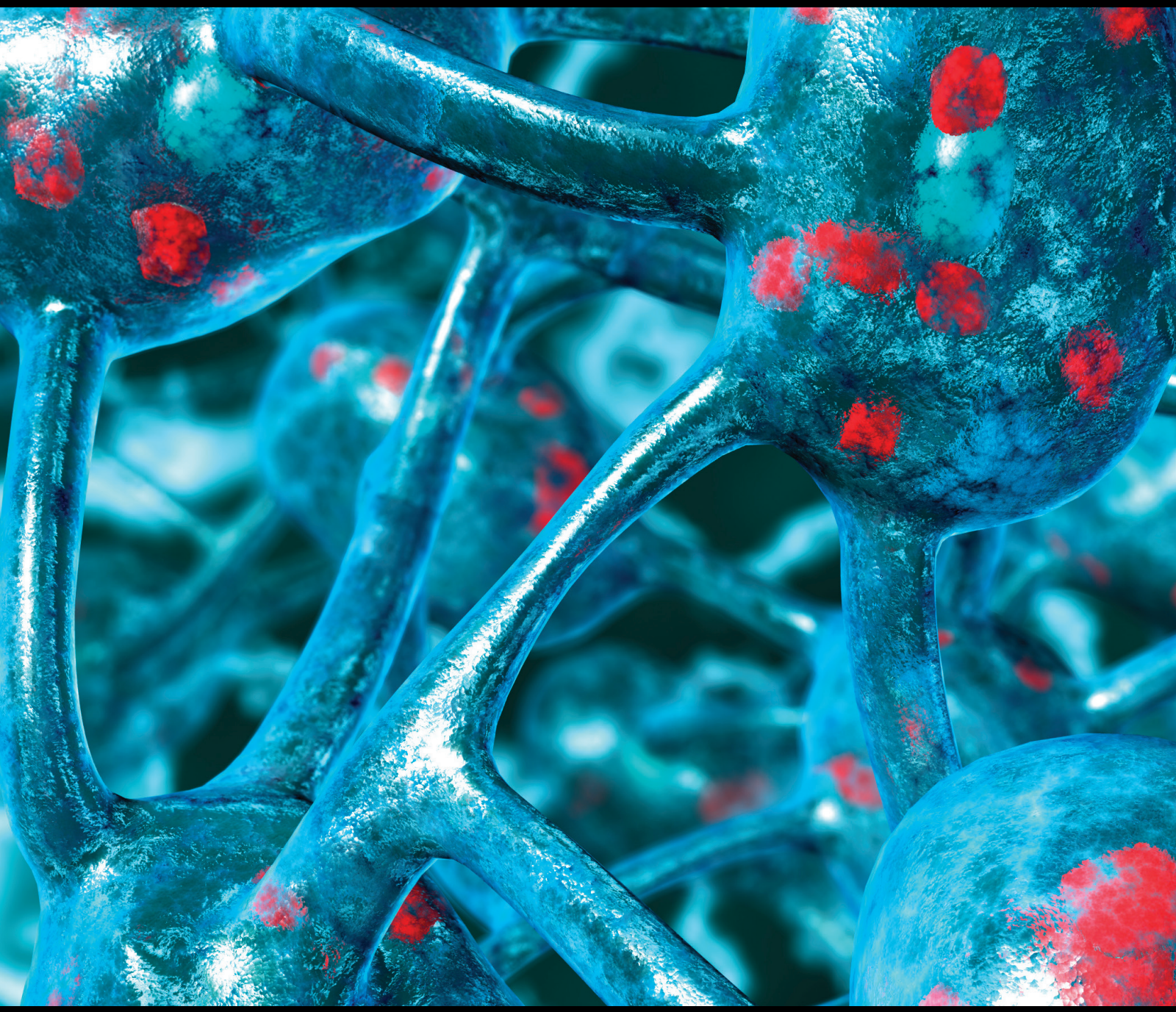
Parkinson's Disease

Rehabilitation Procedures in the Management of Parkinson's Disease

Guest Editors: Alessandro Picelli, Talia Herman, Serene S. Paul, and Laurie A. King



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Editorial Board

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Editorial

Rehabilitation Procedures in the Management of Parkinson's Disease

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Parkinson's disease (PD) is a chronic and progressive neurodegenerative condition characterized by a progressive depletion of dopaminergic neurons in the substantia nigra pars compacta [1]. It affects approximately 7 million, primarily elderly, people worldwide [2]. Motor cardinal signs of PD include bradykinesia, rigidity, resting tremor, and postural instability, as well as deterioration of muscle strength, cardiorespiratory fitness, performance of balance, gait, and mobility tasks [2–4]. In addition to motor symptoms, people with PD may suffer from nonmotor complications such as sensory complaints, autonomic dysfunction, fatigue, apathy, sleep disturbances, depression, and cognitive decline (i.e., executive function) [2, 4]. Disability can occur at all stages of PD leading to decreased independence, inactivity, social isolation, and reduced quality of life by performance of activities of daily living and various aspects of mobility such as gait, transfers, balance, and posture [5].

