eta_p^2 = 0.103$

Confidence intervals = standard error

(2) Movement Modality. No main effects or interactions were found for the slow tempo ($p > 0.1$, $p > 0.3$). In the medium tempo, a significant main effect showed that modality effected entrainment. Overall, participants performed best when stepping in the spot (mean = 0.200, SE = 0.200), followed by finger tapping (mean = −0.476, SE = 0.242), and least well when toe tapping (mean = −0.926, SE = 0.256). Significant differences were revealed between toe tapping and stepping on the spot (±1.126, $p < 0.001$, and CI ± 0.60–1.652) and between finger tapping and stepping on the spot (±0.676, $p = 0.043$, and CI ± 0.022–1.33) but not between the two types of tapping ($p > 0.1$). A significant interaction between groups was driven by a difference between the Parkinson's and older participants (mean diff ± 1.179, $p = 0.016$, and CI ± 0.189–2.168). Figure 4 illustrates how people with Parkinson's made the most errors when toe tapping and the least for stepping on the spot and that the older group was the most consistent (i.e., errors closest to 0) for all three movement modalities in the medium tempo. No significant differences were revealed between Parkinson's and the Younger group performances ($p > 0.3$), or between controls groups ($p > 0.1$). However, the interaction statistic does not withstand Bonferroni adjustment for alpha p. In the fast tempo, post hoc analysis of the main effect revealed a mean difference between finger tapping and stepping on the spot (±1.548, $p = 0.009$, and CI ± 0.208–2.005), and toe tapping and stepping on the spot (±.649, $p = 0.005$, and CI ± 0.207–1.091), but not between finger and toe tapping ($p > 0.1$). Overall in the fast tempo, participants performed with negative error when finger tapping (mean = −0.771, SE = 0.590), closest to 0 when toe tapping (mean = 0.128, SE = 0.241) and with positive error when stepping on the spot (mean = 0.777, SE = 0.163).

Repeated measures ANOVA results revealed the following:

A main effect of modality $F(2, 124) = 7.035$, $p = 0.001$, and $\eta_p^2 = 0.102$

An interaction with group, $F(4, 124) = 2.629$, $p = 0.038$, and $\eta_p^2 = 0.078$

Confidence intervals = standard error

3.2.2. Synchronization: Absolute Asynchrony

(1) Cue Type. A main effect of cue type was revealed in the slow tempo. Significantly more Absolute Asynchrony was evident in the metronome condition (mean = 66.265 ms, SE = 4.130) compared to the music condition (mean = 50.433 ms, SE = 3.519). Post hoc tests show a mean difference between cue type was ±15.832 ms, $p < 0.001$, and CI ± 9.635–22.029. A significant interaction between groups was also revealed, although the p value did not withstand Bonferroni adjustment for multiple comparisons. Pairwise comparisons confirmed this; Absolute Asynchrony did not differ between Parkinson's and older groups ($p = 0.051$), Parkinson's and the younger group ($p > 0.1$), nor between control groups ($p > 0.8$) in the slow tempo. In the medium tempo, no main effect of cue type ($p > 0.6$) or interaction between groups ($p > 0.5$) was revealed. A main effect of cue type was revealed in the fast tempo. Significantly more Absolute Asynchrony was evident in the metronome condition (mean = −27.488 ms, SE = 3.025) compared to the music condition (mean = −7.940 ms, SE = 3.187). Post hoc tests show a mean difference between cue type was ±19.548 ms, $p < 0.001$, and CI ± 13.580–25.516 ms. No interaction between groups was found in the fast tempo ($p = 0.068$). Figure 5 illustrates the general effect of cue type on synchronization ability in all tempo.

Repeated measures ANOVA results revealed the following:

Slow tempo: a main effect of cue type $F(1, 43) = 26.544$, $p < 0.001$, and $\eta_p^2 = 0.382$and an interaction with group, $F(2, 43) = 3.692$, $p = 0.033$, and $\eta_p^2 = 0.147$

Medium tempo: no significant main effect ($p > 0.6$) or interaction between groups ($p > 0.5$).

Fast tempo: a main effect of cue type $F(1, 47) = 43.417$, $p < 0.001$, and $\eta_p^2 = 0.480$, and no interaction, $p = 0.068$

Confidence intervals = standard error

(2) Movement Modality. In the slow tempo, a significant main effect of modality on Absolute Asynchrony was revealed. The most errors occurred when toe tapping (mean = 72.419 ms, SE = 4.436), followed by finger tapping (mean = 60.370 ms, SE = 4.172), and the least when stepping on the spot (mean = 42.258 ms, SE = 4.489). Pairwise comparisons showed that the difference between finger tapping and toe tapping was significant (±12.049 ms, $p = 0.005$, and CI ± 3.855–20.243), the difference between finger tapping and stepping on the spot was significant (±18.112 ms, $p < 0.001$, and CI ± 8.471–27.754), and the difference between toe tapping and stepping on the spot was also significant (±30.161 ms, $p < 0.001$, and CI ± 20.901–39.421). There was no interaction between groups ($p > 0.3$).

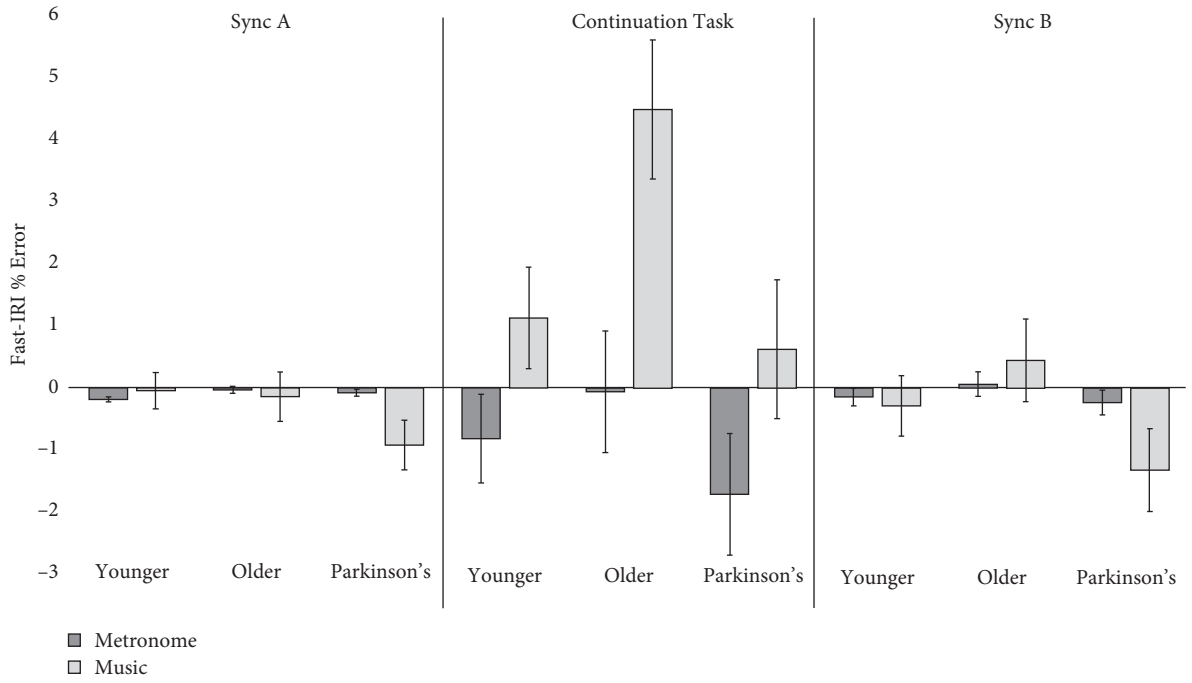

Figure 3: The significant main effect of cue type on entrainment ability (IRI % Error) and the significant interaction between groups in the fast tempo. *Y*-axis shows IRI % Error. *X*-axis shows the temporal nature of the experimental paradigm.

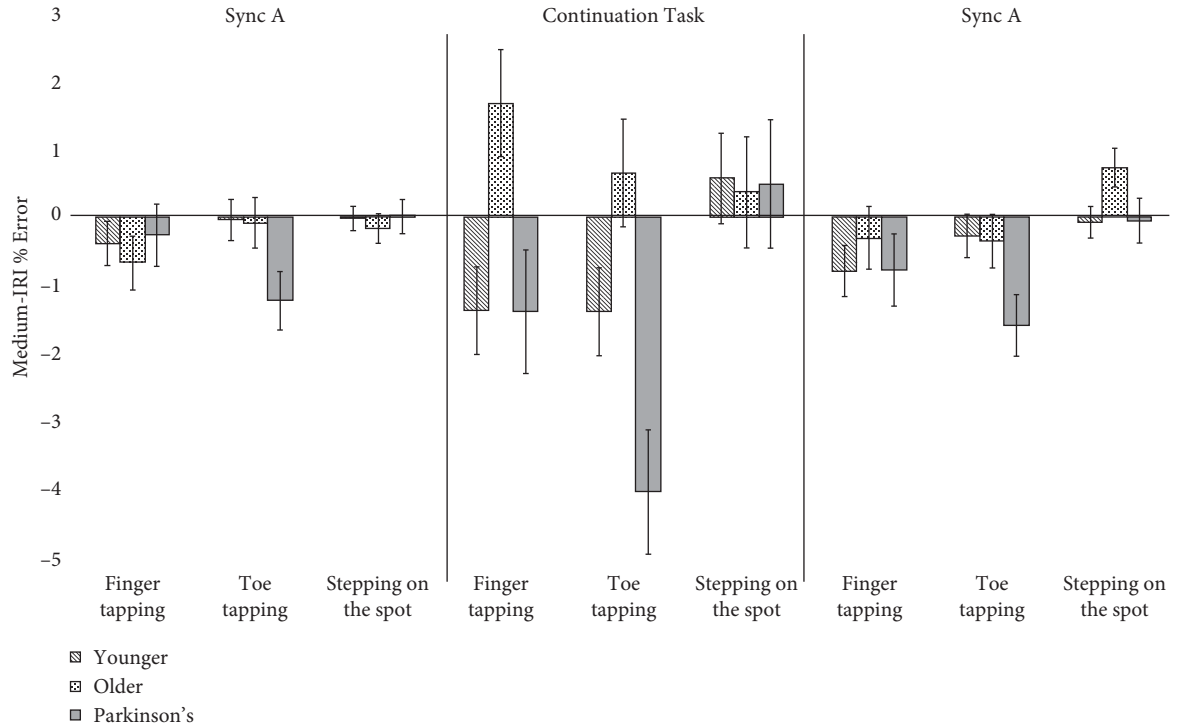

Figure 4: The significant main effect of movement modality on entrainment ability (IRI % Error) and the significant interaction between groups in the medium tempo. *Y*-axis shows IRI % Error. *X*-axis shows the temporal nature of the experimental paradigm.

In the medium tempo, a significant main effect of modality was also revealed. Pairwise comparisons showed the overall mean difference between finger tapping and toe tapping was ±7.841 ms, $p = 0.01$, and CI ± 1.992–13.690; between finger tapping and stepping on the spot, ±19.077, $p < 0.001$, and CI ± 11.436–26.718; and between toe tapping and stepping on the spot, ±26.918, $p < 0.001$, and CI ± 19.405–34.431. Although an interaction between groups was revealed, it did not withstand Bonferroni correction. Post hoc pairwise comparisons confirmed groups

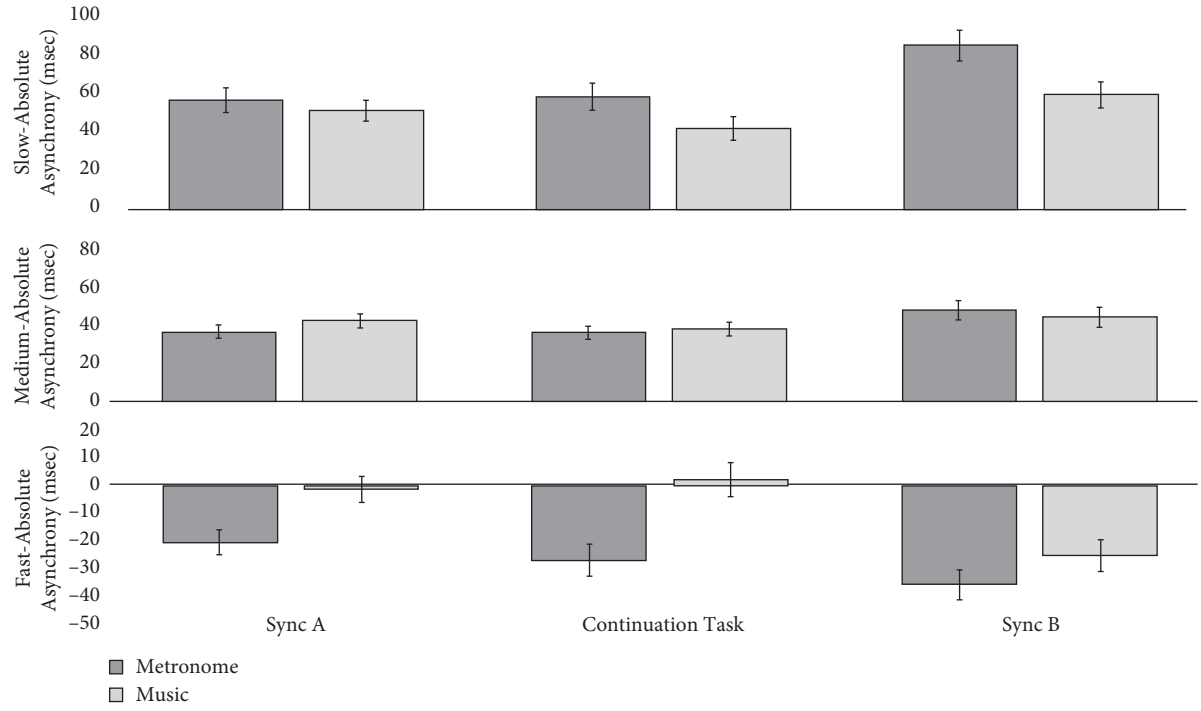

Figure 5: The effect of cue type on Absolute Asynchrony in all tempi by group. Y-axis shows the mean of Sync A and Sync B Absolute Asynchrony in ms. X-axis shows group by cue type.

did not significantly differ (Parkinson's and older: $p = 0.065$; Parkinson's and younger: $p > 0.1$; and controls $p > 0.5$). For people with Parkinson's, stepping on the spot produced the best results in terms of the least asynchrony (20 ms), followed by finger tapping (39 ms), whereas toe tapping produced the most asynchrony (48 ms) (Figure 6). For the fast tempo, a main effect of modality was revealed showing that overall, participant performed the most asynchrony when toe tapping (mean = −44.931 ms, SE = 3.926), followed by finger tapping (mean = −33.398 ms, SE = 2.957), and the least when stepping on the spot (mean = 25.186 ms, SE = 4.129). Pairwise comparisons showed that the difference between finger tapping and toe tapping was significant (±11.533 ms, $p = 0.003$, and CI ± 4.167–18.900), the difference between finger tapping and stepping on the spot was significant (±58.584 ms, $p < 0.001$, and CI ± 50.342–66.826), and the difference between toe tapping and stepping on the spot was also significant (±70.118 ms, $p < 0.001$, and CI ± 59.795–80.441). The between-group interaction analyses showed a significant difference between the Parkinson's and younger group (±19.574 ms, $p = 0.009$, and CI ± 4.309–34.838) and also between the Parkinson's and older group (±18.112 ms, $p = 0.038$, and CI ± 0.838–35.386). The control groups did not differ significantly ($p > 0.9$). However, this result did not withstand Bonferroni correction.

Repeated measures ANOVA results revealed the following:

Slow tempo: a main effect of modality $F(2, 86) = 22.879$, $p < 0.001$, and $\eta_\rho^2 = 0.347$, and no interaction between groups ($p > 0.3$)

Medium tempo: a main effect of modality $F(2, 66) = 31.938$, $p < 0.001$, and $\eta_\rho^2 = 0.492$, and an interaction between groups $F(4, 66) = 3.089$, $p > 0.022$, and $\eta_\rho^2 = 0.158$

Fast tempo: a main effect of modality $F(2, 94) = 150.058$, $p < 0.001$, and $\eta_\rho^2 = 0.761$, and an interaction between groups $F(4, 94) = 2.818$, $p = 0.038$, and $\eta_\rho^2 = 0.107$

Confidence intervals = standard error

3.2.3. Pacing Stability: IRICoV

(1) Cue Type. In the slow tempo, analyses of *IRICoV* across all three sections of the experimental paradigm revealed no main effect of cue type ($p > 0.7$) and no interaction between groups ($p > 0.5$). A main effect of cue type was revealed in the medium tempo. The mean difference between metronome and music was ±2.197 ms, $p = 0.011$, and CI ± 0.511–3.883 with more variance observed for music than for metronome (Table 6). No interaction between groups was revealed in this tempo ($p > 0.9$). In the fast tempo, a main effect of cue type was revealed with a mean difference of ±1.439 ms, $p = 0.011$, and CI ± 0.344–2.533, with more variance observed in the music condition compared to the metronome (Table 6). There were no interactions between groups in fast tempo ($p > 0.1$). The effect of cue type on *IRICoV* in the medium and fast tempi did not withstand Bonferroni correction for multiple comparisons.

Table 6 shows data relating to IRI CoV for cue type and movement modality.

Figure 6: The effect of movement modality on Absolute Asynchrony in all tempi by group. *Y*-axis shows Absolute Asynchrony in ms. *X*-axis shows group by movement modality.

Table 6: IRI coefficient of variation for slow, medium, and fast tempi by movement modality.

Tempo	Cue type	Mean (ms)	Std. error (ms)	95% confidence interval	
				Lower bound	Upper bound
Slow	Metronome	36.24	1.72	32.82	39.67
	Music	35.71	1.34	33.04	38.38
Medium	Metronome	25.27	0.89	23.50	27.04
	Music	27.47	1.11	25.25	29.69
Fast	Metronome	20.94	0.70	19.54	22.35
	Music	22.38	0.69	21.00	23.76
	Modality				
Slow	Finger tapping	38.87	1.52	35.83	41.91
	Toe tapping	42.97	2.04	38.89	47.04
	Stepping on the spot	26.10	1.77	22.56	29.63
Medium	Finger tapping	30.03	0.97	28.08	31.98
	Toe tapping	31.77	1.27	29.24	34.30
	Stepping on the spot	17.32	1.40	14.53	20.11
Fast	Finger tapping	25.31	0.85	23.61	27.02
	Toe tapping	26.75	0.94	24.86	28.63
	Stepping on the spot	12.93	0.75	11.43	14.43

(2) Movement Modality. In all tempi, significant main effects were revealed in *IRICoV*, and no interactions between groups (Table 6). In slow tempo, the mean difference between finger tapping and toe tapping was significant ±4.099 ms, $p = 0.015$, and CI ± 0.826–7.371, and between finger tapping and stepping on the spot ±12.772 ms, $p < 0.001$, and CI ± 8.748–16.797, and also between toe tapping and stepping on the spot ±16.871 ms, $p < 0.001$, and CI ± 12.096–26.646. In the medium tempo, there was a significant mean difference between finger tapping and stepping on the spot was ±12.711 ms, $p < 0.001$, and CI ± 9.711–15.710, and between toe tapping and stepping on the spot ±14.449 ms, $p < 0.001$, and CI ± 11.100–17.799. The difference between finger tapping and toe tapping was not significant ($p = 0.08$). In the fast tempo, the mean difference between finger tapping and stepping on the spot was ±12.386 ms, $p < 0.001$, and CI ± 10.510–14.260, and also between toe tapping and stepping on the spot ±13.818 ms, $p < 0.001$, and CI ± 11.587–16.049. The difference between finger tapping and toe tapping was not significant ($p = 0.09$).

4. Discussion

This study investigated how different sound cues and different types of movements affected rhythmical motor behaviours at different tempi in people with and without Parkinson's. Overall, the findings suggest that (a) music helps people with Parkinson's maintain entrainment better than metronomes and (b) that stepping on the spot enables people with Parkinson's to entrain better than either finger or toe tapping. We also note that our results suggested that age did not effect entrainment, synchronization, or pacing stability. Specifically, in relation to our first hypothesis, music did support entrainment better than metronomes, as measured using IRI % Error in the medium but also in the fast tempo. The effect of entrainment was especially noticeable during the continuation task as illustrated in Figure 2. This will be discussed in Section 4.1, in relation to priming and the potential for therapeutic use of imagined music. It was also notable that people with Parkinson's did not differ from controls, even in the slow tempo, and that they were able to resynchronize (i.e., latch on to the beat again in Sync B) as successfully as controls. With regard to our second hypothesis, tempi did affect the results for Absolute Asynchrony, and all groups, not just the people with Parkinson's performed worse (i.e., with significantly more asynchrony) in the slow tempo condition. Figures 5 and 6 illustrate the change in direction of asynchrony error in the fast tempo. It is notable that negative error is only performed in the fast tempo when tapping, and not stepping on the spot and this will be discussed further in Section 4.2 in relation to ideas concerning emergent timing. This point is related to our final hypothesis, for which we confirmed that stepping on the spot enabled better timed motor behaviour for all measures compared to tapping. This has important implications for research in understanding how embodied entrainment may differ from effector entrainment and may also be connected to emergent timing. Therapeutically, these findings suggest that RAS training could be used for other types of movements that may be used to improve functional mobility for people with Parkinson's. These results are discussed in the following sections.

4.1. Music Effect. Overall, the type of cue did not affect pacing stability, yet music reduced asynchrony in the slow and fast tempo (there was no difference in the medium tempo). These findings suggests that, in this sample, the music did not create a demand effect for people with Parkinson's as was found in Brown and Marsden [1] and Brown et al., [72], although this was a different type of task. Furthermore, although it did not matter in terms of synchronization ability which cue type was heard in the medium tempo, in the slow and fast tempi conditions, the music more than the metronomes helped people with Parkinson's to synchronize as well as controls. This provides useful baseline information for practitioners in terms of using music to help engage people with Parkinson's in movements programmes. For example, fatigue is a common symptom of Parkinson's [87], but music has been shown to promote ergogenic effect (i.e., reduce the perception of fatigue to enable continued exercise) [69, 70]. However, practitioners should take care to individualize musically enhanced rehabilitation programmes as, although most participants with Parkinson's in this study anecdotally reported enjoying the music more than the metronomes, some reported feeling that the music "pushed them out of the way." Although no significant differences were found in the Gold Beat Alignment Test, a more extensive measure of rhythmic perception and production abilities, such as the BAASTA [88], may have revealed more fine-grained differences. As suggested in Dalla Bella et al. [12], individual differences in rhythmic perception and production abilities may be a fundamental aspect with regard to the usefulness of music in terms of external rhythmic auditory guidance.

The findings relating to the phenomenon of entrainment in this study showed that music had a much larger effect than metronomes during the continuation task for all participants in terms of maintaining entrainment in the absence of heard cues (i.e., during the continuation task). In this study, similar to the comments reported in Thaut et al. [20], several participants explained that they maintained entrainment by singing the music inside their minds. For example, one participant with Parkinson's explained "The beat was like a shadow inside my head, but I could keep singing along with the music." and another reflected, "The problem with metronome was that once you lost it, there was no way to find your way back." These, and other similar comments regarding strategies involving subvocalization, suggest that understanding what occurs between paced and unpaced motor timing may have useful application in Parkinson's rehabilitation. It could be that the repetition of rhythmic musical phrases (including melodies, with or without lyrics) induces a priming effect than can be further enhanced with training. Not only is the underlying beat of music memorable [64–66], studies investigating the phenomenon and prevalence of "sticky tunes" or "earworms" (91.7% of people experience a weekly earworm [89, 90]) suggest our musical imaginations can be triggered by two musical features common in RAS therapy; repetition and musical simplicity. Similarly, the familiarity and likeability of the music is important and will be considered in a follow-up paper. Schaefer and colleagues [91] have suggested that heard and imagined music can modulate movement in subtly different ways. In their fMRI study (with neurotypical participants using a wrist inflection movement task), Schaefer and colleagues showed that when listening to heard music, more activation was observed in the cerebellum, whereas when listening to imagined music more activation was observed in the presupplementary motor area. The phenomenon of endogenous timing strategies (as opposed to spontaneous motor tempo [42]) has been described as a form of "covert, internal synchronization" ([31], p. 969), whereby people generate temporal expectations from the rhythm of what they have been listening to. Clayton [92] described the phenomena as intraindividual entrainment. This suggests that the music itself is a form of priming, and that in turn RAS therapy co-opts this as a form of training, explaining to some extant to reports of "carry over effects," i.e., the

continued effects of RAS training on gait for some weeks, or even months posttraining. In order to extend RAS training beyond the reliance on the continuous presentation of stimuli [44, 93], further research is required to develop strategies to harness the musical imagination in the form of RAS therapy. Only one study has shown that imagined music can help walking for people with Parkinson's [94], but the present study provides support for the supposition of Schaefer and colleagues [91, 95] who also suggested the impact of the cue may depend on the type of movement.

4.2. Movement Effect. The findings of this study also demonstrated that the stepping on the spot task was better than finger tapping, and especially toe tapping, in terms of entrainment, synchronization, and pace stability for all participants. Importantly, this type of stationary "walking" enabled people with Parkinson's to perform at the same level as control groups, showing that to some extant, the principles of RAS training extend to other types of movements. In a similar way that people with Parkinson's reported music mostly enabled subvocalizing, the stepping on the spot task was described as an easy and natural movement in comparison to tapping, especially toe tapping. As one participant described, "I just let my body do the movement. It felt natural, and when I knew the song, it was easy to keep it going inside my head."

This is pertinent in relation to Parkinson's because although entrainment, though also considered as a neural oscillatory process [96], is managed behaviourallyin part by the "afferent feedback of the movement". This in turn is thought to be involved in the anticipatory processes necessary for sensorimotor synchronization ([95], p. 3). The accumulation from the different sensory channels is embedded in the sensory accumulator model [33, 97]. Leman and Maes [98] described the way in which the sensorimotor networks in the human body mediate the affective experience of music as embodied music cognition. The findings herein suggest that whole body continuous movement (i.e., stepping on the spot) helps people with Parkinson's to entrain, synchronize, and pace better than more discrete effector movements such as tapping. Therefore, we suggest the term *embodied entrainment* to describe this phenomenon.

The findings relating to the differences in movement modalities are also important because of the overlap between event-based timing and discrete movements and emergent timing and continuous movement (e.g., [99, 100]). Ivry and Richardson [101] suggested a multiple timer model speculating on the characteristic functional roles of the basal ganglia and cerebellum in timing. However, when comparing the models using stimuli set at a rate of 550 ms, Spencer and Ivry [7] did not find any group differences in their Parkinson's study which the authors suggested was due to the relatively spared effector control in their Parkinson's sample. Interestingly, a recent study [102] suggests that there is a transition between these two modes of timing at 600 ms (whereby a reliance on event-based timing is observed < 600 ms). In the present study, the findings show a switch in the direction of error (from negative to positive (Figure 6)) specific to stepping on the spot in the fast tempo, but not tapping which remained negative. This suggests that the emergent timing processes involved in continuous movement may enable people with Parkinson's to engage with motor actions at a faster pace. This information may be useful in therapeutic application when considering which movements to rehabilitate at which speeds.

4.3. Limitations. Although extension of the synchronization-continuation paradigm provided two sets of data measuring asynchrony, and the novel use of equipment did reduce participant demand, we acknowledge that even with this large sample of people with Parkinson's, the findings reported herein will require replication in order to be considered robust. Furthermore, although we chose to use each musical excerpt only once to ensure learning effects did not occur during the experiment that does not necessarily mean that participants were more able to entrain with more familiar musical stimuli, or at stimuli closer to their own spontaneous motor tempo. However, these questions will be addressed in a separate paper. Moreover, we acknowledge that the choice of movement modalities was not directly comparable in that stepping on the spot is an interlimb coordinated movement, whereas finger and toe tapping require rather more cognitive attention. However, the requirement for participants to stay in one spot (rather than walk with forward trajectory) did require some adjustment for some participants. Future studies may consider using motion capture technology to compare the timing, amplitude, and synchrony of movements pre- and post-rehabilitation programmes. Finally, we acknowledge that including participant commentary as insight for strategies for behaviour is not sufficient in terms of the requirements for data. However, we believe the inclusion of the voice of the participants with Parkinson's is a necessary and valuable contribution and in line with the guidance for patient and public involvement provided by Parkinson's UK.

4.4. Future Directions. The efficacy of many interventions relies on adherence to the therapeutic programme and ideally continued practice to maintain training effects afterwards [10]. Music provides an engaging auditory stimuli, which research in sports and exercise science has shown in itself has an energizing and/or motivating effect on movement [70]. For example, the experience of "groove" as inducing the pleasurable urge to move, as well as other dynamic acoustic features [103], may shed light on the mechanisms by which music supports entrainment [14, 34, 73]. Moreover, although current research focusing on the neural mechanisms of timing is essential, studies considering the potential of heard and imagined music (both primed and self-generated) and remembered music could be designed in parallel. For example, the role of musical memory, especially autobiographical memory, has also yet to be explored and utilized in people with Parkinson's as it has successfully in other associated pathologies (e.g., music and dementia [104, 105]). Salient musical memories may also be

associated with movements, and in particular with dancing [51, 53, 106, 107]. As Schaefer [95] has commented, the impact of the cue may depend not only on the type of movement involved but also on the salient strength of the music (whether perceived externally or represented internally) as the phenomena of entrainment and synchronization rely on both conscious and unconscious processes.

5. Conclusion

This is the first study to demonstrate that people with Parkinson's can entrain as well as control when primed by music rather than metronomes beeps. We suggest that when using the body to produce timed sequences of action (herein operationalized as stepping on the spot rather than finger or toe tapping), people with Parkinson's can reach performance levels as accurately and with as much stability as those observed in healthy individuals. This is especially true when using music as the pacing cue. Music may trigger body dynamics and facilitate the emergence of embodied timing, which requires less cognitive control than predictive timing. These findings provide possibilities for direct application to therapeutic approaches for motor rehabilitation to help people with Parkinson's learn to use alternative strategies. As such, learning to entrain to an inner jukebox of tunes may help people with Parkinson's learn to manage movement better and therefore reduce the risks of falls.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

The data of this study were disseminated as work in progress by the first author at the 15th International Conference for Music Perception and Cognition in Graz, Austria, 23–29 July 2018; presented as a poster at the Parkinson's UK Conference in York, 13 November 2018; and presented as a spoken paper at the 17th Rhythm Production and Perception Workshop in Traverse City, Michigan, USA, 17–20 June 2019. This research was undertaken at the University of Hertfordshire during the first author's postdoctoral research fellowship.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Dawn Rose is responsible for conception and design of experiment, acquisition of data, analysis and interpretation of data, and preparation, writing, and submission of final manuscript. Yvonne Delevoye-Turrell is responsible for analysis and interpretation of data, revision of intellectual content, and preparation, writing, and approval of final manuscript. Laurent Ott is responsible for extraction and analyses of data and approval of final manuscript. Lucy Annett is responsible for conception and design, interpretation of data, revision of intellectual content, and approval of final manuscript. Peter Lovatt is responsible for conception and design, revision of intellectual content, and approval of final manuscript.

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Supplementary Materials

Supplementary Table S1: an overview of medication regimens for Parkinson's as reported by participants with Parkinson's. (*Supplementary Materials*)

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Research Article

Balance and Gait Improvements of Postoperative Rehabilitation in Patients with Parkinson's Disease Treated with Subthalamic Nucleus Deep Brain Stimulation (STN-DBS)

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Background. Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a surgical treatment to reduce the "off" state motor symptoms of Parkinson's disease (PD). Postural instability is one of the major impairments, which induces disabilities of activities of daily living (ADLs). The effectiveness of STN-DBS for postural instability is unclear, and the effect of rehabilitation following STN-DBS has remained uncertain. *Objective*. The purpose of this study was to examine changes in balance ability, gait function, motor performance, and ADLs following 2 weeks of postoperative rehabilitation in PD patients treated with STN-DBS. *Methods*. Sixteen patients were reviewed retrospectively from February 2016 to March 2017. All patients were tested in their "on" medication state for balance and gait performance using the Mini-Balance Evaluation Systems Test (Mini-BESTest) and the Timed "Up and Go" (TUG) test before the operation, after the operation, and during the discharge period. The UPDRS motor score (UPDRS-III) and Barthel Index (BI) were assessed before the operation and during the discharge period. Rehabilitation focused on muscle strengthening with stretching and proactive balance training. Friedman's test and the post hoc Wilcoxon's signed-rank test were used to analyze the balance assessments, and ANOVA and the post hoc Tukey's test were used to analyze gait performance. The significance level was $p < 0.05$. *Results*. During the discharge period, the Mini-BESTest and TUG were significantly improved compared with the preoperative and postoperative periods ($p < 0.05$). There were no differences between preoperative and postoperative periods in the Mini-BESTest ($p = 0.12$) and TUG ($p = 0.91$). The BI and motor sections of the UPDRS did not differ significantly between the preoperative and postoperative periods ($p = 0.45$, $p = 0.22$). *Conclusion*. The results of this study suggest that postoperative rehabilitation improves balance and gait ability in patients with PD treated with STN-DBS.

1. Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) has become an effective therapy for advanced Parkinson's disease (PD). STN-DBS reduces motor symptom severity, including the tremor, bradykinesia, rigidity, and dystonia, during the medication "off" state. Patients with advanced PD show postural instability and have an increased

risk of falls in daily living [1]. The effects of STN-DBS on posture and balance function are unclear [2–8]. A meta-analysis of nonsurgical PD patients showed a significant effect of physical therapy on balance function as measured by the Timed "Up and Go" (TUG) test, Functional Reach test, and Berg Balance Scale [9]. However, the effectiveness of postoperative rehabilitation with STN-DBS in PD has not been well studied. Only one article has reported significant improvements of the UPDRS motor score and activities of daily living (ADLs) scores (Functional Independence Measure and Barthel Index (BI)) with postoperative rehabilitation in PD patients [10]. They did not assess balance function.

The purpose of this study was to investigate the effects of postoperative rehabilitation on balance and gait function in patients with PD treated with STN-DBS using evaluations that could detect more specific balance and gait dysfunctions.

2. Methods

2.1. Participants. In this retrospective study, 32 PD patients who underwent STN-DBS in our hospital from February 2016 to March 2017 were recruited. The inclusion criteria were that the patients had received STN-DBS and undergone two-week postoperative physical therapy. The indications for STN-DBS were (i) a good response to levodopa (over 30% improvement on the L-dopa challenge test); (ii) motor complications (dyskinesia, fluctuation); (iii) no dementia or psychiatric problems; and (iv) a precise diagnosis of PD by neurologists specializing in movement disorders. The exclusion criteria of this study were (i) unable to walk independently; (ii) severe complications such as lumbar spondylolisthesis that impaired the patient's balance ability; (iii) postoperative psychiatric problems; (iv) orthostatic hypotension; or (v) lack of clinical data in the medical record.

2.2. Therapeutic Exercise. All patients underwent muscle strengthening with stretching and proactive balance training for 40 minutes by experienced physical therapists for approximately 14 days during their hospitalization period (Table 1). Therapeutic exercise consisted of (i) range of motion (ankle, knee, hip, and trunk), (ii) dynamic balance exercise in the quadrupedal and standing positions, and (iii) gait training. The patients underwent modulation of DBS and appropriate medication to achieve the best "on" state.

2.3. Clinical Evaluations. Before the surgery (PRE), subjects were tested in all clinical evaluations when they were in the "on" medication state, typically 60–90 minutes after intake of antiparkinsonian medicine. Three days after the implantation of STN-DBS (POST), subjects' balance and gait functions were assessed in the "on" state at the same time as above with antiparkinsonian medicine without stimulation because it was necessary to wait for attenuation of the microlesion effect before starting stimulation. During the discharge period (DISC), typically two weeks after the surgery, the subjects underwent all clinical evaluations with both stimulation and adjusted antiparkinsonian medication that brought about the "on" state. Generally, medications were reduced in the discharge period according to the stimulation.

2.3.1. Mini-Balance Evaluation Systems Test. The balance function of PD patients was assessed with the Mini-Balance Evaluation Systems Test (Mini-BESTest). The Mini-BESTest is a measurement that evaluates balance control and consists of four sections: anticipatory postural adjustments (APA), automatic postural responses (Reactive), sensory integration (Sensory), and dynamic balance during gait (Dynamic gait). This assessment has 14 items with a scale of zero (poor) to two (good), and the maximum score is 28 points [11].

2.3.2. Timed "Up and Go" Test. Gait function was assessed with the TUG test. The TUG test evaluates the time of a movement sequence that involves rising from a chair, walking three meters, turning, returning to the chair, and sitting down on the same chair at a comfortable pace [12]. In addition, the TUG test was assessed with a cognitive task, counting backward by sevens from 100 (TUG-cognitive) [11]. Both the TUG and TUG-cognitive tests are simple but useful tests to assess mobility function and the fall risk of PD patients.