The management of PD has traditionally centered on drug therapy with levodopa viewed as the "gold standard" treatment [5]. However, even with optimal medical management, people with PD experience deterioration in bodily functions as well as limitations in daily activities and participation [5, 6]. On these bases, the role of rehabilitation has gained a prominent place in the overall management of PD. Specifically, there is a move towards using rehabilitation procedures as an adjunct to pharmacological and surgical treatments with an emphasis on multidisciplinary management of this multidimensional condition [5, 7]. Rehabilitation for PD aims to maximize functional ability and minimize secondary complications by focusing on improving balance, posture, gait, upper limb function, physical capacity, and cognition, as well as minimizing falls, in order to optimize individuals' independence, safety, and well-being, thereby enhancing quality of life [7].

In this special issue of Parkinson's disease, we invited investigators to submit their contributions about rehabilitation procedures in the management of people with PD. We particularly focused on articles proposing some evidence for innovative rehabilitation protocols (including treatments based on motor-cognitive approaches) and comparing the effects of different rehabilitation therapies. Other articles explored rehabilitation strategies such as physical activity, physiotherapy, electromechanical and robot-assisted training, virtual reality, and telerehabilitation. Finally, we focused on the role of cognitive dysfunction in PD rehabilitation. This issue highlights the emerging and important role that rehabilitation plays in the management of motor and nonmotor symptoms of PD. The wide range of topics included in this

issue demonstrates the complexity of the disease and the need for a multidisciplinary approach to rehabilitation for PD.

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Research Article

Acute and Chronic Effect of Acoustic and Visual Cues on Gait Training in Parkinson's Disease: A Randomized, Controlled Study

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In this randomized controlled study we analyse and compare the acute and chronic effects of visual and acoustic cues on gait performance in Parkinson's Disease (PD). We enrolled 46 patients with idiopathic PD who were assigned to 3 different modalities of gait training: (1) use of acoustic cues, (2) use of visual cues, or (3) overground training without cues. All patients were tested with kinematic analysis of gait at baseline (T0), at the end of the 4-week rehabilitation programme (T1), and 3 months later (T2). Regarding the acute effect, acoustic cues increased stride length and stride duration, while visual cues reduced the number of strides and normalized the stride/stance distribution but also reduced gait speed. As regards the chronic effect of cues, we recorded an improvement in some gait parameters in all 3 groups of patients: all 3 types of training improved gait speed; visual cues also normalized the stance/swing ratio, acoustic cues reduced the number of strides and increased stride length, and overground training improved stride length. The changes were not retained at T2 in any of the experimental groups. Our findings support and characterize the usefulness of cueing strategies in the rehabilitation of gait in PD.

1. Introduction

Parkinson's disease (PD) is a degenerative neurologic disorder characterized by motor and nonmotor symptoms. Gait disorders are a hallmark of idiopathic PD and several studies have highlighted a typical parkinsonian walking pattern characterized by reduced speed, increased duration of the stance phase, shorter stride length, and increased number of strides [1, 2]. Although many symptoms respond well to antiparkinsonian drugs, gait and balance impairment often show a poor response to pharmacological treatment. In this frame, physical therapy acquires an important role in contributing to the management of this kind of symptoms. Advanced rehabilitation techniques have been proposed over the years: these include treadmill walking [3], direct current stimulation [4], and ground training with cues [5]. Cues are defined as external stimuli of different type, that is, instructional, auditory, visual, and sensory, and are applied to improve gait performance via the activation of different strategies of motor control. Auditory cues, for instance, are believed to provide an external rhythm that bypasses internal rhythm deficit [6] and visual cues engage the visual-cerebellar motor pathway to facilitate the generation of a better gait pattern [7], whereas sensory cues enable the voluntary activation of the dorsolateral premotor control system, thus bypassing the failure of supplementary motor area in controlling automatic movement [8, 9].

Several studies show that the use of external cues is effective in improving gait parameters [5]. However only a few of these studies are randomized controlled trials and virtually none of them has compared the chronic effect of different external cues. In our practice, we have noted that

some patients tend to respond better to a specific type of cue, which prompts the idea that cues may have a different profile of effect.

Rehabilitation of gait is progressively becoming a mainstay in the management of advanced phases of PD. Several approaches have been proposed in recent years, including individual or group rehabilitation in the outpatient setting and home-based therapy [10, 11]. In general, these studies show that home exercises are less effective in improving balance, gait, and functional measures and that home-based therapy is associated with lower compliance and higher complication rates (i.e., falls or muscle-tendon injuries), especially in patients with balance impairment or other medical complications [12–14]. Frazzitta et al. have shown the effectiveness of a combined gait training modality based on visual or auditory cues, associated or not with treadmill device, delivered to inpatients over a period of 4 weeks [15].

The aim of the present study was the comparison and the characterization of the acute and chronic effects of visual and acoustic cues, used individually, in gait rehabilitation of PD. The study was conducted on PD patients hospitalized for neurorehabilitation at our Unit and was designed as a randomized controlled study for parallel groups, where patients were assigned randomly to one of the following groups for gait training: (1) use of acoustic cues (rhythmical sounds), (2) use of visual cues (stripes of contrasting colour), or (3) overground training without any cues. The objective of the study was to quantify the changes induced by the 3 different approaches applied for 4 weeks in an intensive rehabilitative programme on (i) gait parameters, measured by means of the kinematic analysis of gait, and (ii) the clinical picture, measured by means of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Functional Independence Measure (FIM).