2.3.3. Barthel Index. ADLs assessment was conducted with the BI, which is widely used as the most common ADLs assessment tool. The BI consists of 10 multiple choice items of basic ADLs, with a total scoring range of 0–100 [13]. Higher scores reflect greater physical performance in ADLs.

2.3.4. Unified Parkinson's Disease Rating Scale Motor Score. The Unified Parkinson's Disease Rating Scale (UPDRS) has been widely used as a clinical rating scale for PD [14]. The UPDRS consist of six different sections, and Part 3 (UPDRS-III) reflects the motor performance of PD patients with 14 items (numbers 18 to 31, with a maximum score of 108). Previous studies used numbers 20–26 as cardinal signs (tremor, rigidity, and bradykinesia, with a maximum score of 80), and numbers 29 to 30 as postural instability and gait disability (PIGD) signs (PIGD, with a maximum score of 8) [4]. A higher score reflects the severity of the PD symptoms. In this study, the UPDRS was assessed by a neurologist specializing in movement disorders.

2.3.5. Levodopa Equivalent Daily Dose. According to Tomlinson et al. [15], the levodopa equivalent daily dose (LEDD) in mg was calculated as regular levodopa dose (levodopa × 1), entacapone (levodopa × 0.33), pramipexole (×100), ropinirole (×20), rotigotine (×30), selegiline-oral (×10), rasagiline (×100), amantadine (×1), and apomorphine (×10).

2.4. Statistical Analysis. Three periods (PRE, POST, and DISC) of the total Mini-BESTest scores, four subscores

Table 1: Proactive balance muscle strengthening.

Preparation	Active assistive range of motion exercise for ankle, hip, and trunk joints
Dynamic balance exercise	Quadrupedal balance (cat and dog, diagonal balancing exercise)
	Standing balance (toe-heel weight bearing, one-leg standing, step position)
Gait exercise	Active assistive gait training

(APA, Reactive, Sensory, and Dynamic gait), and LEDD were analyzed with Friedman's test. Wilcoxon's signed-rank test for multiple comparisons was performed as a post hoc test when significant outcomes were found in the primary analyses.

The three periods of the TUG and TUG-cognitive test scores were analyzed with one-way repeated measures analysis of variance (ANOVA). The post hoc Tukey test for multiple comparisons was performed when a significant outcome was found on primary analysis. The UPDRS-III scores and BI scores in the "on" state were compared with Wilcoxon's signed-rank test (PRE and DISC). In all tests, the significance level was $p < 0.05$. All statistical analyses were performed using JSTAT version 2.0. This retrospective study was approved by the institutional ethics review board (JHS 17-0043).

3. Results

A total of 32 postoperative cases underwent rehabilitation from February 2016 to March 2017. Sixteen patients were excluded according to the exclusion criteria. One of sixteen patients could not be assessed at PRE because of the dysfunction of gait that resulted from a sudden "off" state. Ten of sixteen patients could not be included because of overlap with another examination or lacking the assessment data in the medical records. Five of sixteen patients could not be assessed due to severe complications (one, orthostatic hypotension; two, lumbar spondylolisthesis; one, knee osteoarthritis; one, severe psychiatric disease). After applying the inclusion and exclusion criteria, 16 patients (5 females and 11 males) remained in this study. Table 2 shows the demographic data of the 16 included patients and the 16 excluded patients.

3.1. Clinical Scale Results. All clinical scale results are presented in Table 3.

3.2. Mini-Balance Evaluation Systems Test. Friedman's test showed significant differences among PRE, POST, and DISC ($p < 0.01$) assessments in the total score of the Mini-BESTest. The post hoc Wilcoxon's signed-rank test showed that there were significant differences between the PRE and DISC ($p < 0.01$) assessments and between the POST and DISC ($p < 0.01$) assessments of the total score of the Mini-BESTest, whereas there was no significant difference between PRE and POST ($p = 0.12$) assessments in the total score of the Mini-BESTest.

In the four subscores (i.e., APA, Reactive, Sensory, and Dynamic gait) of the Mini-BESTest, Friedman's test showed significant differences among the PRE, POST, and DISC assessments in all subscores. The post hoc Wilcoxon's signed-rank test showed significant differences between PRE and DISC assessments in all subscores except Reactive ($p = 0.065$). In the comparison of the POST and DISC assessments, there were significant differences in all subscores. There were no significant differences between PRE and POST assessments in all subscores.

3.3. Timed UP and Go Test. One-way repeated measures ANOVA showed significant differences among the PRE, POST, and DISC assessments in the TUG ($F_{2,15} = 5.95$, $p < 0.01$) and TUG-cognitive scores ($F_{2,15} = 5.32$, $p = 0.011$). The post hoc Tukey's test showed significant differences between the RE and DISC assessments in the TUG ($p = 0.026$) and TUG-cognitive scores ($p = 0.031$) and between the POST and DISC assessments in the TUG ($p < 0.01$) and TUG-cognitive scores ($p = 0.016$), while there were no differences between the PRE and POST assessments in the TUG ($p = 0.91$) and TUG-cognitive scores ($p = 0.96$).

3.4. UPDRS-III. Wilcoxon's signed-rank test showed no significant differences between the PRE and DISC assessments in the UPDRS-III total score ($p = 0.45$), UPDRS-III cardinal score ($p = 0.31$), and UPDRS-III PIGD score ($p = 0.49$).

3.5. Barthel Index. Wilcoxon's signed-rank test showed no significant differences between the PRE and DISC assessments in the BI score ($p = 0.22$).

3.6. Levodopa Equivalent Daily Dose. Wilcoxon's signed-rank test showed that there were significant differences between the PRE and DISC assessments and between the POST and DISC assessments in the LEDD ($p < 0.01$), while there were no significant differences between the PRE and POST assessments ($p = 0.87$). Some patients reduced their antiparkinsonian medication in the POST phase, but most of them maintained their LEDD.

4. Discussion

This is the first study to examine the detailed balance and gait abilities of post-STN-DBS surgery PD patients who received postoperative rehabilitation. The present results demonstrated that the postoperative rehabilitation in PD patients treated with STN-DBS was effective in improving balance and gait functions. These findings suggest that the balance and gait functions of PD patients who received rehabilitation treated with STN-DBS could surpass the previous well-medicated balance and gait functions, even though both were in the "on" state.

Many articles reported that the STN-DBS operation was less effective for the axial symptoms of PD patients

Table 2: Demographic data of 32 PD patients.

	Included ($n = 16$)	Excluded ($n = 16$)
Age, years, median (IQR)	61.5 (9.5)	65.5 (11.5)
Sex, females, n (%)	5 (31)	11 (68)
Duration of disease, years, median (IQR)	13.0 (8.0)	13.5 (4.3)
Duration of medication, years, median (IQR)	11.5 (7.0)	11.0 (4.5)
Hoehn and Yahr stage, median (IQR)	3.0 (1.0)	3.0 (0.3)
Final stimulation setting, median (IQR)		
Pulse, microseconds	60.0 (0.00)	60.0 (7.5)
Hz	130.0 (0.0)	130.0 (15.0)
Volts	1.68 (1.21)	2.00 (0.95)
First LEDD	1216 (614)	1281 (473)
Final LEDD	555 (315)	713 (334)
Dominant affected side, right (%)	12 (75)	9 (56)

IQR, interquartile range; LEDD, levodopa equivalent daily dose.

Table 3: The effects of operation and rehabilitation with stimulation.

	PRE	POST	DISC	p value Friedman test		p value (PRE-POST)	p value (POST-DISC)	p value (PRE-DISC)
Mini-BESTTest, median (IQR)								
Total score	19.0 (5.75)	19.0 (5.5)	23.1 (5.5)	<0.01**		0.12	<0.01**	<0.01**
Subscore, APA	4.0 (1.75)	4.0 (1.75)	5.0 (1.0)	<0.01**		0.84	<0.01**	<0.01**
Subscore, reactive	2.5 (4.5)	2.0 (2.75)	4.0 (3.5)	0.038*		0.52	0.017*	0.065
Subscore, sensory	4.5 (2.5)	5.0 (2.75)	6.0 (1.0)	0.035*		0.64	0.042*	<0.01**
Subscore, dynamic gait	8.0 (1.0)	9.0 (2.0)	9.0 (1.75)	0.011*		0.84	0.031*	0.016*
LEDD (mg), median (IQR)	1216 (614)	1216 (508)	555 (315)	<0.01**		0.87	<0.01**	<0.01**
	PRE	POST	DISC	p value ANOVA	F	p value (PRE-POST)	p value (POST-DISC)	p value (PRE-DISC)
TUG (seconds), mean (SD)	9.8 (3.9)	10.1 (4.2)	8.1 (2.3)	<0.01**	5.95	0.91	<0.01**	0.026*
TUG-cognitive (seconds), mean (SD)	16.2 (7.3)	16.6 (11.9)	11.9 (6.1)	0.011*	5.32	0.96	0.016*	0.031*
	PRE		DISC			p value Wilcoxon signed-rank test		
UPDRS-III	17.5 (7.75)		13.5 (9.75)			0.45		
UPDRS-III cardinal score	10 (3.5)		7.5 (7.75)			0.31		
UPDRS-III PIGD score	2 (2.5)		1.5 (2.75)			0.49		
BI, median (IQR)	82.5 (17.5)		90.0 (25.0)			0.22		

IQR, interquartile range; SD, standard deviation; Mini-BESTest, Mini-Balance Evaluation Systems Test; PRE, preoperation; POST, postoperation; DISC, discharge; LEDD, levodopa equivalent daily dose; TUG, Timed Up and Go test; UPDRS-III, unified Parkinson's disease rating scale motor score; UPDRS-III cardinal score, unified Parkinson's disease rating scale motor score-cardinal score (20–26); UPDRS-III PIGD score, unified Parkinson's disease rating scale motor score-postural instability and gait disability score (29-30); BI, Barthel Index. * and ** are $p < 0.05$ and $p < 0.01$ for intergroup comparisons.

[2–6]. It was difficult to determine whether the deterioration of axial symptoms was caused by the disease progression itself or the STN-DBS surgery. The present study showed that the STN-DBS operation did not cause deterioration of the axial symptoms. Some authors suggested that postural instability might be induced by the disturbance of the "dopa-responsive" symptoms (such as rigidity, bradykinesia, and tremor) and "nondopaminergic" automatic spinal circuits [16, 17]. Other researchers concluded that STN-DBS was an effective treatment for the "dopa-responsive" motor symptoms but not for the "nondopaminergic" motor symptoms [3]. The balance improvement in the present study might mean that the postoperative rehabilitation in PD patients treated with STN-DBS could have some effect on the "nondopaminergic" motor symptoms.

There has been only one article that reported the effectiveness of postoperative rehabilitation for PD patients treated with STN-DBS [10]. The authors reported that the STN-DBS operation improved the Motor score of UPDRS-III and the ADLs scores (Functional Independence Measure and BI) of PD patients whose Hoehn and Yahr stages were from 2 to 4. In the present study, there were improvements in detailed balance ability and gait function but not in the BI and UPDRS-III. These results might suggest that the BI and UPDRS-III are not appropriate assessment batteries for early detection of balance deficits. In the present study, the included patients were relatively early-stage patients whose Hoehn and Yahr stages were from 2 to 3, and the aim of the operation was the reduction of medication, motor complications, and duration of the "off" state. The "on" state ADLs scores of patients were comparably good even before

the operation. Although the ADLs and UPDRS-III scores of the present patients were not significantly different between baseline and after rehabilitation, PD patients showed balance deficits at baseline and showed improvements in the balance scores and gait performance during the discharge period. This might indicate that the Mini-BESTest could detect early balance deterioration in PD patients, and postoperative rehabilitation in PD patients treated with STN-DBS could maximize the balance ability of mild PD patients.

5. Limitations

One limitation of this study is that this was a retrospective study with no control group. Because of the ethical constraints, the authors could not intentionally have control patients who did not receive postoperative rehabilitation after the STN-DBS operation. In addition, because of the study design, this study could not evaluate the isolated effect of postoperative rehabilitation and STN-DBS. A further study should plan specific training programs with a dose-matched control study. Moreover, the precise duration of the "on" state was not compared before and after the operation. This study only showed the reduction of LEDD as a benefit of the STN-DBS itself. To solve this issue, the assessment of "on" phase duration should be included in a future study.

6. Conclusion

In summary, the results of a retrospective study that assessed the effectiveness of rehabilitation in PD patients treated with STN-DBS were presented. This study appears to demonstrate that the operation itself did not aggravate the postural instability of PD patients, and postoperative rehabilitation with stimulation improved balance ability and gait performance in PD patients.

Data Availability

The numeric data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Clinical Study

The CuePed Trial: How Does Environmental Complexity Impact Cue Effectiveness? A Comparison of Tonic and Phasic Visual Cueing in Simple and Complex Environments in a Parkinson's Disease Population with Freezing of Gait

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Background. The optimal prescription of cueing for the treatment of freezing of gait (FoG) in Parkinson's disease (PD) is currently a difficult problem for clinicians due to the heterogeneity of cueing modalities, devices, and the limited comparative trial evidence. There has been a rise in the development of motion-sensitive, wearable cueing devices for the treatment of FoG in PD. These devices generally produce cues after signature gait or electroencephalographic antecedents of FoG episodes are detected (phasic cues). It is not known whether these devices offer benefit over simple (tonic) cueing devices. *Methods*. We assembled 20 participants with PD and FoG and familiarized them with a belt-worn, laser-light cueing device (Agilitas™). The device was designed with 2 cueing modalities—gait-dependent or "phasic" cueing and gait-independent or "tonic" cueing. Participants used the device sequentially in the off, phasic, or tonic modes, across 2 tasks—a 2-minute walk and an obstacle course. *Results*. A significant improvement in mean distance walked during the 2-minute walk test was observed for the tonic mode (127.3 m) compared with the off (111.4 m) and phasic (116.1 m) conditions. In contrast, there was a nonsignificant trend toward improvement in FoG frequency, duration, and course time when the device was switched from off to tonic and to phasic modes for the obstacle course. *Conclusions*. Parkinson's disease patients with FoG demonstrated an improvement in distance walked during the two-minute walk test when a cueing device was switched from off to phasic and to tonic modes of operation. However, this benefit was lost when patients negotiated an obstacle course.

1. Introduction

Freezing of gait (FoG) is a common problem in people with Parkinson's disease (PD) and affects up to 87% of patients who have lived with the disease for over 10 years [1]. Whilst PD is a complex, multisystem disorder, FoG has been reported to have a greater impact on quality of life than any other symptom [2]. As the most common cause of falls in

PD, FoG can have serious implications for patient morbidity, mortality, and quality of life. These implications have broader health economics consequences.

Current treatments for FoG generally involve manipulation of daily levodopa dose and timing, coupled with exercise and physiotherapy. There is also promising evidence for amantadine, methylphenidate, and subthalamic nucleus stimulation for the management of FoG, as well as case report level evidence for serotonin and norepinephrine reuptake inhibitors (SNRIs) [3, 4]. The clinical benefit from these interventions is often limited, and a clear need exists for further research aimed at establishing the efficacy of alternate methods of FoG management.

Cueing has long been recognized as a remarkably effective treatment in some patients with FoG [5]. However, given the complex neurobiology of FoG, each patient may respond differently to different cue modalities (e.g., visual, auditory, somatosensory, or cognitive) [6]. To date, there are no established predictors of patient responsiveness to a specific cueing strategy. In a recent meta-analysis that compared visual, auditory, and somatosensory cueing modalities, it was found that all three sensory modalities were comparably effective in a laboratory environment [6]. In contrast, an experimental study reported that visual cues were superior to auditory and vibration cues at assisting people with PD who had difficulties with gait initiation [7]. Unfortunately, the cues delivered in these studies were either (i) fixed, (ii) used a predetermined pulse, or (iii) voluntarily patient triggered. As such, much less is known about the efficacy of motion-triggered (phasic) cues for managing symptoms of FoG in people with PD. Ginis et al. [8, 9] have identified that there are difficulties with the long-term consolidation and transfer of the effects of cueing and further explored the possibilities that exist with advancing technologies, for the management of FoG with external cueing.

The capacity for miniaturization of electronic componentry has spawned the rapid development of a new generation of patient-worn devices, which may be used as cueing devices for the treatment of FoG [10–17]. A range of algorithms for the detection of FoG and the provision of gait-dependent cues are now in the public domain, and the Bachlin–Moore algorithm continues to be improved [10, 12]. In a recent meta-analysis of 23 studies [18], it was shown that studies seeking to detect FoG episodes using wearable sensors were highly variable with respect to the body part used to detect the events. There was also a significant degree of heterogeneity in the mode of cue delivery between studies, with an increasingly complex matrix of design options now available (e.g., modality, pulsed vs. continuous, patient vs. gait-initiated, and mechanical-aid associated). Collectively, these variables have made it difficult to determine the transferability of the reported outcomes to the real-world environment. To progress this field, there is a clear need for head to head comparative studies, where cue modality and/or environment is manipulated, to better understand the utility of cueing devices in all their forms.

The prescription of wearable devices for invivo use remains a significant problem. It is, however, a laudable goal in the knowledge that symptoms of FoG are generally most troublesome for patients in their home environments [15].

While the field continues to move apace, fundamental questions regarding the optimal prescription of cues in specific environments need to be answered. Importantly, we are unaware of how the newer motion-dependent technologies are compared with older technologies in simple versus complex environments. Will the quest for smarter, wearable cueing devices create a treatment that is of any more use than the inexpensive technologies that already exist? To begin to address this question, we designed a laboratory-based experiment with contrasting environments (simple and complex) to test the effectiveness of two different visual cueing modalities provided by a belt-worn cueing device worn by a PD population with FoG.

2. Method

A case series of 20 people with PD who were assessed by 3 local movement disorder neurologists in Brisbane, Australia, were included in the study. Patients were invited to participate in the study, if they were determined by their treating neurologist to have clinically significant FoG, and all participants reported a score ≥3 on item 3 of the Freezing of Gait Questionnaire [19] (Table 1). Participants were excluded if they had (i) a significant medical comorbidity that compromised their mobility; (ii) any visual impairment not corrected with lenses; or (iii) any significant cognitive impairment (Mini Mental State Exam total score <25). The study's protocol was registered with Clinicaltrials.gov (NCT02356536) and approved by the Human Research Ethics Committees at the three Brisbane-based hospitals involved in the trial. All volunteers provided written informed consent in accordance with the Declaration of Helsinki.

Eligible participants completed the Freezing of Gait Questionnaire [19] to establish the frequency and impact of their FoG symptoms, while the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS-III) was used to determine the severity of their motor symptoms. Following the assessments of symptom severity, participants were asked to perform 2 walking tasks that included (i) the 2-minute walk test (2MWT) and (ii) an obstacle course (Figure 1). The obstacle course involved standing from a seated position, walking 7 metres to an open doorway. After passing through the doorway, participants turned left and traversed an uneven walking surface, before weaving between four markers situated on the floor at 2-metre intervals. Once the final marker had been passed, participants turned left and made their way to a seat to sit down. Upon resting their back against the backrest of the seat, participants were asked to stand, turn 180° to their right, and walk towards a chair situated 10 metres away, at the other end of the room. While walking to the chair, participants were required to step over 4 foam obstacles that stood 0.15 metres tall and 1 metre apart. Before sitting, participants completed a full 360° turn in each direction.

While performing each of these tests, participants wore a small belt-mounted device that was designed to detect the

Table 1: Patient characteristics.

	Mean (frequency)	SD (% sample)
Age	70.1	7.2
Gender (male)	15	75
UPDRS-III	36.4	13.5
Falls Efficacy Scale	34.8	12.8
Freezing of Gait Questionnaire	14.3	4.4
Montreal Cognitive Assessment	26.5	2.5
Standardised Mini Mental State Examination	28.4	1.2

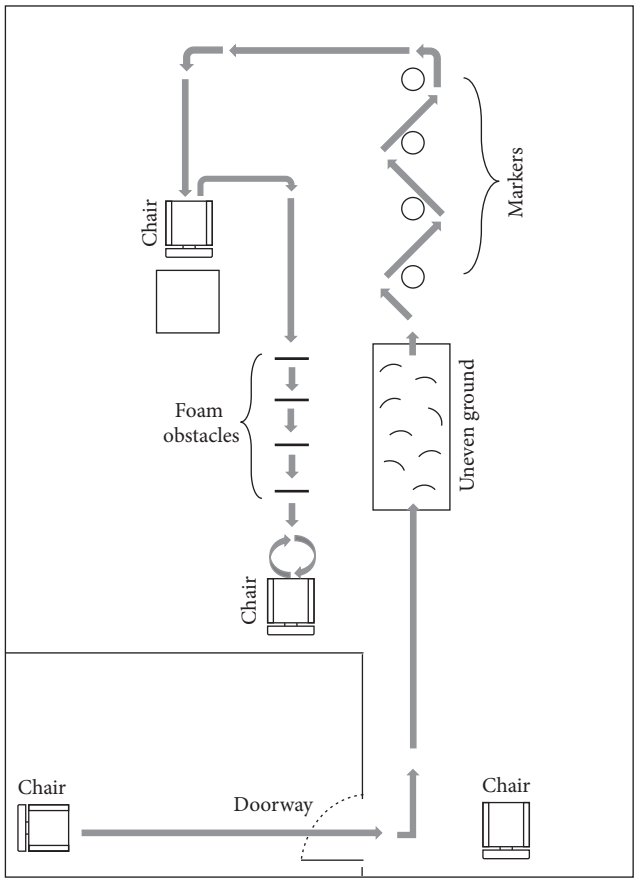

Figure 1: Schematic drawing of the 33-metre obstacle course.

onset of FoG in people with PD using a series of incorporated microsensors (Figure 2). Specifically, this device used built-in accelerometers and gyroscopes sampling at 25 Hz to detect a series of signature kinematic patterns that are known to be antecedents of FoG episodes. When the device detected a kinematic pattern that was indicative of a gait disruption that would typically precede a FoG episode, an incorporated red-light laser pointer was triggered and projected a red dot several metres in front of the participant. While the light was active, the device continued to analyse the data from the in-built sensors and once the data suggested the resumption of steady state walking for at least 3 seconds, the light was extinguished, unless further triggered. To limit the risk of the device not providing a visual cue when an actual freezing episode occurred (i.e., false negatives), the FoG detection algorithm was deliberately calibrated to favour

Figure 2: The belt-worn freeze-detecting visual cueing device. Note: the image shows the pilot light pointing upwards. By turning the device, the orientation of the visual cue can be personalised for each individual.

false positives (i.e., illuminating for complete and near FoG episodes). In addition to the FoG detection mode (i.e., the gait-dependent or "phasic" mode), it was also possible to set the laser pointer to provide a continuous or "tonic" visual cue or to switch it off. To evaluate the efficacy of the visual cueing device and to objectively determine the differences between phasic and tonic visual cueing modes, participants completed the two walking tasks for each of the 3 visual cueing modalities (i.e., off, phasic, and tonic). All trials were video recorded to assist with analysis, and to limit the potential influence of a learning effect and/or fatigue on the reported outcomes, the order of testing conditions was varied between participants. To ensure that the participants were optimally medicated at the time of testing, all procedures were undertaken within 1 to 2 hours of the participants' scheduled levodopa intake.

Following data collection, an associate investigator reviewed the video recordings of the 2MWT and the obstacle course on two occasions separated by at least one week. At each of these time points, the investigator identified the number and duration of FoG episodes experienced by each participant while performing the tasks with each of the visual cueing modalities. Statistical comparison of the two assessments indicated excellent intrarater reliability for the quantification of both the number (ICC: 0.930 to 0.975) and duration (ICC: 0.976 to 0.999) of FoG episodes for all visual cueing modes. In addition to recording the number and duration of freezing episodes, the distance covered by the participants during the 2MWT was also recorded in metres, while the time taken to complete the obstacle course was measured in seconds.

3. Statistical Analysis

The Shapiro–Wilk test was used to confirm that the primary outcomes were not normally distributed ($p < 0.05$) and supported the decision to use nonparametric statistical procedures. To statistically compare any mean differences between the off, phasic, and tonic visual cueing modalities for the frequency and duration of freezing episodes, the distance covered during the 2MWT, and/or the time taken to complete the obstacle course, the Friedman test was used. When a significant main effect was identified for cue type, pairwise comparisons were conducted with the Wilcoxon signed-rank test to further explore differences between the different visual cueing modalities. All statistical procedures were conducted using SPSS v.24, and the level of significance was set at $p < 0.05$.

4. Results

The results of the statistical analyses indicated that, while there was a gradient of improvement from the off to phasic and to tonic modes for all three measures, neither the frequency nor the duration of FoG episodes recorded during the 2MWT reached statistical significance (Table 2). However, a significant main effect was returned for distance walked by the patients during the 2MWT, with pairwise comparisons indicating that the participants walked further with the tonic visual cue compared with the off ($p = 0.026$) and phasic ($p = 0.008$) visual cue modalities.

While negotiating the obstacle course, there was no statistically significant improvement in FoG frequency ($p = 0.192$), FoG duration ($p = 0.173$), and course time ($p = 0.357$) from the off condition to the tonic condition and the phasic condition (Table 3).

Whilst ultimately proving to be underpowered, due to the small differences in performance across modalities, the joint probability of the observed gradients of the 18 means across both courses was $p < 0.001$ (0.00002).

5. Discussion

Although FoG is a disabling and common problem in PD, there is a growing body of evidence for the benefits of cueing strategies in its treatment [6]. Specifically, previous research reports that the use of external cues can improve a range of gait parameters in PD patients, including gait speed, stride length, step variability, and cadence [20]. It is not known, however, whether cueing that is triggered in response to the specific kinematic events that precede the occurrence of a FoG episode is more effective than cueing that is fixed and independent of the FoG episode. Furthermore, it is not known how environment complexity may impact the effectiveness of these two cue modalities. While there is no accepted terminology for fixed versus motion-sensitive cues, we have chosen the terms "tonic" and "phasic" cueing as we believe these to be apt and widely understood terms that have historical neurophysiological meaning.

The results of our study showed that PD patients with FoG walked a greater distance during a 2-minute walk test with a tonic visual cue, compared with both the off ($p = 0.026$) and phasic ($p = 0.008$) cueing conditions. Because the distance walked improved but not the FoG duration and frequency, one explanation could be that the tonic availability of a visual cue for participants simply increased step amplitude and inhibited the sequence effect known to precede FoG. However, when subjects were asked to complete an obstacle course, there was a nonstatistically significant reduction of freezing episodes, freezing times, and course completion times when the device was switched from the off to tonic and to phasic modes.

Taken together, these results may suggest a superiority of a tonic cueing strategy in the simple environment of the 2-minute walk task but not in the complex environment of the obstacle course. While main effect measures and pairwise comparison of means were otherwise nonsignificant, it bears consideration that the differential gradients observed for every measure favoured tonic cueing during the simple 2MWT, while phasic cueing was better in the complex obstacle course. The reduced benefit of tonic cueing during the obstacle course could point to an influence of "environmental attention burden" on the cue's effectiveness and possibly shines further light on the pathophysiology of FoG and the mechanism of action of cueing.

There are currently four prevailing models that are used to understand the phenomenon of FoG [21]: (i) the threshold model; (ii) the neural reserve model; (iii) the cognitive model; and (iv) the decoupling model. However, the complex findings presented in this study do not specifically fit with any of these models and, hence, leads us to speculate that the central place of attention and attention regulation may be sufficiently important to warrant the proposition of a fifth distinct "Bayesian" model. There has been an increasing interest in conceptualizing neurological function and dysfunction through the lens of Bayes' theorem [22]. In the neurosciences, the approach has been useful, with the notion that the reconciliation of priors (that is, previously-encoded programs) with current data (that is, sensory input) can go awry. Attention acts as the modulator between these two domains, and it appears that the model fits with what is observed in FoG and may be supported by our findings.

Freezing occurs as an intermittent, dynamic process, precipitated by events thought to confer attentional cost to the subject, such as dual tasking, anxiety, or turning. It arises in a setting where there is already a loss of gait automaticity. Our findings pose the question of whether the disruption of misplaced attention brought on by cueing somehow facilitates a return to automaticity or a cortical takeover of the movement as suggested by Plotnik et al. [23].

Recent work utilizing virtual reality paradigms and fMRI scanning in simulated FoG shows an impaired "change" activation in the pre-supplementary motor area (SMA) region purported to be due to reduced feed-forward processing [24]. Circumstances requiring internally driven motor control (priors) are known to utilize bottom-up, dorsal visual pathways, described as covert attention. It is suggested that it is this covert attention that requires support and that it may be plausible that visual cueing's mechanism of action is through supporting this system.

Table 2: The frequency and duration of freezing episodes and the distance walked by the participants during the 2MWT completed under the off, tonic, and phasic visual cue conditions. Data represent means and standard deviations.

	Visual cue modality			Main effect	Pairwise comparisons		
	Off	Tonic	Phasic	p value	Off vs. tonic	Off vs. phasic	Tonic vs. phasic
FoG frequency (n)	1.11 (2.23)	0.95 (1.65)	1.06 (1.71)	0.459			
FoG duration (s)	5.42 (11.82)	2.68 (5.61)	3.47 (5.75)	0.114			
Distance (m)	111.44 (80.51)	127.30 (87.06)	116.08 (81.89)	0.014	0.026	0.394	0.008

Note. Off = no visual cue; tonic = continuous visual cue (i.e., gait-independent); phasic = FoG-sensitive visual cue (i.e., gait-dependent).

Table 3: The frequency and duration of freezing episodes and the time taken to complete the obstacle course under the off, tonic, and phasic visual cue conditions. Data represent means and standard deviations.

	Visual cue modality			Main effect	Pairwise comparisons		
	Off	Tonic	Phasic	p value	Off vs. tonic	Off vs. phasic	Tonic vs. phasic
FoG frequency (n)	2.88 (2.69)	1.82 (2.24)	1.71 (1.57)	0.192			
FoG duration (s)	28.88 (43.91)	18.41 (48.41)	15.35 (36.07)	0.173			
Course time (s)	99.76 (51.83)	82.65 (55.12)	81.06 (43.07)	0.357			

Note. Off = no visual cue; tonic = continuous visual cue (i.e., gait-independent); phasic = FoG-sensitive visual cue (i.e., gait-dependent).

Although untestable in a moving patient, it seems likely that tonic cueing may provide more optimal attention network and pre-SMA support in a simple environment and facilitate a return to automaticity and motor priors. In a more complex environment, such as an obstacle course with greater attentional demands, attention must be made available for current environmental sensory data in preference to motor priors. As such, a tonic visual cue would not suffice in this setting and another mechanism would be needed.

Plotnik et al. [23] suggested that a cortical takeover of movement occurs with cueing. The question arises as to whether a cortical takeover or a return to automaticity might predominate and whether this is dependent on the attention burden of the environment being negotiated.

6. Conclusions and Future Directions

This study suggests a superiority of tonic visual cueing over phasic or no visual cueing in a PD population with FoG when performing a 2-minute walk test in a simple environment. However, this finding was not maintained in the complex environment of an obstacle course in the same population. A nonsignificant differential gradient of improvement of all measures favouring tonic cueing in a simple environment and phasic cueing in a complex environment was observed. This may have implications for the use of visual cueing as a treatment for FoG in PD populations.

Further research is needed to consolidate this study's findings and determine whether there is benefit of phasic cueing over both continuous and pulsed tonic cueing. Furthermore, there is a clear need for studies to examine the effectiveness of patient-worn cueing devices for a longer duration of time, in a home environment, where freezing is often worse.

For this to be achievable, beyond the detection of antecedents of an impending freeze, the device would need to be capable of reliably detecting and measuring the FoG episodes themselves, to meaningfully function as a remote patient monitoring device. Given the heterogeneity of FoG, this task represents a significant challenge but is an exciting prospect in the treatment of these symptoms.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Do Upper and Lower Camptocormias Affect Gait and Postural Control in Patients with Parkinson's Disease? An Observational Cross-Sectional Study

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Gait impairments and camptocormia (CC) are common and debilitating in patients with Parkinson's disease (PD). Two types of CC affect patients with PD, but no studies investigated their relative contribution in worsening gait and postural control. Therefore, we investigated spatiotemporal gait parameters, gait variability, and asymmetry and postural control in PD patients (Hoehn & Yahr ≤4) with upper CC and lower CC and patients without CC. This observational cross-sectional study involving patients with PD and upper CC ($n = 16$) and lower CC ($n = 14$) and without CC ($n = 16$). The primary outcome measure was gait speed assessed by the GAITRite System. The secondary outcome measures were other spatiotemporal parameters, gait variability, and asymmetry. Postural control and balance were assessed with posturography and the Mini-BESTest. Patients with lower CC showed a higher H&Y stage ($p = 0.003$), a worse PDQ8 ($p = 0.042$), and a lower Mini-BESTest score ($p = 0.006$) than patients with PD without CC. Patients with lower CC showed a reduced gait speed ($p = 0.012$), stride length, and velocity than patients with PD without CC. Upper CC patients showed a higher stride length than lower CC ones ($p = 0.007$). In the eyes open and closed condition, patients with lower CC showed a higher (worse) velocity of CoP displacement in mediolateral direction and length of CoP than patients with PD without CC. No significant between-group differences were measured in gait variability and asymmetry. In conclusion, lower CC was associated with more severe gait and postural control impairment than patients with upper CC and without CC. Categorizing CC based on the bending fulcrum is compulsory to identify patients with the worst performance and to implement specific rehabilitation programs.

1. Introduction

Gait impairments and camptocormia (CC) are common and debilitating in patients with Parkinson's disease (PD) [1–6]. They impose substantial disability on these patients, increasing the risk of falling, and related injuries, and reducing the quality of life [1–6]. According to a recent conceptual model, gait disturbances can be characterized using a principal component analysis in five independent domains: pace, rhythm, variability, asymmetry, and postural control domains [7]. In PD, the three principal gait impairments (gait slowness, increased variability, and postural control deficits) fall into these domains [5].

In the current literature, the influence of postural abnormalities on gait disturbances has been rarely explored. On the one hand, it depends on the fact that a consensus of diagnostic criteria on postural abnormalities in PD has been only recently reached. Pisa syndrome was defined as at least

10° lateral flexion of the trunk, which typically resolves by passive mobilisation or supine positioning [3]. Antecollis relates to forward flexion of the neck (minimum 45°) [3]. Finally, camptocormia (CC) has been recently fully characterised as a sagittal plane deformity originating either in the thoracic or lumbar spine appearing during standing or walking and resolving in the supine position [2].

On the other hand, CC has been incorrectly considered as a single entity. Nowadays, a consensus has been reached in differentiating forward trunk flexion in lower and upper camptocormias. The former refers to "an involuntary flexion of the spine of at least 30° at the lumbar fulcrum (L1-Sacrum)." The latter refers to "an involuntary flexion of the spine of at least 45° at the thoracic fulcrum (C7 to T12-L1)" [2]. This additional classification allows the clinician to define deformities in the sagittal plane better and then to investigate whether the different types of CC would impose specific disability in patients with PD.

So far, only two studies have explored the influence of postural abnormalities in gait dynamics and postural control [8, 9]. Geroin et al. reported for the first time that patients with Pisa syndrome (PS) showed higher (worse) postural instability than age-matched patients with PD but without PS and healthy controls (irrespective of side and severity). Patients with PD and PS reported a significantly higher velocity of the Center of Pressure (CoP) displacement in the mediolateral and anteroposterior directions than the other two groups, with the worst performance in the eyes, closed condition. No significant differences were reported on spatiotemporal gait parameters among groups [8]. In a recent observational cross-sectional study, Tramonti et al. investigated gait dynamics using 3D Gait analysis and clinical scales in patients with PD and PS, with CC, and without postural deformities. Gait speed, stride, and step length decreased in patients without postural abnormalities and PS and CC groups compared to healthy subjects. Functional abilities and disease severity were worse in the PS and CC patients than patients without postural abnormalities. Kinematic data revealed a marked reduction in the lower-extremity range of motion (ROM) in the patients with PS. However, the CC group showed a more noticeable reduction in hip and knee joints range of motion suggesting an increased hip flexion pattern during gait [9]. The main study limitation is the lack of distinction between upper and lower CC. The diagnosis of CC should take into account both the bending angle and fulcrum to be correctly categorised and differentiated from a generically stooped posture [2].

To our knowledge, no studies to date have explored the relative contribution to gait impairment and postural control of the upper and lower CC in patients with PD. Moreover, gait variability and asymmetry have not been previously investigated in these populations. The primary aim of this study was to investigate gait speed differences in patients with PD with upper and lower CC and patients with PD without CC.

The secondary aim was to investigate changes in the other spatiotemporal gait parameters according to the conceptual models of gait [7] between patients with PD with upper and lower CC and patients with PD without CC. We hypothesized that patients with lower CC would be more affected than other groups in both gait and postural control due to biomechanical constraints to the lumbar/sacral region.

2. Materials and Methods

2.1. Study Design and Setting. An observational cross-sectional study involving patients with PD with upper CC and lower CC and without CC (PD) was conducted. Patients were recruited from the outpatient's clinic of the Movement Disorders Division and the UOC Neurorehabilitation Unit of the University Hospital (AOUI Verona, Italy) from March 2018 to October 2018.