2. Materials and Methods

2.1. Subjects. The subjects were enrolled among consecutive PD patients hospitalized in the Neuro-Rehabilitation Unit of the C. Mondino National Neurological Institute of Pavia, Italy. Hospitalization for neurorehabilitation is a routine procedure at our Institute, as we know from our long-time experience and from data from the literature that inpatient-delivered rehabilitation, with strictly supervised physical therapy, is associated with a greater benefit in patients affected by PD with moderate-severe degrees of motor impairment [16, 17]. We also know from our clinical experience that, for a correct use of cues, at least for the initial sessions, patients need clear instructions and supervision from the therapist. Taking into consideration all these conditions, we opted for an inpatient setting for our trial to limit bias caused by poor compliance or by cues misuse.

Forty-six patients (24 males, 22 females; age 74.4 ± 7.1 years) affected by Idiopathic Parkinson's Disease, according to the UK Brain Bank diagnostic criteria, were included in this randomized, controlled, parallel-group study. Patients were hospitalized upon referral of a neurologist trained in Movement Disorders, who visited the patients in the outpatient clinic and prescribed rehabilitation for any or a combination of the following conditions: decline in global motor performances, increase in the risk of falls, marked reduction of walking endurance, or worsening of bradykinesia.

Inclusion criteria were Hoehn and Yahr stage between II and IV, MMSE > 23, and no changes in antiparkinsonian drug treatment in the previous 6 months. Exclusion criteria were positive history for neoplasms, cardiovascular disease, respiratory disease, clinically significant muscular-skeletal disease, other neurological conditions, uncorrected visual or auditory disturbances, or hospitalization in the previous 3 months.

Patients were divided into 3 groups who were randomly assigned to three different treatment approaches for gait training (with a 1 : 1 : 2 ratio): walking in the presence of rhythmical sounds (Acoustic Group, $n = 11$), walking on stripes of contrasting colour with respect to the floor (Visual Group, $n = 11$), and overground training without cues (Control Group, $n = 24$).

2.2. Cueing Strategies and Rehabilitative Intervention. Patients in all the 3 groups underwent 5 daily rehabilitation sessions per week for 4 consecutive weeks. These sessions consisted in 40 min treatment with passive muscle stretching, exercises for rigidity and joint mobility, specific motor exercise for hypokinesia, weight shifting, and balance training for posture and movement strategies to prevent falls. In addition, patients underwent 5 daily sessions per week for 4 weeks dedicated to gait training as described below. Each session lasted 20 minutes.

In the Acoustic Group, cues consisted in a rhythmical digital sound ("beep") emitted by a digital metronome, with a frequency ranging between 60 and 120 Hz. The beep cadence was personalized and optimized for each patient during the first rehabilitative session by the physical therapist.

In the Visual Group, cues consisted in coloured stripes placed on the floor perpendicularly to the walking direction. The interstripe distance was personalized and optimized by the physical therapist during the first rehabilitative session. The physical therapist tested each subject with different distances between the stripes, starting from a minimum distance of 25 cm to a maximum of 60 cm. The therapist asked the patient to walk over the stripes trying to step over the next stripe and avoiding trampling on them.

In the Control Group, gait training was performed overground, without the use of any cue.

2.3. Study Design and Protocol. All patients were examined by a neurologist with expertise in Movement Disorder at the beginning of hospitalization (T0), at the end of the neurorehabilitation period (+4 weeks, T1), and 3 months after discharge from the hospital (T2). At each time point, the patients were tested with the Unified Parkinson's Disease Rating Scale, motor part (UPDRS-III) [18] and with the Functional Independence Measure (FIM) [19].

For the evaluation of the *chronic effect* of the 3 types of gait rehabilitation, the kinematic analysis of gait was recorded a T0, T1, and T2 in uncued condition in all 3 experimental groups. The *acute effect of cues* was evaluated at T0 in

the Acoustic and Visual Groups by recording gait during conditioning with the visual or the auditory cue.

All patients enrolled in the study were tested in the morning, always in the ON condition.

Antiparkinsonian drugs schedule was kept steady for the entire study duration.

2.4. Kinematic Analysis of Gait. Kinematic analysis of gait was performed with a 6-camera optoelectronic system (ELITE, BTS Engineering, Milan, Italy) by an experienced laboratory technician with a sampling rate of 100 Hz. Twenty-one spherical reflective markers (15 mm in diameter) were applied along the body according to the Davis protocol [20]. Synchronized acquisition and data processing were performed using the Analyzer software (BTS, Milan, Italy). In order to perform kinematic analysis of gait, patients were instructed to walk at their normal speed along a 7-meter walkway. For every session, at least four gaits per patient were recorded and analysed.

We collected the following variables: number of strides needed to walk 7 meters, speed of gait, stride duration and stride length, percentage duration of swing and stance phases.

2.5. Ethics Approval. The local Ethics Committee approved the study protocol and all the participants gave their written informed consent before enrolment.

2.6. Power Analysis. We considered as our primary outcome measure the chronic effect of gait rehabilitation with cues on the number of strides at the end of the 4-week rehabilitation period. We knew from our clinical experience that patients with PD employed an average of 6-7 strides to walk the 7-meter walkway of our laboratory. Based on our practice and on data from the literature we considered as clinically meaningful a difference between groups after rehabilitation greater than one stride, which corresponds to a difference of at least 20% between groups [21].

Therefore, we calculated the sample size with the following parameters: confidence interval (two sided) 95%; power 80%; difference between groups 20% (with a standard deviation between 20 and 25% for each group). The suggested sample size was of 42 patients. We planned to enlarge the study group of a further 10% considering possible drop-outs, so we decided to enroll 46 patients, to be distributed into the 3 different arms.

2.7. Statistical Analysis. The Statistical Package for the Social Sciences (SPSS) for Windows, version 21.0, was used for the calculation.

For each variable we evaluated "skewness" and "kurtosis" to assess normality. Moreover the data were plotted using a "*Q*-*Q* plot" that confirmed normal distribution of all tested variables. For qualitative variables we used cross-tabs analysis, performing statistical significance with chi-square or Fisher exact test by case. Quantitative variables are presented as mean values ± standard deviation.

Regarding the *acute effect* of cues on gait parameters, we performed an intragroup analysis comparing data recorded with and without cues walking using Student's *t*-test for paired groups. For the purpose of our study, we did not assess intergroup differences for acute effects.

Regarding the *chronic effect of the different modalities of gait training*, we performed both an intragroup and an intergroup analysis. To assess intragroup effects in presence of multiple time measurements (T0 versus T1 versus T2), we performed an ANOVA (analysis of variance) test for repeated measures, with post hoc Bonferroni's correction, for each study group. To assess differences between groups, at each time point, we used an ANOVA test for multiple unpaired groups, with Bonferroni's post hoc. The level of significance (α) was set for convention as $p < 0.05$, always corrected if necessary.

Table 1: Baseline parameters.

	Acoustic cues	Visual cues	Controls
Number of subjects	11	11	24
Age (years, m ± sd.)	78.1 ± 6.1	73.2 ± 6.9	72.1 ± 7.3
Sex (F/M)	4/7	6/5	12/12
Disease duration (years, m ± sd.)	10.0 ± 3.1	9.0 ± 2.4	10.5 ± 5.2
Patients with freezing (%)	21.2%	20.6%	22.1%
UPDRS-III	32.1 ± 9.8	29.1 ± 7.9	32.8 ± 10.8
FIM score	102.0 ± 10.2	105.8 ± 11.5	101.9 ± 19.2
Number of strides (m ± sd.)	7.2 ± 3.3	6.8 ± 2.5	7.0 ± 4.1
Stride duration (ms)	1250.5 ± 317.2	1362.9 ± 216.6	1336.7 ± 247.9
Stride length (cm)	83.5 ± 25.7	84.8 ± 19.2	86.3 ± 20.5
Stance (% of stride)	73.8 ± 7.5	71.3 ± 3.5	69.5 ± 6.0
Swing (% of stride)	26.2 ± 7.5	28.7 ± 3.5	30.5 ± 6.0
Speed (m/s)	0.63 ± 0.22	0.62 ± 0.1	0.64 ± 0.2

3. Results

Demographic and clinical characteristics of the 3 groups are shown in Table 1. The table also shows the baseline gait parameters for the 3 groups under investigation. No statistically significant differences were found between groups.

3.1. Acute Effect of Cues on Gait Parameters. Use of acoustic cues induced a significant increase in stride duration and in stride length (Table 2). Visual cues caused a decrease in the number of strides, an increase in the percentage of time spent in the swing phase with a corresponding reduction in the time spent in the stance phase, and a reduction in the gait speed (Table 3).

3.2. Chronic Effect of the 3 Types of Gait Training

3.2.1. Gait Parameters. At the end of the 4-week rehabilitation programme, in the Acoustic Group we observed a significant decrease in the number of strides, an improvement in stride length, and an increase in the speed of gait (Table 4).

In the Visual Group we found a significant reduction in the number of strides, an increase in the speed of gait,

Table 2: Acute effects of acoustic cueing: comparison of gait with and without cue conditioning. Data are expressed as mean ± sd. The right column reports the p values for group comparison.

	Walking without cue conditioning	Walking with cue conditioning	p value
Number of strides	7.2 ± 3.3	7.3 ± 2.5	NS
Stride duration (ms)	1250.5 ± 317.2	1374.8 ± 381.0	<0.05
Stride length (cm)	83.5 ± 25.7	102.1 ± 31.6	<0.05
Stance (% of stride)	73.8 ± 7.5	75.5 ± 4.6	NS
Swing (% of stride)	26.2 ± 7.5	24.5 ± 4.6	NS
Speed (m/s)	0.63 ± 0.22	0.69 ± 0.32	NS

Table 3: Acute effects of visual cueing: comparison of gait with and without cue conditioning. Data are expressed as mean ± sd. The right column reports the p values for group comparison.