2.2. Participants. Forty-six patients with PD (mean age 70.9 ± 6.6) were divided into three groups: patients with upper CC ($n = 16$), lower CC ($n = 14$), and without CC ($n = 14$). The severity of forward trunk flexion was evaluated using a software-based measurement of the undressed (with underwear) body patients' pictures. The lateral view pictures of the patients were taken with the camera lens at approximately waist level. The measurements were performed by an experienced rater using a freeware program Kinovea® [10].

Patients were diagnosed with CC when presenting an "involuntary flexion of the spine appearing during standing or walking and resolving in the supine position of at least 30° at the lumbar fulcrum (L1-sacrum and hip flexion, i.e., lower CC) or at least 45° at the thoracic fulcrum (C7 to T12-L1, i.e., upper CC)" [2].

At the enrolment, all patients underwent a neurological screening and physical examination. Inclusion criteria were age ≥18 years old; clinical diagnosis of PD according to MDS clinical diagnostic criteria [11]; Hoehn & Yahr (H&Y) stage ≤4 in the "ON" medication phase and on their usual antiparkinsonian treatment. Exclusion criteria were severe dyskinesia or "on-off" fluctuations; PD medication modification in the 3 months preceding the enrolment; the presence of PS [3]; a history of major spinal surgery or muscle and/or skeletal spine diseases (namely, vertebral fractures, spondylodiscitis, and inflammatory myopathy); need for assistive devices to rise from a chair or bed; other neurological (i.e., vertigo and vestibular disorders), orthopedic, or cardiovascular comorbidities that could interfere with gait; and ability to walk for at least 10 meters without the use of device. Patients gave their written, informed consent after being informed about the experimental nature of the study. The authorization has been obtained for disclosure (consent-to-disclose) of any recognizable persons in photographs. The study was carried out following the Helsinki Declaration, approved by the local Ethics Committee (prog. no. 2399).

2.3. Testing Procedures. Demographic and clinical variables were collected by an MDS specialist and included age, gender, Unified Parkinson's Disease Rating Scale total score and Part III (UPDRS III), H&Y stage, PD phenotype (rigid-

akinetic, tremor-dominant, or mixed type) [12], Montreal Cognitive Assessment (MOCA) Score [13]; Parkinson's Disease Questionnaire-8 Score (PDQ8) [14], the number of falls in the previous month [15], the Mini-BESTest [16], and the Numeric Rating Scale (NRS) to quantify back pain.

All patients underwent instrumental gait assessment using the GAITRite walkway system (CIR Systems Inc, Havertown, PA) 7.92 m in length and sampling at a frequency of 120 Hz. The patients walked at a self-selected comfortable speed without walking aids. The data from the three trials were collected, and their average was calculated. Gait parameters were selected following a model developed in older adults and validated in PD composed of five domains [7, 17]: (1) pace domain: gait speed (cm/s), stride, and step length (cm), width of base of support (cm), and stride velocity (cm/sec); (2) rhythm domain: cadence (step/min), step time (sec), swing time (sec), stance time (sec), single support time (sec), and double support time (sec); (3) phases: swing %, stance %, single %, and double support % of gait cycle; (4) asymmetry domain: step length and stance time calculated as the absolute difference between left and right step means; (5) variability measures were quantified using the coefficient of variation, e.g., stride length variability = 100 × (SD of stride length/average stride length) [18, 19]. The coefficient of variability for the stride length, base of the support, double support time, and stride velocity was computed as related to falling in older adults [20].

Posturography was performed in the standing position on an electronic monoaxial platform (Technobody©). The feet position on the platform was standardized using a V-shaped frame for all patients. The distance between the two malleoli was 3 cm, and the medial borders of the feet were extra rotated 12° with respect to the anteroposterior axis. The patients were evaluated while standing upright without the use of upper limb support in the eyes open (EO) and the eyes closed (EC) condition, each lasting 30 s [8]. The following outcomes were recorded: the velocity of the CoP displacement in the anteroposterior and mediolateral direction (mm/sec), length of CoP trajectory (mm), and sway area (mm^2) (Figure 1).

The primary outcome measure was gait speed while secondary outcome measures were other spatiotemporal parameters, gait variability and asymmetry, and stabilometric outcomes.

2.4. Statistical Analysis. Descriptive statistics included calculation of frequency tables, means, and standard deviation. Absolute and relative frequencies were calculated for categorical data and tested by Fisher's Exact test after checking the minimum acceptable number of expected frequencies (<5). Variables were tested for normality with the Shapiro–Wilk test. When the continuous variables were normally distributed, the comparisons across groups (PD vs upper CC vs lower CC) were performed with parametric tests. The equality of variances (homogeneity) was checked using Levene's test. If variances were heterogeneous, we used Welch's ANOVA test, otherwise the one-way ANOVA. The post hoc comparisons were performed with the Tukey test. When the continuous variables were not normally distributed, the comparisons across groups (PD vs upper CC vs lower CC) were performed with nonparametric Kruskal–Wallis H test. The post hoc comparisons were performed with the Mann–Whitney U test.

Further, Pearson's or Spearman's coefficient was used to analyze the correlations between spatiotemporal gait parameters (gait speed and stride length), posturographic parameters (eyes open/close velocity of mediolateral CoP displacements and length of CoP), and H&Y stage in the three groups. All tests were bilateral at $p < 0.05$. Statistical analysis was carried out using the SPSS for Mac statistical package, version 20.0.

3. Results

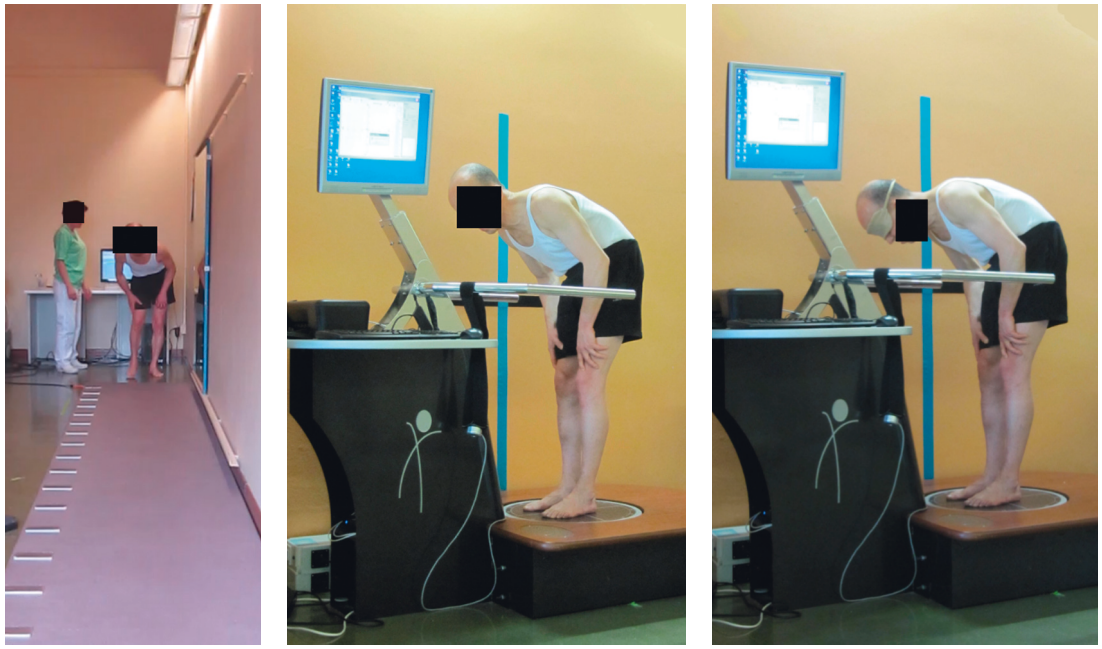
Patients recruited were receiving chronic therapy with a dopaminergic drug and showed good motor compensation in appendicular function. None had psychiatric disturbances. Patients with upper CC had a forward trunk flexion of $47.64 \pm 2.66^\circ$, and 8 showed a back pain with NRS of 3.2 ± 1.7. Patients with lower CC had a forward trunk flexion of $48.24 \pm 13.85^\circ$, and 9 showed a back pain with NRS of 4.7 ± 2.2. Patients without CC had a forward trunk flexion of $19.12 \pm 20.25^\circ$, and 8 showed a back pain with NRS of 3.1 ± 1.4.

We found a main effect for the H&Y ($F = 5.04$; $df = 2$, $p = 0.011$), PDQ8 ($p = 0.043$), and the Mini-BESTest ($F = 5.55$; $df = 2$, $p = 0.007$) (Table 1). Post hoc analysis revealed a significant difference between PD and patients with lower CC in the H&Y stage ($p = 0.003$), PDQ8 ($p = 0.042$), and Mini-BESTest ($p = 0.006$).

3.1. Primary Outcome Measures. A significant main effect in the gait speed ($F = 5.37$; $df = 2$, $p = 0.011$) was measured. Post hoc analysis revealed that patients with lower CC had a significantly reduced gait speed than patients with PD ($p = 0.012$).

3.2. Secondary Outcome Measures. A significant main effect in the stride length ($p < 0.001$), step length ($p < 0.001$), and stride velocity ($F = 5.39$; $df = 2$, $p = 0.011$) was reported. Post hoc analysis revealed a significant difference in stride length between PD and patients with lower CC ($p < 0.001$) and between patients with lower CC and upper CC ($p = 0.007$). In step length, a significant difference between PD and patients with lower CC ($p < 0.001$) and between patients with lower CC and upper CC ($p = 0.008$) was measured. Patients with lower CC showed a significant shorter stride and step length than patients with PD and upper CC. In stride velocity, post hoc analysis revealed a significant difference between PD and patients with lower CC ($p = 0.012$). Post hoc analysis revealed that patients with lower CC had a significant slower stride velocity than patients with PD. No statistically significant results were reported in the other spatiotemporal gait parameters.

In the eyes open condition, a significant main effect in the velocity of CoP in the mediolateral direction ($p = 0.004$)



(a) (b) (c)

Figure 1: A patient with lower CC during the gait (a) and posturographic assessment with eyes open (b) and eyes closed condition (c).

Table 1: Demographic and clinical characteristics of the patients.

	Total Group	CC Upper	CC Lower	PD	p Value
Patients, no.	46	16	14	16	
Age, mean (SD), yrs	70.9 (6.6)	71.6 (4.36)	70.3 (8.21)	70.7 (7.3)	0.787[c]
Gender, M/F	31/15	12/4	7/7	12/4	0.283
UPDRS total score	53.1 (23.9)	53 (30.2)	59.6 (18.4)	47.5 (21.1)	0.250[c]
UPDRS III score	29.7 (14.3)	29.2 (17.6)	33.9 (11.9)	26.4 (12.2)	0.283[c]
H&Y stage	2.2 (0.8)	2.2 (0.9)	2.6 (0.6)	1.8 (0.6)	**0.011**[*a]
Dominant phenotype, n (%)					0.131[c]
Tremor type	11 (24)	5 (31.2)	1 (7.2)	5 (31.2)	—
Bradykinetic/rigid type	29 (63)	7 (43.8)	12 (85.7)	10 (62.5)	—
Mixed type	6 (13)	4 (25)	1 (7.1)	1 (6.3)	—
MoCA	24.3 (3.3)	23.7 (3.9)	24.1 (3.1)	25.2 (3.1)	0.545[c]
PDQ8	20.1 (13.3)	18.2 (11.8)	25.9 (13.1)	16.8 (14)	**0.043**[*ac]
Falls	1.1 (1.9)	1.2 (2.5)	1.6 (1.8)	0.5 (0.9)	0.175[c]
Mini-BESTest	19.6 (5.6)	19.1 (6.5)	16.6 (4.7)	22.7 (3.6)	**0.007**[*a]

CC denotes patients with Parkinson's disease and camptocormia according to consensus-based diagnostic criteria (Fasano2018); PD, patients with Parkinson's disease (without CC); SD, standard deviation; M, Male; F, Female; yrs, years; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS III, subitem of UPDRS scale part III; H&Y, Hoehn and Yahr stage; MoCA, Montreal Cognitive Assessment; PDQ8, Parkinson' s Disease Questionnaire-8; Falls, number of falls in the previous month; [a]Welch's ANOVA test; [b]Fisher's exact test; [c]Kruskal–Wallis H test; p significant if < .05; values with * and in bold are considered statistically significant.

and length of CoP ($p = 0.019$) was reported. Post hoc analysis revealed a significant difference between PD and patients with lower CC in the velocity of CoP ($p = 0.003$) and the length of CoP ($p = 0.014$).

Similarly, a significant main effect in the velocity of CoP in mediolateral direction ($p = 0.011$) and length of CoP ($p = 0.015$) was measured in the eyes closed condition. Post hoc analysis revealed a significant difference between PD and patients with lower CC in the velocity of CoP ($p = 0.009$) and the length of CoP ($p = 0.014$).

In eyes open and closed condition, patients with lower CC revealed a higher velocity of CoP in mediolateral direction and length of CoP than patients with PD. We did not find any other statistically significant results.

No significant correlation coefficients were found between spatiotemporal gait parameters (gait speed and stride length), posturographic parameters (eyes open/closed velocity of mediolateral CoP displacements and length of CoP), and H&Y stage in the three groups.

4. Discussion

The main finding of this study is that the patient with lower CC exhibited the highest degree of gait and postural control

Table 2: Multiple pairwise comparisons between the three groups for each outcome measure.

Spatiotemporal gait parameters	CC Upper	CC Lower	PD	p Value main effect
Pace domain				
Gait speed (cm/s)	96.27 (16.62)	79.05 (20.74)	108.55 (30.90)	**0.011***
Stride length (cm)	106.27 (15.36)	83.61 (4.74)	115.26 (21.93)	**<0.001***
Step length (cm)	53 (7.69)	41.67 (8.81)	57.42 (10.95)	**<0.001***
Width of base support (cm)	8.77 (3.04)	9.71 (3.91)	8.95 (3.07)	0.725
Stride velocity (cm/s)	97.05 (16.55)	79.81 (20.91)	109.66 (31.05)	**0.011***
Rhythm domain				
Cadence (step/min)	109.04 (10.89)	113.10 (15)	111.94 (13.23)	0.679
Step time (sec)	0.55 (0.06)	0.54 (0.07)	0.54 (0.06)	0.723
Swing time (sec)	0.42 (0.04)	0.38 (0.04)	0.40 (0.03)	0.149
Stance time (sec)	0.69 (0.07)	0.68 (0.11)	0.68 (0.09)	0.924
Single support time (sec)	0.42 (0.04)	0.38 (0.04)	0.40 (0.03)	0.149
Double support time (sec)	0.28 (0.04)	0.30 (0.10)	0.28 (0.08)	0.966
Phases				
Swing % of gait cycle (%)	37.48 (1.43)	36.26 (3.22)	37.31 (2.62)	0.673
Stance % of gait cycle (%)	62.52 (1.44)	63.73 (3.22)	62.70 (2.62)	0.687
Single support % of cycle	37.49 (1.41)	36.25 (3.23)	37.32 (2.61)	0.643
Double support % of cycle	25.07 (2.87)	27.35 (6.51)	25.36 (5.12)	0.704
Asymmetry				
Step length difference (cm)	4.12 (2.65)	2.97 (2.11)	2.36 (1.51)	0.072
Stance time difference (sec)	0.01 (0.03)	0	0	0.365
Coefficient of variability				
Stride length, CV	5.18 (1.96)	5.83 (2.62)	4.77 (2.11)	0.479
HH base support, CV	22.88 (12.79)	22.97 (13.33)	24.06 (11.11)	0.957
Double support time, CV	14.81 (11.08)	13.24 (7.06)	13.65 (7.92)	0.995
Stride velocity, CV	7.74 (2.89)	9.24 (4.29)	7.78 (2.95)	0.674

CC denotes patients with Parkinson's disease and camptocormia according to consensus-based diagnostic criteria [2]; PD, patients with Parkinson's disease (without CC); p significant if <0.05; values with * and in bold are considered statistically significant.

Table 3: Multiple pairwise comparisons between the three groups for each posturography measure.

Posturography	CC Upper	CC Lower	PD	p Value main effect
Variables eyes open				
VEL_MED_AP (mm/sec)	4.25 (2.08)	5.78 (3.55)	3.56 (1.31)	0.086
VEL_MED_ML (mm/sec)	3.25 (1.34)	4.57 (2.03)	2.56 (1.09)	**0.004***
Length CoP (mm)	149.12 (62.92)	206.50 (106.65)	121.18 (43.90)	**0.019***
Sway area (mm^2)	93.62 (108.71)	125.14 (110.33)	79.56 (61.72)	0.518
Variables eyes closed				
VEL_MED_AP (mm/sec)	6.18 (2.76)	7.78 (5.21)	4.37 (1.63)	0.050
VEL_MED_ML (mm/sec)	4.56 (1.78)	6.28 (3.45)	3.37 (1.74)	**0.011***
Length CoP (mm)	215.50 (86.26)	282.21 (163.26)	157.25 (59.65)	**0.015***
Sway area (mm^2)	168.44 (171.36)	181.86 (122.67)	113 (125.57)	0.069

CC denotes patients with Parkinson's disease and camptocormia according to consensus-based diagnostic criteria [2]; PD, patients with Parkinson's disease (without CC); CoP, centre of pressure; VEL_MED_AP, velocity of anteroposterior CoP displacement; VEL_MED_ML, velocity of mediolateral CoP displacement; p value, Kruskal–Wallis test; P significant if <0.05; values with * and in bold are considered statistically significant.

impairment. Our data extend previous data on the influence of CC on functional performance during walking and, for the first time in the literature, showed that the two types of CC may affect (or not) gait and postural control [2, 9].

According to the literature [2, 3], the presence of CC was associated with higher neurological severity, worse balance performance, and quality of life than patients without CC, as reported in Table 1. However, only patients with lower CC reported scores significantly worse than patients without CC. Gait analysis and postural assessment showed that lower CC was associated with a significant reduction in performance in the pace domain (except for the width of the base of support). Besides, a significant increase in the velocity of the CoP displacement in mediolateral direction and length of CoP in both eyes open and closed conditions was reported. This finding was significantly different between upper and lower CC strengthening, the hypothesis that lower CC affects gait more than the upper type. Thus, the forward trunk flexion by lower fulcra may be the most disabling postural abnormalities in patients with PD.

CC is not a levodopa-responsive abnormality that can be (before being more fixed) fully reversible in the supine position and using manoeuvres like "sensory tricks" (i.e., the patients to stand up straight or against a vertical reference) [4]. The existing evidence suggests that CC may have multifactorial pathophysiology involving central and peripheral hypotheses [3, 4]. The former, supported by animal and clinical studies, takes into account an asymmetric functioning of basal ganglia output leading to asymmetric control of trunk muscles tone (dystonia) along with an altered internal model of postural perception [4]. The latter considers CC as a consequence of paraspinal myopathy due to the pathophysiology of PD. However, this possibility needs to be further investigated [4]. Distinct muscles patterns might be involved in the bimodal distribution of forward trunk flexion. In the upper CC, a bilateral overactivity of abdominal external and internal oblique along with rectus abdominis muscles has been described [4, 21–23].