	Walking without cue conditioning	Walking with cue conditioning	p value
Number of strides	6.8 ± 2.5	4.5 ± 1.3	<0.05
Stride duration (ms)	1362.9 ± 216.6	1456.7 ± 270.1	NS
Stride length (cm)	84.8 ± 19.2	89.3 ± 12.0	NS
Stance (% of stride)	71.3 ± 3.5	65.5 ± 2.2	<0.05
Swing (% of stride)	28.7 ± 3.5	34.5 ± 2.2	<0.05
Speed (m/s)	0.62 ± 0.1	0.55 ± 0.1	<0.05

and an increase in the duration of the swing phase with a corresponding reduction in the stance phase. At T1 the reduction in the number of strides was associated with an increase in stride length, which however did not reach a statistical significance (Table 5).

In the Control Group we detected an increase in stride length and in gait velocity (Table 6).

When comparing the 3 groups (Figure 1), at T1 we found that the number of strides was significantly lower in both groups treated with cues (Acoustic and Visual) with respect to Controls, while the stride length increased significantly more in the Acoustic Group and in the Control Group than in the Visual Group. In all the three groups of patients, the improvement in gait parameters was lost at the 3-month follow-up (T2).

Interestingly, at T1 in the Visual Group we observed a significant increase in the time spent during the swing phase (with a corresponding decrease in the stance phase). This redistribution normalized the gait pattern of the patients, bringing the swing/stance ratio within the normal variability range in this treatment group (Figure 2).

3.3. UPDRS and FIM Scales. UPDRS-III significantly decreased at T1 in all the 3 groups under evaluation, whereas at T2 the improvement in UPDRS-III was no longer detectable.

FIM significantly improved at T1 in all groups of patients, but the gain was not preserved at T2. No statistically significant differences were found between groups at any time point in neither scale (Table 7).

4. Discussion

In the last years rehabilitation has assumed a growing importance as part of a multidisciplinary approach to PD. One of the most affected motor tasks in PD is gait, due to a deficit of internal rhythmic signals, which interferes in motor performance [7].

Data from the literature show that external stimuli (acoustic, visual, and somatosensory) are able to modulate the motor pattern in PD, helping the patients to start and maintain a rhythmic motor task [8]. Cued gait training seems to represent a precious aid for managing PD symptoms not (or not any longer) responding to dopaminergic drugs, as cues seem to be able to access rhythmic entrainment mechanisms also in the absence of dopaminergic stimulation. Indeed McIntosh et al. [6] studied the effect of acute rhythmic auditory stimulation (RAS) in patients with idiopathic Parkinson's disease also during the OFF phase and reported an improvement in the majority of patients. Cues may also be effective in freezing, a severe gait disturbance that responds poorly to dopaminergic stimulation [6]. Arias and Cudeiro [22] investigated the acute effect of RAS on the gait of PD patients with and without freezing of gait during the end-of-dose periods. The authors report a significant reduction in the number and duration of freezing episodes under RAS conditioning, with a reduction in the time to turn and an increase in cadence and velocity in both groups of patients, with and without freezing.

Most of the randomized controlled trials aimed at evaluating the effect of auditory and visual cues on gait in PD have focused on the immediate effect on gait of the cues [23–41]. Some other studies evaluated the chronic effect (generalization) of auditory and visual cue, individually [42, 43] or used in combination [15, 44, 45]. In general, this wealth of studies showed that both auditory cueing and acoustic cueing are effective in improving some parameters of walking. Auditory cueing seems more effective on speed, cadence, and step length, whereas visual cues ameliorate speed cadence and step length [5, 46]. A limited number of studies have evaluated the retention of the beneficial effect, once the rehabilitation has been stopped [42, 43, 45, 47, 48]. The duration of follow-ups ranges from 4 to 8 weeks, and findings are quite controversial. In general, the improvement in gait parameters induced by visual or auditory cues is maintained at the shortest revaluations, but it progressively wanes when the follow-up duration stretches beyond 2 months.

To the best of our knowledge, no randomized controlled trial has analyzed comparatively the acute and chronic effect of the 2 types of cues used individually. An attempt to indirectly compare the efficacy of the two cues on gait parameters was made by Spaulding in the meta-analysis of 2002, where he concluded that auditory cues provided a more consistent and positive effect on gait parameters of PD patients when compared to visual cueing [46]. This aspect seems important, since the different types of cues are believed to engage anatomic pathways with a differential modality [6–8] and, in our practice, we have noticed that patients may respond preferentially to one type of cue, some showing more marked improvement with visual cues, others with auditory cues.

Table 4: Effect of acoustic cues on gait parameters: kinematic analysis of gait was performed in uncued conditions at baseline (T0), at the end of the 4-week rehabilitation period (T1), and at a 3-month follow-up (T2). Data are expressed as mean ± sd.

	T0	T1	T2	p value T1 versus T0	p value T2 versus T0
Number of strides	7.2 ± 3.3	6.2 ± 1.7	7.0 ± 4.3	<0.05	NS
Stride duration (ms)	1250.5 ± 317.2	1246 ± 263.4	1292.5 ± 214.2	NS	NS
Stride length (cm)	83.5 ± 25.7	106.7 ± 10.7	91.5 ± 11.7	<0.05	NS
Stance (% of stride)	73.8 ± 7.5	70.2 ± 3.1	74.5 ± 7.0	NS	NS
Swing (% of stride)	25.5 ± 6.9	28.5 ± 4.3	24.9 ± 8.9	NS	NS
Speed (m/s)	0.63 ± 0.22	0.77 ± 0.3	0.68 ± 0.32	<0.05	NS

Table 5: Effect of visual cues on gait parameters: kinematic analysis of gait was performed in uncued conditions at baseline (T0), at the end of the 4-week rehabilitation period (T1), and at a 3-month follow-up (T2). Data are expressed as mean ± sd.

	T0	T1	T2	p value T1 versus T0	p value T2 versus T0
Number of strides	6.8 ± 2.5	5.2 ± 1.0	7.1 ± 3.2	<0.05	NS
Stride duration (ms)	1362.9 ± 216.6	1332.9 ± 263.1	1384.1 ± 196.1	NS	NS
Stride length (cm)	84.8 ± 19.2	94.0 ± 29.5	84.1 ± 17.0	NS	NS
Stance (% of stride)	71.3 ± 3.5	62.6 ± 4.0	70.4 ± 4.5	<0.05	NS
Swing (% of stride)	27.6 ± 3.5	36.6 ± 3.5	29.1 ± 4.6	<0.05	NS
Speed (m/s)	0.62 ± 0.1	0.71 ± 0.2	0.65 ± 0.6	<0.05	NS

Table 6: Effect of gait training without cues on gait parameters: kinematic analysis of gait was performed at baseline (T0), at the end of the 4-week rehabilitation period (T1), and at a 3-month follow-up (T2). Data are expressed as mean ± sd.

	T0	T1	T2	p value T1 versus T0	p value T2 versus T0
Number of strides	7.0 ± 4.1	6.8 ± 3.5	7.4 ± 2.1	NS	NS
Stride duration (ms)	1336.7 ± 247.9	1351.8 ± 267.7	1301.7 ± 254.1	NS	NS
Stride length (cm)	86.3 ± 20.5	103.9 ± 20.7	93.3 ± 25.6	<0.05	NS
Stance (% of stride)	69.5 ± 6.0	68.8 ± 6.8	67.3 ± 5.1	NS	NS
Swing (% of stride)	30.2 ± 6.0	31.1 ± 6.7	31.5 ± 4.4	NS	NS
Speed (m/s)	0.64 ± 0.2	0.74 ± 0.3	0.66 ± 0.7	<0.05	NS

In the present study we investigated the effect of visual or auditory cues upon gait parameters both acutely (walking under cueing) and chronically (walking without cueing after a four-week rehabilitation program). We also investigated whether there was any retention of the effect at 3 months.

Regarding the acute effect, we found a significant increase in stride duration and in stride length when patients were exposed to acoustic cues, while a decrease in the number of strides and a reduction in gait speed were observed in patients exposed to visual cues. The worsening of some features of gait, such as the increase of stride duration with the acute acoustic cue and the reduction of speed with the acute visual cue, was not totally surprising because we realized that a proper use of cues by PD patients requires supervision by the therapist and a learning process by the patient to integrate the cue in the automaticity of gait. At the time of acute evaluation the patients had met the therapist only once and they were not familiar with cues. This observation seems relevant for the practical approach to gait training with cues, because it suggests that the adoption of the cueing strategy in the home-unassisted rehabilitation requires an adequate assisted training to avoid that the patients fail to internalize the cues aid or do so with a less functional motor pattern.

At the end of the rehabilitation program, the patients were tested under the uncued paradigm to evaluate the chronic effects of cues. The number of strides was significantly reduced only in the patients that underwent cued rehabilitation. This finding represents an important goal in the rehabilitation of PD gait, typically characterized by a tendency to an increase in the number of steps. It is known that in PD patients the activity of the internal rhythm pacemaker is dysfunctional and therefore we speculate that the observed reduction in the number of strides was promoted by the pacing effect of the external cues adopted [1–7].