In contrast, in the lower subtype, combined activation of rectus abdominis and iliopsoas muscles has been reported [4]. Our finding suggested two mutually nonexclusive hypotheses. From a biomechanical perspective, the lower CC may compromise the iliopsoas function. As reported by the physiological literature, the iliopsoas muscle flexes the femur in the standing position and acts as a stabilizer of the femoral head in the hip acetabulum in the first 15° of movements. Finally, it maintains the director action from 15° to 45° degrees and acts as an effective flexor of the femur from 45 to 60° [24]. The reduced stride length and gait speed found in patients with lower CC might be explained by the pathological flexion of the trunk during gait limiting the hip extension. The reduction of hip extension, indeed, is a primary factor in the reduction of the ROM at the hip, step length, and gait speed [5, 9]. Moreover, the excessive flexor muscle activity at the knee and ankle further reduced lower limb joint torques during walking [6].

From a neurological perspective, gait slowness may be the result of more severe hypokinesia (reduced step size), bradykinesia (increased step duration), and axial rigidity. It would explain why patients with lower CC displayed a severe neurological severity, as measured by the H&Y stage.

Walking can be understood as a repeated sequence of the centre of mass displacements to maintain lateral and forward stability [6]. A decrease of gait speed is a self-imposed compensatory strategy to maintain balance during walking in PD. The low gait speed observed in patients with lower CC can be related to a worsening of balance control, as measured by the mediolateral CoP displacement. The abnormal flexed posture observed in lower CC pushes the CoP forward the base of support at the limits of stability. The literature emphasised that the lateral control of balance is impaired in patients with PD showing elevated lateral trunk sway during stance and walking [5] and it is associated with falls [6]. Patients with lower CC might be less prone to sway in the anteroposterior direction than in the mediolateral direction because of the hyperflexed posture limiting the hip range of motion in the anteroposterior direction. As a consequence, the patient with lower CC reported a higher number of falls than the other two groups, albeit not significant.

The three groups were comparable in gait variability and asymmetry, suggesting that these domains might be independent of the CC and related to the disease severity itself [6]. According to the literature, our results suggest that gait variability is independent of gait speed, cadence, and stride length [25]. An increase in gait variability in PD is expected in comparison with healthy controls presumably related to basal ganglia dysfunction and not to CC [25, 26]. Gait speed and stride length parameters showed in our PD patients were similar to findings reported in older adults [27]. It suggests that the stage of disease and phenotype have a primary role in impairing gait and balance in PD.

The main study limitation is the lack of 3D gait analysis to assess trunk and lower limbs during gait quantitatively. Larger sample size may strengthen the statistics of the study and display significant differences among groups not found in our preliminary report.

5. Conclusions

Lower CC was associated with more severe gait and postural control impairment than upper CC and without CC. Categorizing CC based on the bending fulcrum is compulsory to identify patients with the worst outcome and to implement specific rehabilitation programs. Future rehabilitation studies are needed to assess the rehabilitation effects on the severity of the forward trunk flexion and postural control in patients with lower camptocormia (Tables 2 and 3).

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

Christian Geroin, Marialuisa Gandolfi, Nicola Smania, and Michele Tinazziare contributed equally to this work.

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Research Article

Age Matters: Objective Gait Assessment in Early Parkinson's Disease Using an RGB-D Camera

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Background. Gait alterations are hallmarks for the diagnosis and follow-up of patients with Parkinson's disease (PD). In normal conditions, age could affect gait dynamics. Although it is known that objective assessment of gait is a valuable tool for diagnosis and follow-up of patients with PD, only few studies evaluate the effect of aging on the gait pattern of patients with PD. *Objective*. The purpose of this study was to assess differences in gait dynamics between PD patients and healthy subjects and to investigate the effects of aging on these differences using a low-cost RGB-D depth-sensing camera. *Methods*. 30 PD patients and 30 age-matched controls were recruited. Descriptive analysis was used for clinical variables, and Spearman's rank correlation was used to correlate age and gait variables. The sample was distributed in age groups; then, Mann–Whitney U test was used for comparison of gait variables between groups. *Results*. PD patients exhibited prolonged swing ($p = 0.002$) and stance times ($p < 0.001$) and lower speed values ($p < 0.001$) compared to controls. This was consistent in all age groups, except for the one between 76 and 88 years old, in which the controls were slower and had longer swing and stance times. These results were statically significant for the group from 60 to 66 years. *Conclusion*. Gait speed, swing, and stance times are useful for differentiating PD patients from controls. Quantitative gait parameters measured by an RGB-D camera can complement clinical assessment of PD patients. The analysis of these spatiotemporal variables should consider the age of the subject.

1. Introduction

PD is the second most common neurodegenerative disorder worldwide, and its incidence is highly increasing even surpassing other neurological diseases such as Alzheimer's disease. Primary motor symptoms of PD include bradykinesia, rigidity, postural instability, and tremor [1]. Some of these symptoms affect the lower limbs and alter gait pattern of patients.

Spatiotemporal characteristics of gait are recognized as valuable tools for evaluation and decision-making processes regarding treatment of several illnesses, such as Parkinson's disease (PD), stroke, and multiple sclerosis [2]. Shortened steps, reduced travel speed, increased support phase, and reduced swing phase are some of gait changes reported in PD patients.

Usually, gait is examined via visual assessment (naked eye) by trained physicians or neurologists. Although this approach is informative, the results from these observations are often limited because they depend on the restrictive consultation time and the experience of the clinician who performed the assessment [3, 4]. In this context, gait analysis through naked eye becomes even more complex if we consider that about 35% of adults over 70 years have gait

changes [5] including slower and shorter steps [6, 7]. This means that even healthy elderly patients may have gait changes similar to those found in PD. Little is known about the relationship between gait and age in patients with PD [8–10], and most studies compare spatiotemporal gait variables without considering the age as a possible confounder factor.

Technology supporting human motion analysis has made important advances in the past three decades; however, despite being useful, the routine applicability and accessibility of this technology have been limited [11]. Gait parameters can easily be obtained using three-dimensional motion analysis cameras, foot switches, body-mounted inertial tracking unit sensors, instrumented walkway systems (e.g., GAITRite), and accelerometers [3]. These instruments can provide accurate quantitative data regarding many variables; however, their routine implementation in clinical environments requires a high-quality patient preparation, longer time, expensive equipment, accessibility, and technical expertise and demands a special place [12–14].

Portable motion sensing devices, such as the Microsoft Kinect®, are depth cameras originally developed for video gaming. This technology uses infrared light to detect anatomical landmark positions in three dimensions, allowing them to analyze gait and limb movements [15]. This device has been proposed as a solution to the constraints of objective assessment of gait analysis because of its portability, low cost, convenience, and simple use in clinical and research laboratories [3]. Several clinical studies have favored the use of Kinect®, reporting adequate concordance with motion and gait laboratories on the assessment of healthy subjects' identification of steps [16], postural control, speed, length of step, and gait cycle [13] and the assessment of movements of upper extremities [17]. However, there is still a paucity of research regarding potential usefulness of the Kinect™ system for assessing gait in clinical populations.

The aim of this research is to perform a quantitative gait analysis using a portable movement capture system (Kinect) to describe the relationship between age and gait variables in PD patients and to compare gait changes between PD patients and healthy subjects according to age distribution.

2. Methods

2.1. Patient Selection and Clinical Assessment. Thirty PD patients and 30 healthy subjects (age-matched) were recruited for this cohort study. PD diagnosis was made by the movement disorder specialist at the institution following the UK Parkinson's Disease Society Brain Bank diagnostic criteria [18]. Exclusion criteria considered the absence of any other neurological disease or severe comorbidity, which may affect gait, the absence of dementia, and the ability to walk without aids. All participants were evaluated in a single session by an expert neurologist who administered the MDS-UPDRS part III to determine the severity of motor symptom. The Dynamic Gait Index (DGI) and the Freezing of Gait Questionnaire (FOGQ) were also administered by the neurologist. Classically, patients with greater motor involvement have higher scores in the MDS-UPDRS part III, higher scores in FOGQ, and lower scores in DGI. Montreal Cognitive Assessment (MoCA) test was administered as a cognitive screening tool. Data on PD characteristics were also obtained for the PD group. Institutional review boards of both the Universidad Icesi and Fundación Valle del Lili, Cali, Colombia, approved the study. This work was conducted according to the Helsinki Declaration. Informed consent was obtained from all subjects (patients and controls).

2.2. Gait Analysis Method: E-Motion Capture System and Kinect Sensor. The Microsoft Kinect sensor has an RGB-D camera designed for applications in the gaming industry. Kinect is able to detect and track 20 different body joints (Figure 1(a)). Comparisons between the Kinect and benchmark references have shown a high agreement [19, 20]. Also, this device has been used in different research areas, like e-health [21, 22], security and surveillance [23–25], and UAV and robot vision [26]. In e-health approaches, this device has displayed good reliability in clinical context [27]. Furthermore, Kinect has been tested for PD diagnosis; some researchers have used this device to measure and quantify different symptoms like gait [21], arm swing [28], postural instability, and tremor [29] in PD patients.

Therefore, we used the e-motion capture system, which contains the e-motion software developed by the CENIT research center from Universidad Icesi. This system contains a motion sensing device (Kinect™ V1 or V2), a computer with the e-motion software, free interface capture area, and a rater (physician or trained nurse). The e-motion software captures [19] skeleton information from the Kinect and records it in the computer, using an ID to identify the patient in later analysis. From the skeleton information, we can extract information from different joints and analyze it. For the patients' ankles, we obtain a set of coordinate points with distance (vertical axis) and time (horizontal axis) information (Figure 1(c)).

Using the e-motion software, we extract the ankle information from the captured skeleton information and postprocess it to obtain gait parameters. In this postprocessing, we use wavelet transform to convert the distance versus time information into a binary signal with swing and stance phases differentiated. This binary signal allows us to compute gait parameters, such as swing time, stance time, and speed used for gait analysis. Although it is possible to obtain additional parameters, like stride length, only relevant parameters are used in a clinical context.

To obtain gait information, 30 PD patients and 30 controls were recruited. For this study, the subjects were instructed to walk on a flat walkway (approximately 4 meters in length and 2.5 meters wide) toward the Kinect® device (Figure 1(b)). For each subject, we performed three barefoot walking trials; for which all PD patients were evaluated in the "ON" state. For this study, the acceptable field of view was restricted to a range of 1.5–3.5 m from Kinect™. This distance allowed for a minimum of one full gait cycle per limb to be recorded per walking trial.

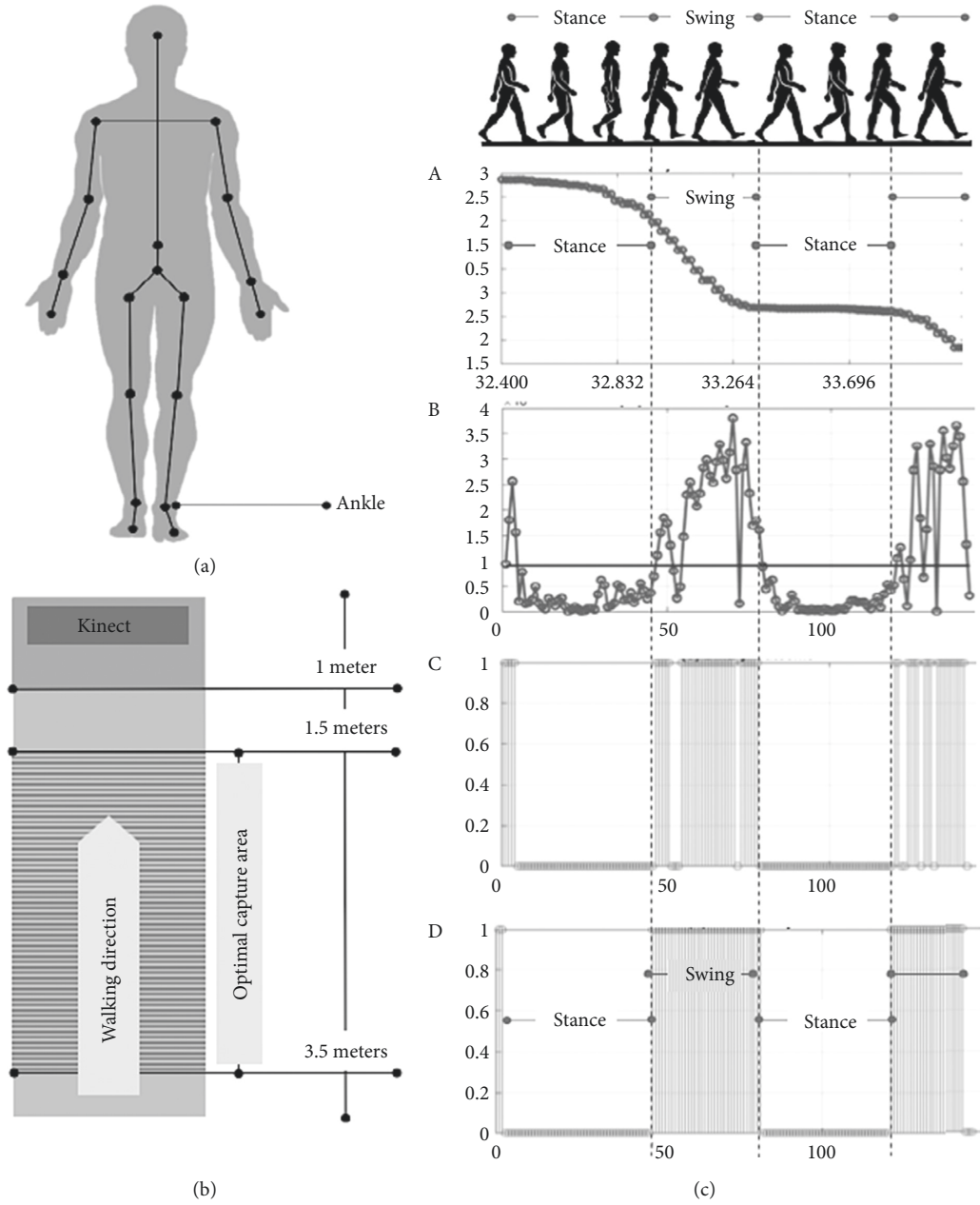

Figure 1: (a) General setting and results obtained with e-motion system. (b) Capture area. (c) Recorded and binarized signal.

Recently, Kinect has gained popularity for various applications in PD diagnosis. However, in this research, Kinect limits the capture area, which restricts the walking length to 4 meters. Some researchers have addressed this limitation using multiple Kinect devices [12], but synchronizing these devices is challenging. Main advantages of the Kinect as a sensor for PD diagnosis are portability, affordability, and touchless.

2.3. Signal Processing Techniques and Gait Phase Estimation. Wavelets have demonstrated their utility in biomedical signal analysis since 1996, when Michael Unser suggested some applications for wavelet techniques on biomedical applications like noise reduction, image enhancement, and detection of microcalcifications in mammograms; image reconstruction and acquisition schemes in tomographies and magnetic resonance imaging; and multiresolution methods for registration and statistical analysis of functional images of the brain. As a conclusion, Unser claims that wavelet transforms are not a panacea and should be used with caution [30]. Additionally, wavelets are now being applied in gait phase extraction, biomedical signal compression [31], recognition of cardiac patterns [32], EMG classification and decoding [31, 33], main features detection and extraction on ECG [32] and PPG [34], and diagnosis of epilepsy [35].

For the gait phase identification, we apply wavelet decomposition using the Daubechies family in one-level decomposition, with eight vanishing moments (db8) because in previous research, it was one of the decomposition with less average error [36]. In one-level decomposition, we obtain two resultant signals, one with approximation coefficients or in this case a gait signal denoised, and the second one generates a signal with detailed coefficients, which reflects clear changes in gait phases. This decomposition allows us to obtain information in two domains: spectral and time. The swing phase corresponds to the moment where the ankle is in motion and the stance phase to the moments where the ankle is static on the floor. After the wavelet decomposition, we establish the mean value as a threshold (denoted by horizontal line in Figure 1(c)) to define swing and stance phases. The swing phase is defined as the values above the average value and the stance phase is defined as the values below the average value. This classification was based on the signal structure. The structure suggests that moments with descending changes represent a swing phase and the other ones represent the stance phase. We use the coefficients from the second signal of the one-level decomposition to generate a binary signal, in which the one values represent the swing phase and the zero values represent the stance phase (Figure 1(c)). Using binary signal, we established a time and distance reference in each phase. Based on these values and on the ankle information, we estimate the following variables:

2.3.1. Stance Time. It is the duration of time (s) of limb movements tracked in the support phase during a walking trial in the acceptable field of view of Kinect.

2.3.2. Swing Time. It is the duration of time (s) of limb movements tracked in the swing phase during a walking trial in the acceptable field of view of Kinect.

2.3.3. Speed. It is the rate of motion, measured in meters per second (m/s), during a walking trial in the acceptable field of view of Kinect.

2.4. Statistical Methods and Data Analysis. Categorical variables were expressed with relative frequencies and total counts. Continuous variables were assessed with median and interquartile range or with mean and standard deviation based on their normality distribution determined by the Shapiro–Wilk test. A bivariate analysis comparing PD patients and healthy subjects was based on Mann–Whitney U and Pearson's X^2 test. Spatiotemporal gait variables of each leg were analyzed together, independently of their laterality. To assess gait-related changes (speed, stance time, and swing time) with respect to age, Spearman's rank correlation was used. Subsequently, groups were classified according to the age quartiles distribution and bivariate analyses were made for each age group. A significant difference was reached with p values ≤ 0.05. Statistical analyses were performed using STATA© 13.0 (StataCorp, TX USA).

3. Results

Sixty subjects (30 PD patients and 30 healthy subjects) were included. Both groups had a median age of 66 years (IQR 59–75). No significant differences were found by comparing the groups for sex, age, or MoCA test score. Table 1 shows the sociodemographic characteristics of the sample.

3.1. Clinical Background and Parkinson's Disease Characteristics. The median duration of the disease was 5 years (IQR 1–7). Hoehn and Yahr stage classification was stage I for 17% of the PD patients, stage II for 73%, and stage III for the remaining 10%. The mean MDS-UPDRS part III score was 39.06 (±13.74), the mean DGI was 19.73 (±4.07), and the mean FOGQ score was 6.73 (±4.95).