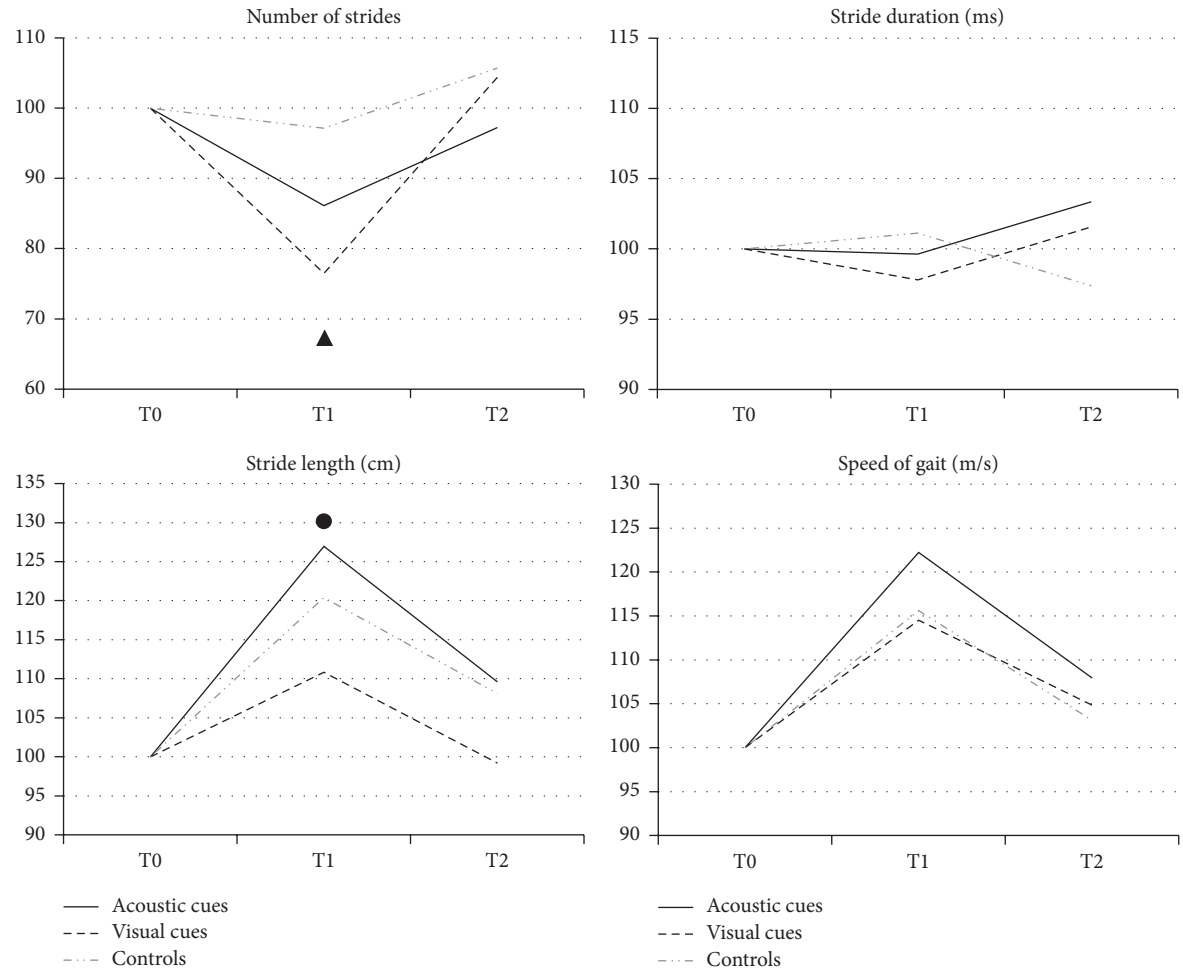

Figure 1: Effect of the different modalities of gait training on gait parameters recorded by means of the kinematic analysis. Baseline values are normalized to 100% and changes represented as % variation from baseline. ▲ Acoustic Group versus Controls $p < 0.05$ and Visual Group versus Controls $p < 0.05$. ● Acoustic Group versus Visual Group $p < 0.05$ and Controls versus Visual Group $p < 0.05$.

Interestingly the reduction in the number of strides showed a differential pattern in the two cued groups, possibly related to different mechanisms of pacing: in the Acoustic Group it was associated with an elongation in stride length, while in the Visual Group it was associated with a redistribution of the stance-swing phase of gait. It is tempting to speculate that auditory cues, once internalized with the 4-week training, are capable of providing an automatic (subcortical?) rhythm that facilitates all components and movements of gait, probably including also arms swing (although we do not have data to substantiate this speculation at this time), leading to an increased length of steps. Conversely, visual cues, with the indication to calibrate the step on a specific and steady length (the distance between tapes), may act through a less automatic, more "corticalized," modality of training that leads to an increased attention of the patient during the swing phase for hitting the target distance.

It is important to underline that in all the three groups there was a significant increase in gait speed, without any statistical differences between groups at T1. Speed of gait represents one of the most comprehensive features of gait in Parkinson's disease which may become in certain cases an independent indicator of disease severity [21]. Our finding suggests that gait speed is not influenced by cues, being rather the effect of the multimodal exercise modalities proposed within our rehabilitative programme.

Despite the chronic effect observed at T1, we could not detect any retention after 3 months in none of the groups. This feature probably results as a combination of the progression of neurodegeneration, typical of PD, with the well-known deficit of implicit learning in PD subjects [9]. It is important however to note that our patients received precise indications to stop using cues after discharge. In the real life setting, it is conceivable that retention could be promoted by a long-term, less intensive rehabilitation with cues at home. Several studies have shown the feasibility of adopting cued gait training at home to suggest that cued training at home may actually prolong the effectiveness of inpatient treatment [33, 49, 50]. To the best of our knowledge no study has evaluated this possibility and future investigations are needed to verify its impact and feasibility.

In conclusion, our study further supports the usefulness of rehabilitation in improving gait disorders in PD. The

Table 7: Scores at UPDRS-III and FIM at baseline and at follow-ups.