When PD clinical characteristics were classified according to age distribution, compared with the other age groups, the patients between 76 and 88 years displayed the highest MDS-UPDRS part III 43.5 (±8.84), the highest FOGQ (7.83 ± 4.95), and the lowest DGI (18.83 ± 6.27) scores. Contrarily, patients between 67 and 75 years displayed the lowest MDS-UPDR part III (33.66 ± 12.44) scores and the ones between 40 and 59 years the lowest FOGQ (4.87 ± 5.59) and the highest DGI (21.62 ± 2.87). Table 2 shows the PD characteristics for each patient group according to the age distribution.

3.2. Gait Differences between Groups. Compared to the control group, PD patients showed prolonged swing times (PD = 0.90, healthy = 0.81 seconds, $p = 0.002$), prolonged stance times (PD = 1.29, healthy = 1.16 seconds, $p < 0.001$), and lower speed values (PD = 0.86, healthy = 0.94 m/s, $p < 0.001$). Table 3 shows the comparison of gait parameters measured using the e-motion capture system.

3.3. Gait-Related Changes with respect to Age. When gait variables and age were related, a negative correlation was found for speed (PD: rho = −0.072, healthy: rho = −0.360) and positive correlations were found for swing (PD: rho = 0.086, healthy: rho = 0.40) and stance times (PD: rho = 0.07, healthy: rho = 0.27). These correlations were significant only in the healthy subjects group (speed, $p = 0.004$; stance time, $p = 0.035$; swing time, $p = 0.001$).

Below 76 years, compared to healthy subjects, PD patients exhibited lower speed values and prolonged swing and stance times. These results were statistically significant for the 60 to 66 years group and almost achieved significance in the one between 67 and 75 years. Over 75 years, healthy subjects displayed lower speed values and prolonged swing and stance times compared to PD patients; these differences were no statically significant (see Table 3).

4. Discussion

Gait assessment is fundamental for the diagnosis and follow-up of patients with PD. Since the evaluation of motor alterations can be highly subjective and taking into account that the use of technologies for gait analysis is expensive and

Table 1: Clinical background and characteristics of the sample.

Variables	PD patients ($n = 30$)	Healthy subjects ($n = 30$)	p value
Age			
Years (median, IQR)	66 (IQR 59–75)	66 (IQR 59–75)	0.88
40–59	8 (26.6%)	8 (27)	
60–66	8 (26.6%)	7 (25%)	0.90
67–75	8 (26.6%)	9 (28%)	
76–88	6 (20%)	6 (20%)	
Gender			
Male	17 (57%)	19 (63%)	0.60
Female	13 (43%)	11 (36%)	
Education			
Elementary school	9 (30%)	5 (17%)	
Highschool	10 (33%)	10 (33%)	0.20
Graduate	11 (37%)	15 (50%)	
Occupation			
Employee	8 (27%)	15 (50%)	
Housewife	7 (23%)	5 (17%)	0.08
Retired	15 (50%)	10 (33%)	
MoCA test	22 (IQR 16–26)	22.5 (IQR 21–24)	0.57

Table 2: PD patient characteristics by age group.

Variables	40–59 years ($n = 8$)	60–66 years ($n = 7$)	67–75 years ($n = 9$)	76–88 years ($n = 6$)
Years of disease	1 (IQR 0–4)	6 (IQR 3–7)	6 (IQR 2–7)	5.5 (IQR 1–9)
Age at diagnosis	52 (43–56.5)	59 (55–63)	64 (61–70)	74.5 (71–76)
Subtype of PD				
TD	3 (37.50%)	1 (14.29%)	2 (22.22%)	2 (33.33%)
PIGD	5 (62.50%)	6 (85.71%)	7 (77.78%)	4 (66.67%)
Hoehn and Yahr scale				
I	4 (50%)	0 (0%)	1 (11.11%)	0 (0%)
II	3 (37.50%)	6 (85.71%)	7 (77.78%)	6 (100%)
III	1 (12.50%)	1 (14.29%)	1 (11.11%)	0 (0%)
Test				
MDS-UPDRS part III	39.5 ± 18.44	41.71 ± 13.12	33.66 ± 12.44	43.5 ± 8.84
FOGQ	4.87 ± 5.59	7.71 ± 4.99	6.88 ± 4.72	7.83 ± 4.95
DGI	21.62 ± 2.87	19.42 ± 3.15	18.88 ± 3.98	18.83 ± 6.27
Patients with fall risk	1 (6.25%)	1 (6.67%)	4 (23.53%)	2 (16.67%)
MoCA test	23 (20.5–24)	24 (24–26)	20 (15–24)	18.5 (17–22)

Table 3: Spatiotemporal gait parameters obtained from the e-motion capture system in the PD patient group and the healthy subjects group.

Gait variable	Speed (m/s)			Swing time (s)			Stance time (s)		
Age/group	PD patients	Healthy subjects	p value	PD patients	Healthy subjects	p value	PD patients	Healthy subjects	p value
All ages ($n = 60$)	0.86 (IQR 0.73–0.93)	0.94 (IQR 0.86–1.14)	**<0.001**	0.90 (IQR 0.80–1.09)	0.81 (IQR 0.71–0.92)	**0.002**	1.29 (IQR 1.13–1.57)	1.16 (IQR 0.95–1.27)	**<0.001**
40 to 59 years ($n = 16$)	0.89 (IQR 0.80–1.04)	0.97 (IQR 0.89–1.12)	0.10	0.86 (IQR 0.71–0.94)	0.77 (IQR 0.70–0.84)	0.19	1.22 (IQR 1.07–1.40)	1.1 (IQR 0.99–1.27)	0.13
60 to 66 years ($n = 15$)	0.82 (IQR 0.75–0.86)	1.08 (IQR 0.95–1.29)	**<0.001**	0.90 (IQR 0.86–1.06)	0.75 (IQR 0.7–0.81)	**<0.001**	1.38 (IQR 1.26–1.54)	1.04 (IQR 0.75–1.19)	**<0.001**
67 to 75 years ($n = 17$)	0.85 (IQR 0.56–0.89)	0.91 (IQR 0.80–1.28)	**0.004**	0.91 (IQR 0.84–1.23)	0.84 (IQR 0.680.97)	0.05	1.35 (IQR 1.22–2.06)	1.26 (IQR 0.78–1.38)	0.05
76 to 88 years ($n = 12$)	0.89 (IQR 0.52–1.03)	0.87 (IQR 0.77–0.91)	0.72	0.88 (IQR 0.72–1.47)	0.92 (IQR 0.901.05)	0.60	1.21 (IQR 1.08–2.14)	1.22 (IQR 1.17–1.3)	0.93

is almost restricted for research purposes, we attempted to assess the main gait variables using a low-cost system that can be easily accessed during a medical consultation. According to our results, compared with healthy subjects, PD patients' gait is slower and has longer swing and stance times. While this is true, these changes are highly influenced by the patient's age and disease stage.

4.1. PD Patients Are Slower and Had Prolonged Swing and Stance Times. As expected, based on existing research, we found lower speed values in the PD group. This could be explained by bradykinesia and gait changes related to the disease, such as high cycle time, a high step number, and a shortened stride length, all of which are related to a slow gait [37, 38].

Regarding differences in swing time, higher values were found in the PD group, which was unexpected based on the results proposed by previous studies [38, 39]. We think this could be explained by the fact that PD patients are slower and need more time to perform a step. This means that both swing and stance phases are prolonged. Compared to healthy subjects, the stance time values were prolonged in the PD group. Previous studies on gait analysis in PD have also shown a higher stance time phase compared to controls, which they have associated with longer double limb support [19, 22].

4.2. Speed, Stance, and Swing Time Differences Are Influenced by Age. When the sample was age-stratified, we observe gait differences change depending on the age of the compared groups. This finding can be explained by two factors: the first one is associated with the progression and the burden of the disease and the second one is related to the gait changes induced by the aging process in the control group.

Nonsignificant differences in the younger group: although descriptive results showed that patients in the younger group were slower and had prolonged swing and stance times compared to controls, these results did not reach significance. Patients in the younger group had the shortest disease duration (1 IQR 0–4), the second lowest MDS-UPDRS part III, the highest DGI, and the lowest FOGQ score which could be associated with a lower disease burden and fewer gait changes. Therefore, differences in gait kinematics in young PD patients can be very subtle, especially, in patients in early disease stages, in which lower limb involvement is less frequent and gait alterations are almost restricted to arm swing changes.

Statistically significant results ($p < 0.001$) were found for speed in the 60 to 75 years group; this finding supports that speed changes could be useful in the differentiation between PD patients and healthy subjects in that age range. Swing and stance time differences were only significant between 60 and 66 years ($p < 0.001$) and showed a trend to reach significance ($p = 0.05$) in the 67 to 75 years group, which could be associated with the sample size increasing type 2 error.

Nonsignificant differences in the oldest group: although patients in this group have the highest burden of disease (highest scores in the MDS-UPDRS and FOGQ and the lowest scores in the DGI), healthy subjects in this group already have gait changes induced by age. As will be discussed later, older subjects tend to be slower and their gait kinematic is also altered in relation to the physiological aging process.

4.3. Gait Changes Related to Age Are Different between PD Patients and Healthy Subjects. For the healthy group, a significant negative correlation was found between age and speed; this finding is similar to the reports in elderly Caucasian and Asian populations [40–42]. The physiologic loss of muscle strength, the deterioration of motor cortical regions, and the development of a more cautious with slower speed and a reduced stride length [43] could explain why gait slowness is negatively correlated with age. Although there are no studies that correlate the swing or stance times with aging, our results suggest that there is a positive relationship between age and both gait variables. Reductions in stride length [44], reductions in walking speed, and reductions in cadence [45], which are associated with a longer stance time and prolonged double support times in the elderly population, could explain this finding.

For the PD group, the correlations between age and the gait spatiotemporal variables mentioned above were not significant. PD patients have different patterns of motor impairment, and the progression of motor symptoms varies according to the age of onset and the duration of the disease. Some studies suggest that patients with an older age of onset have a faster rate of motor progression, worsening of motor symptoms in a shorter time, and greater balance impairment than those with early onset of disease [46, 47]. This individual variability in the progression of PD could explain why the correlations between the age of the patients and the spatiotemporal variables of gait were not significant.

4.4. Limitations and Advantages. The data obtained from the other Kinect reference points were not considered because the main objective of this work was to characterize gait only using the data on lower limbs. Space-related variables (e.g., asymmetry) were not calculated because the test field captured by Kinect® was not long enough to estimate them. However, the use of Kinect® in this clinical context has reported relative and overall reliability regarding spatiotemporal parameters [21, 48, 49] further advances in software and hardware are essential to enhance Kinect's sensitivity for kinematic measurements [50, 51]. Nevertheless, because Kinect is an inexpensive and portable device, it provides opportunities in the field of medicine and telemedicine, allowing easy access to gait assessment in clinical space and allowing remote diagnose in rural areas, where there are no clinical experts.

4.5. Challenges and Future Research. Precision medicine is a growing field that enables objective characterization of patients. E-motion is a diagnostic aid that could be used with other complementary technologies to improve and quantify gait assessment of patients diagnosed with neurological

diseases such as PD. We consider that the strategy used for data collection presents relevant advantages in terms of cost, accessibility, and space [21, 48], compared to gait laboratories. Although Kinect system is no longer in production, there are other RGB-D cameras that can be used with the e-motion software. The operation of these cameras does not require specialized training, and they can be placed in almost any doctor's office without making major adjustments to the test area, making the device adaptable to any medical environment. In future research, a larger number of subjects will be evaluated for establishing cutoff points that could help in the differentiation of patients diagnosed with PD from controls and to monitor the symptoms and severity of the disease. The analysis of the information obtained from upper limbs and technical limitations of our approach will be considered in the development of future research.

5. Conclusion

The development and improvement of new and more portable technologies may allow for an objective evaluation of quantitative gait parameters that can complement clinical assessment and follow-up of patients, potentially detecting earlier stages of neurodegenerative diseases such as PD. Age is an important factor that affects gait; therefore, the analysis of spatiotemporal variables should be individualized, considering the age of the patient.

Data Availability

The gait data used to support the findings of this study are restricted by the IRB of the Fundación Valle del Lili in order to protect patient privacy.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Clinical Study

Repetitive Transcranial Magnetic Stimulation Does Not Improve the Sequence Effect in Freezing of Gait

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Introduction. The sequence effect (SE) is a reason contributing to freezing of gait (FOG) in Parkinson's disease (PD) patients. There is no effective treatment for the SE. The objective of the current study is to investigate the effect of repetitive transcranial magnetic stimulation (rTMS) on the SE in PD patients with FOG. *Methods*. 28 PD patients with FOG received either real or sham 10-Hz rTMS over the supplementary motor area (SMA). The effects of rTMS on the SE, FOG, and some gait parameters were evaluated. *Results*. rTMS did not improve the SE. Real rTMS had beneficial effects on FOG and some gait parameters, and this effect lasted for at least four weeks. *Conclusions*. High-frequency rTMS over the SMA cannot alleviate the SE in PD patients with FOG. rTMS has a long-lasting beneficial effect on FOG; however, this effect is not achieved by improving the SE but may be through improving some other gait parameters.

1. Introduction

Freezing of gait (FOG) is a disabling and common symptom in Parkinson's disease (PD) characterized by brief episodes of inability to step or by extremely short steps that typically occur on initiating gait or on turning while walking [1, 2]. The mechanisms underlying FOG are poorly understood. Impairments in rhythmicity [3], symmetry [4], and bilateral coordination [5] have been reported to be associated with FOG episodes. In addition, diminished stride length is also a critical factor that results in FOG [6]. Nieuwboer et al. [7] suggested that freezing whilst walking could stem from stride-to-stride variability, which results in failure to generate normal amplitude in step length, comparing with those that do not experience freezing [8, 9]. This magnitude of stride-to-stride fluctuations further increase in patients in the "off" state [3, 8, 10], hastening, or an increase in cadence with a decrease in step length, often deteriorate FOG [7]. In PD patients, the decreased amplitudes might further destabilize normal gaits and induce a vicious circle of progressively shorter step length, resulting in FOG [7]. This progressive decrease in amplitude of sequential movements is called the sequence effect (SE), which is a common feature in PD patients [10].

The treatment of FOG is difficult. As the SE has been suggested as a reason contributing to FOG [10, 11], alleviating the SE should be an approach to help improve FOG. However, it has been demonstrated that levodopa has no impact on the SE [10]. Therefore, development of new effective therapeutic strategies is necessary. Repetitive

transcranial magnetic stimulation (rTMS) is a noninvasive method to stimulate the human brain, and high-frequency facilitatory rTMS has been shown improving motor symptoms in PD patients. Despite the discrepant results [12–15], there are increasing studies that have reported benefit effects of rTMS on FOG [16]. A previous study found that rTMS has no effect on the SE during hand movement [17]. However, whether rTMS could alleviate the SE in FOG has never been investigated. We thus investigated the potential benefits of rTMS on the SE in PD patients with FOG in the current study.

2. Methods

2.1. Participants. PD patients were diagnosed according to the MDS Clinical Diagnostic Criteria and were recruited from the Movement Disorders Clinic of the Xuanwu Hospital of Capital Medical University. 30 idiopathic PD patients with FOG were identified using the item 3 of the FOG questionnaire (a positive answer to FOG-Q3—"Do you feel as if your feet are glued to the floor while walking, making a turn, or while trying to initiate walking?"). In 24 of the 30 (80%) self-reported freezers, FOG was recorded during clinical testing or spontaneous behavior. Subjects were included if they were able to walk 10 meters repeatedly more than 3 times without aids. Patients with other neurological or orthopedic conditions that might affect gait or posture, comorbidities of neurological disease other than PD, history of deep brain stimulation surgery, or MMSE score ≤24 were excluded. 2 participants were excluded because of deficit of cognitive ability. The experiments were performed according to the Declaration of Helsinki and were approved by the Institutional Review Board of Xuanwu Hospital. The rTMS study was registered at the Clinical Trial Registration (URL: http://www.clinicaltrials.gov.), unique identifier: NCT03219892. Written informed consent was obtained from all participants prior to the experiment.

At least after a 12-hour withdrawal of anti-Parkinson medication, clinical assessments of patients were conducted in their practical off state, including the Movement Disorder Society-Sponsored Revision Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Hoehn and Yahr (H&Y) stage, Montreal Cognitive Assessment (MoCA) Beijing version, Mini-Mental State Examination (MMSE), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD) 17, FOGQ, and parts II and III of the NFOGQ [18] (Supplementary Table 1).

2.2. Gait Assessments. To measure the spatial and temporal gait parameters, an electronic walkway GAITRite (CIR Systems Inc. Clifton, NJ 07012) was employed. Measuring 5.2 m long and 0.89 m wide, the GAITRite collects data through pressure sensors embedded into the carpet. The GAITRite has been found to produce highly reliable measurements, particularly with walking speed, cadence, and step length (intraclass correlations between 0.82 and 0.92 and coefficients of variation between 1.4% and 3.5%) [19]. The GAITRite was positioned in an open space of the center of an outpatient hall so that there was at least 3 meters of space on each side. This arrangement provided sufficient open space to minimize environmental stimuli that may have provoked freezing [20].

Gait assessments were performed in the on state. Participants were instructed to stand still at the starting point of the carpet, walked at the middle rather than the bilateral margin of the carpet, and stopped at the end of the carpet in the on state. All participants walked barefoot along the mat 3 times in a usual speed. When calculating the regression slopes of walking trials, step length for each footstep was measured, while the first and last steps were excluded to avoid patients' instability and limitation of the carpet. Spatiotemporal data for each trial were identified from the second strides within the capture zone, after gait initiation at the beginning of the data capture area. The ambulation time, mean velocity, step count, and mean cadence were measured. The values measured in the 3 walking trails were averaged in each subject. The step length was plotted against step number in each walking trial. Linear regression was used to determine the slope of each regression curve. The averaged regression slope (b) for the 3 walk trails was used to represent the SE in each participant [21]. Once freezing episodes did occur during the walking, and we asked the patients to stop and have a rest. The experiment was repeated when the patients were in a better state until we collected adequate data.

2.3. rTMS Study

2.3.1. Study Design. This experiment was a double-blind, placebo-controlled, single-center trial with a parallel design consisting of two parts: 10-Hz rTMS over the supplementary motor area (SMA, real group) and sham stimulation (sham group) at the practical "on" state. 28 patients were randomized about 2 : 1 into the two groups, to receive either real (N = 18) or sham (N = 10) rTMS protocol. High-frequency rTMS on the bilateral primary motor cortex [16, 22] or SMA [23] has been shown improving FOG in PD patients. A recent study found that rTMS in the SMA had more benefit on FOG than stimulation in the motor cortex [24]. In addition, it has been shown that rTMS on the motor cortex did not improve the SE during hand movements [11]. Therefore, we chose the SMA as the stimulate target in the present study. One of the authors Junyan Sun determined the allocation and group, and it was concealed to both physicians and participants involved throughout the whole course of the study. Patients kept previous medication treatment throughout the trial. The intervention of rTMS was performed at the same time of day for each patient.

2.3.2. Real and Sham rTMS Protocol. We performed the real or sham rTMS in ten sessions over two successive weeks, one session per day for five consecutive days per week. For the real rTMS, a 7-cm handheld figure-of-8 coil was connected to a biphasic magnetic stimulator (Magstim Rapid; Magstim Co. Ltd., UK). To apply focal rTMS over the SMA, the stimulation site was determined as the site 3 cm anterior to

the leg motor area along with the midline [25]. The coil was held so that the induced current was perpendicular to the midline. The stimulus intensity was set at the 90% rest motor threshold for the right tibialis anterior muscle when the leg primary motor area was stimulated. In each session, a 5-second burst of 10-Hz rTMS was repeated 20 times at every minute (in total, 1,000 pulses and 20 minutes' duration). For the sham rTMS, the same stimulation parameters were used, but the coil was placed in 90° turning angulation over the SMA so that no relevant current flow was induced in the cortical tissue [26, 27].

2.3.3. Clinical and Gait Assessments. The assessments were carried out in the clinical "on" state at the same time of the day. Baseline and follow-up evaluations (including MDS-UPDRS III and gait assessment) for each participant were performed before rTMS (baseline) and after the 1st, 5th, 10th sessions and then 2 weeks and 4 weeks after the last session, defined as T_0, T_1, T_2, T_3, T_4, and T_5, respectively. In addition, FOG-Q was evaluated at T_0, T_3, and T_5, respectively. The primary outcome was the rTMS effect on SE. We included FOG-Q as a secondary clinical outcome to evaluate the improvement of FOG. Additionally, MDS-UPDRS III and gait assessment (including ambulation time, cadence, step count, and velocity) is adopted. The flow of participants is presented in Figure 1, and the flow of the research is listed in Figure 2.

2.4. Statistics Analysis. Demographic data were presented as mean ± SD for continuous variables. An independent two samples t-test was performed for the comparison of continuous variables, and the chi-square test was used to compare categorical variables. We applied mixed effect model repeated measures (MMRM) by SPSS 22 to estimate the effect of rTMS on the sequence effect (the averaged regression slope (b) for the 3 walk trails), FOG-Q scores, MDS-UPDRS III scores, and other gait parameters. For each variable, we applied a separate model where the independent variables were the group (real rTMS and sham rTMS) and the visit (T_0, T_1, T_2, T_3, T_4, and T_5) and the group ∗ visit condition interaction term. The threshold for the level of significance was set at $\alpha = 0.05$ (Bonferroni correction).

3. Results

3.1. Participants. Participant demographics and clinical features are described in Supplementary Table 1. There was no significant difference between the two groups in any clinical assessments. Seven patients in the real group had difficulty in initiation, while four patients in the sham group experienced this problem. There was no significant difference between the two groups on this phenomenon (Supplementary Table 1). In the real rTMS group, 2 patients missed the check at T_4 and 2 patients dropped out at T_4 and T_5. In the sham group, 2 patients dropped out at T_4 and T_5. We filled the gaps with the group average. No adverse reactions to the rTMS were reported.

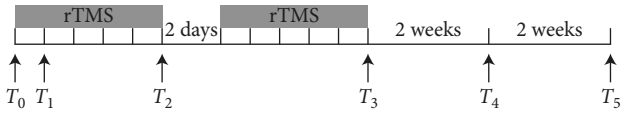

Figure 1: Flow of participants.

3.2. Sequence Effect. There was no difference of the SE between the groups at the baseline. Analysis of regression slope (b) values did not show significant group ∗ visit interaction. Both real and sham rTMS had no effect on the SE (Table 1, MMRM, $p > 0.05$). Figure 3 shows the mean change of the real and sham groups with the time points.

3.3. Clinical and Gait Assessments. In the comparison of other measurements between the real and sham rTMS group, there was a significant interaction between group and visit in FOG-Q, ambulation time, cadence, step count, and velocity. Post hoc analysis showed significantly decreased FOG-Q, MDS-UPDRS III;, ambulation time, and step count, as well as increased cadence and velocity in the real group (Table 2), and the mean values are showed in Supplementary Table 2. We found that real rTMS significantly improved items 2 (facial expression) and 11 (freezing of gait) of MDS-UPDRS III; (Supplementary Table 3). In the real group, the FOG-Q was improved at the T_3 and T_5. The MDS-UPDRS III; scores were significantly decreased from T_3 to T_5 in the real group. Score changes from baseline at T_3, T_4 and T_5 were −4.95 ($p = 0.002$), −6.56 ($p \leq 0.001$), and −4.95 ($p = 0.004$), respectively. There were significant changes of ambulation time and cadence at T_5 compared to the baseline and improvement of velocity at T_4. These results indicated that the real rTMS has an improved effect on FOG-Q, MDS-UPDRS III;, ambulation time, cadence, step count, and velocity. No significant changes were found in the sham group. Figure 4 shows the changes of these assessments across the study in both groups.

4. Discussion

The current research investigated the effect of rTMS on the SE in PD patients with FOG. Contrary to our expectation, high-frequency rTMS did not improve the SE. In contrast, we found that high-frequency rTMS focusing on the SMA can improve FOG, general motor symptoms, and gait performance. Our result together with previous finding indicates that the SE did not respond to levodopa treatment, approving there is still no effective treatment for the SE [10, 16, 17]. We need to develop new therapeutic strategies in future.

PD patients with FOG often have difficulty in initiating the walking sequence to begin with and have short, slow steps when they achieve steady-state walking or turning, and some patients can even freeze when take a small turn [1]. After they recommence walking (often with difficulty), further freezing episodes can occur according to environmental triggers, task constraints, and the ability of the person to compensate using cognitive strategies [28]. As focused on

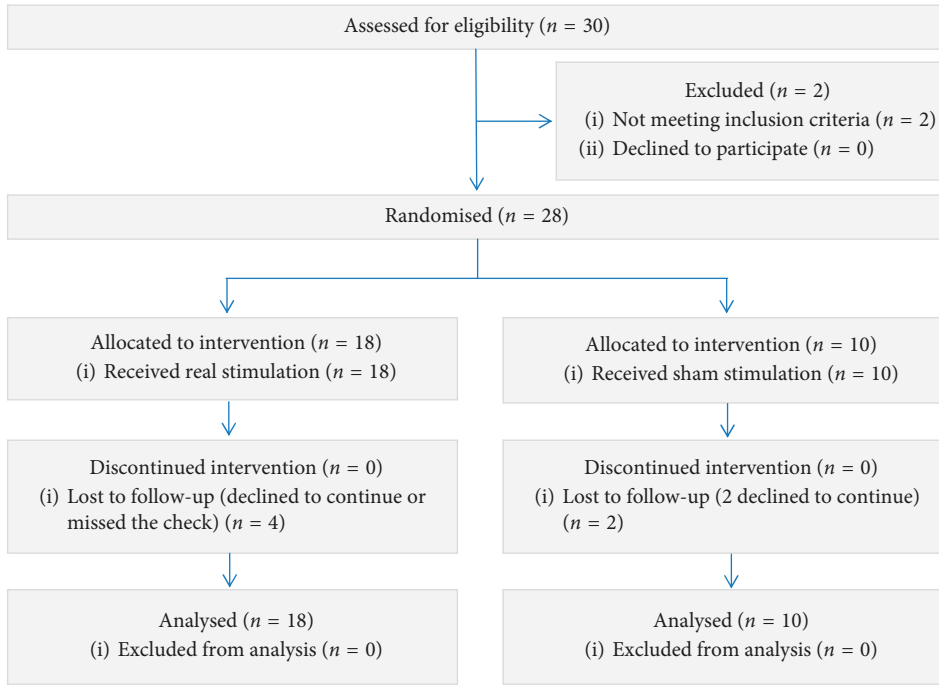

Figure 2

Table 1: Comparison of the sequence effect between and within the groups.

T_n	Real group (mean ± SD)	Sham group (mean ± SD)	MMRM	p value	Post hoc p value	
T_0	−0.611 ± 0.319	−0.521 ± 0.422	Group	0.782	Real	Sham
T_1	−0.718 ± 0.446	−0.797 ± 0.591	Visit	0.287	1.000	1.000
T_2	−0.539 ± 0.670	−0.508 ± 0.397	Group ∗ visit	0.641	1.000	1.000
T_3	−0.744 ± 0.820	−0.385 ± 0.185			1.000	1.000
T_4	−0.281 ± 0.731	−0.430 ± 0.348			1.000	1.000
T_5	−0.644 ± 0.531	−0.612 ± 0.267			1.000	1.000

Post hoc: comparing with T_0; T_n: time points; SD: standard deviation; MMRM: mixed effect model repeated measures.

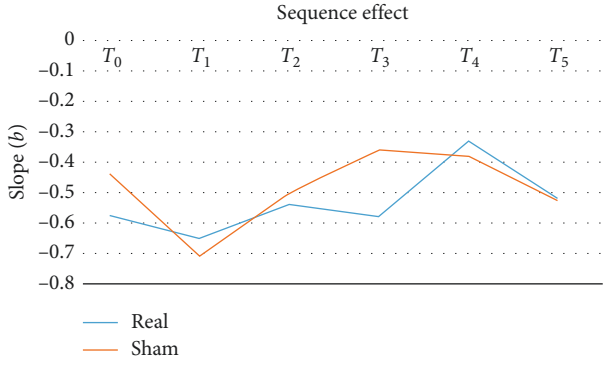

Figure 3: Mean change of the real and sham group with the time points.

the SE, we only recorded the step length during the straight walking, but not during turning.

Cunnington et al. found that individuals with PD generated gradually slowing down movement comparing with controls [10, 16, 27, 29]. SE occurs in sequential automatic movement in the absence of external cues and without attention-focused motor control, such as walking [6, 10]. Nieuwboer et al. and colleagues found the phenomenon of SE in the last three steps preceding a freezing episode in PD patients [7, 30]. Although the SE is a common feature in PD [10, 31] and is a reason contributing to the FOG [10], our understanding on this problem remains limited. It has been speculated that the SE is induced by fatigue [31–33]. However, later investigations showed that fatigue is unlikely a critical reason underlying the SE [11]. A recent report has suggested that higher energetic cost may contribute to the SE [33]. Only few studies have investigated the neural mechanisms underlying the SE, and most of them focused on the SE in hand movement, such as progressive micrographia and gradually slow movement. Reduced motor cortex plasticity [13], functional disconnection between the SMA, rostral cingulate motor area, and cerebellum [11], or reduced volume in the anterior cingulate cortex and cerebellum [34] have been related to the SE. However, as rTMS targeting on either motor cortex [10] or SMA (the current study) has no impact on the SE, it is likely neural networks outside these motor circuits should be also involved in the genesis of the SE. As a clear understanding of neural correlates is critical in

Table 2: Changes of clinical and gait assessments across the study.

MMRM	DF	F value	p value	T_n	Post hoc (p value)	
					Real group	Sham group
FOG-Q						
Group	1	0.280	0.601	T_3	0.003*	1.000
Visit	2	3.641	0.033*	T_5	0.023*	1.000
Group ∗ visit	2	3.445	0.039*			
MDS-UPDRS III						
Group	1	0.941	0.341	T_1	1.000	1.000
Visit	5	3.576	0.005*	T_2	0.038*	1.000
Group ∗ visit	5	1.158	0.334	T_3	0.002*	1.000
				T_4	0.000*	1.000
				T_5	0.004*	1.000
Ambulation time (seconds)						
Group	1	8.535	0.007*	T_1	0.048*	1.000
Visit	5	2.919	0.016*	T_2	1.000	1.000
Group ∗ visit	5	3.158	0.010*	T_3	0.004*	1.000
				T_4	0.000*	1.000
				T_5	0.000*	1.000
Cadence (steps/min)						
Group	1	0.721	0.404	T_1	0.241	1.000
Visit	5	3.214	0.009*	T_2	1.000	1.000
Group ∗ visit	5	2.788	0.020*	T_3	0.178	1.000
				T_4	0.021*	1.000
				T_5	0.000*	1.000
Step count						
Group	1	7.834	0.010*	T_1	0.871	1.000
Visit	5	2.008	0.082	T_2	1.000	1.000
Group ∗ visit	5	2.446	0.038*	T_3	0.090	1.000
				T_4	0.007*	1.000
				T_5	0.009*	1.000
Velocity (cm/sec)						
Group	1	6.471	0.018*	T_1	0.190	1.000
Visit	1	4.890	0.000*	T_2	1.000	1.000
Group ∗ visit	5	3.381	0.007*	T_3	0.010*	1.000
				T_4	0.000*	1.000
				T_5	0.000*	1.000

T_n: test number; post hoc: comparing with T_0; MMRM: mixed effect model repeated measures; DF: degree of freedom. * $p < 0.05$.

developing new therapeutic strategies of the SE, we need to put more efforts in this area.

Our results showed that 10 Hz rTMS over the SMA could significantly improve FOG-Q at T_3 and T_5, respectively, which indicates that rTMS could alleviate FOG in PD, and this effect lasted for at least four weeks after the end of the therapy. This finding is consistent with previous reports of benefit effects of rTMS on FOG [9–12]. We also found significant influence of rTMS on some gait parameters, including decreased ambulation time and step count, as well as increased cadence and velocity. A reduced step count reflects an increased stride length. As our measurement tool, "GAITRite" did not record the stride length for each trail directly, and we calculated averaged stride length in each time as the length of walking divided by the numbers of step count (Supplementary Table 4). Although the impact of rTMS on the stride length did not achieve the significant level (post hoc analysis), there was a trend of increasing stride length in the real group. Diminished stride length and step velocity are associated with FOG in PD patients [35]. Our findings demonstrated that high-frequency rTMS could alleviate FOG by improving stride length and velocity. In addition, rTMS improved MDS-UPDRS III scores, which indicate that high-frequency rTMS could improve general motor symptoms in PD. These findings together approve that high-frequency rTMS could alleviate FOG in PD patients; however, this effect is not achieved by improving the SE but may be through improving some other gait performances.

It has been approved that attention could improve gait problems (e.g., diminished stride length), as PD patients can use attentional control to bypass impaired automatic control to maintain movements [6, 35]. However, as we have asked the patients try to keep the same condition in each gait evaluation, moreover, the patients who received sham stimulation did not show significant change of stride length; the improvement of stride length was mainly a result of rTMS treatment. Attention unlikely had significant impact on our results.

There are some limitations in this study. First, to avoid the falls, the patients were investigated in their on state.

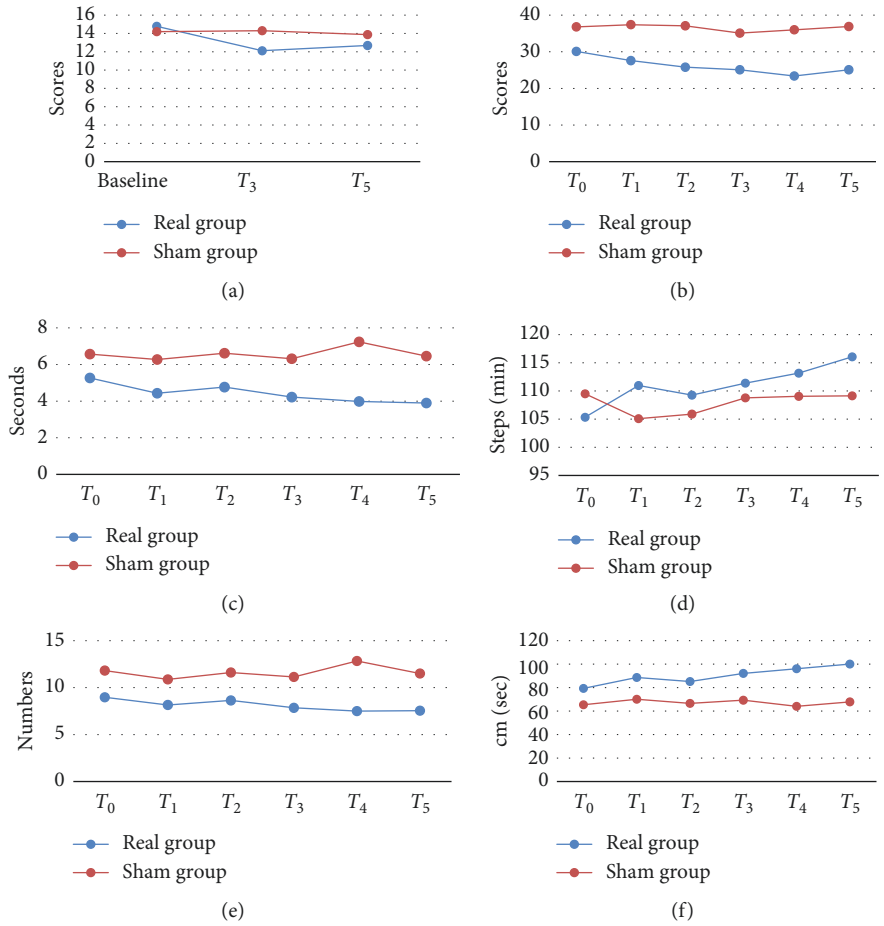

Figure 4: Change of each trail and examination. These results indicated that the real rTMS has an improved effect on (a) FOG-Q, (b) MDS-UPDRS III, (c) ambulation time, (d) cadence, (e) step count, and (f) velocity.

Our results can only reveal the effect of rTMS as an add-on therapy. Second, due to the small sample size, we did not divide the patients with FOG into subgroups according to their phenotypes (e.g., freezing while initiating, freezing while turning, and freezing while straightly walking). More patients should be recruited in future study. Third, we did not use the TMS navigation system to localize the SMA, which will be improved in future studies.

5. Conclusion

In summary, the present study shows that high-frequency rTMS over the SMA cannot alleviate the SE in PD patients with FOG. In contrast, rTMS has a long-lasting beneficial effect on FOG, which is not achieved by alleviating the SE, but may be by improving other gait performances.

Data Availability

Readers can access the data supporting the conclusions of the study from the supplementary information.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

Jinghong Ma and Linlin Gao contributed equally to this work.

Acknowledgments

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Supplementary Materials

Supplementary Table 1: demographics and clinical features. Supplementary Table 2: values of clinical and gait assessments across the study. Supplementary Table 3: changes of MDS-UPDRS III across the study. Supplementary Table 4:

values of cadence and stride length assessments across the study. (*Supplementary Materials*)

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