		T0	T1	T2	p value T0 versus T1	p value T0 versus T2
UPDRS-III	Acoustic cues	32.1 ± 9.8	24.1 ± 9.3	31.6 ± 8.7	<0.05	NS
	Visual cues	29.1 ± 7.9	22.0 ± 4.6	28.8 ± 8.3	<0.05	NS
	Controls	32.8 ± 10.8	27.8 ± 6.3	30.4 ± 8.5	<0.05	NS
FIM	Acoustic cues	102.0 ± 10.2	111.7 ± 9.8	103.1 ± 11.3	<0.05	NS
	Visual cues	105.8 ± 11.5	111.5 ± 11.2	104.3 ± 10.6	<0.05	NS
	Controls	101.9 ± 19.2	107.7 ± 14.7	102.2 ± 15.4	<0.05	NS

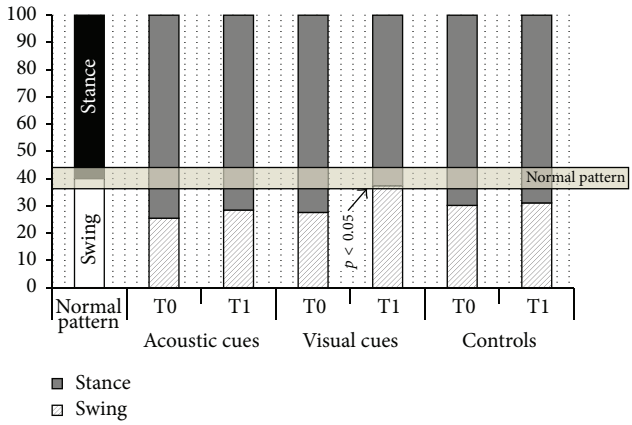

Figure 2: Distribution of stance and swing phases in the 3 treatment groups at T0 and T1. The first column on the left shows the normal percent distribution of the 2 phases of gait. The shaded horizontal bar represents the normal variability of gait pattern in healthy subjects (±4%). Note that parkinsonian gait is characterized by a reduction in the swing phase and that visual cues normalized the distribution of these 2 phases at T1. Visual Group: T0 versus T1 $p < 0.05$. At T1 Visual Group versus Acoustic Group $p < 0.05$ and Visual Group versus Controls $p < 0.05$.

selective impact of different kinds of cues on gait parameters suggests the usefulness of evaluating individually the gait pattern of the patients with gait analysis and testing their performance with different type of cues before the beginning of the rehabilitation programme, in order to optimize efficacy. The tendency to lose effects over months underlines once more the need for a continuative and multidisciplinary approach, characterized by serial visits and repeated rehabilitation cycles over the years.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Screening for Mild Cognitive Impairment in Parkinson's Disease: Comparison of the Italian Versions of Three Neuropsychological Tests

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Mild cognitive impairment (MCI) is frequent in Parkinson's disease (PD). Recently proposed criteria for MCI in PD (PD-MCI) indicate level I diagnosis based on abbreviated assessment and level II based on comprehensive neuropsychological evaluation. The study explored the sensitivity and specificity of the Italian versions of three neuropsychological tests for level I diagnosis of PD-MCI. We recruited 100 consecutive PD patients. After screening for inclusion criteria, 43 patients were included. The sensitivity and specificity of the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Addenbrooke's Cognitive Examination Revised (ACE-R) in comparison to level II diagnosis of PD-MCI were examined. PD-MCI was diagnosed (level II) in 51% of patients. Disease duration was significantly longer and PD motor scales were more severely impaired in MCI group. The receiver-operator characteristics curve documented nonsignificant difference in the performance of the three tests, with slight advantage of MMSE (corrected data). The time of administration favored MMSE. In Italian-speaking PD patients, MMSE might represent a good screening tool for PD-MCI, because of the shorter time of administration and the performance comparable to those of MoCA and ACE-R. Further studies are needed to validate the new PD-MCI criteria across different languages and cultures.

1. Introduction

Cognitive impairment is frequent in Parkinson's disease (PD) [1], and the spectrum of cognitive dysfunction ranges from mild cognitive impairment (MCI) to PD dementia (PD-D) [2, 3]. The diagnosis of PD-D may to some extent be straightforward [4], but recognizing MCI in PD (PD-MCI) is more difficult. Cognitive deficits may occur early in PD course, and they can be documented in up to a quarter of newly diagnosed PD patients [5]. The biological validity of PD-MCI as a clinical entity is supported by converging morphological, functional neuroimaging, neurophysiological, genetic, and cerebrospinal fluid and histological data showing an association between a number of neuropathophysiological variables and cognitive impairment or cognitive decline in nondemented PD patients [2].

Identifying PD-MCI is clinically important, as these patients appear to be at increased risk for developing PD-D [6], and they often present functional impairment and have worse quality of life [2]. In the rehabilitation setting, recognizing PD-MCI is very important, in that it may negatively influence the outcome in patients undergoing motor rehabilitation. Moreover, PD-MCI may itself represent a target for cognitive training [7, 8], pharmacological treatment [9], or their combination.

A task force of the Movement Disorder Society (MDS) has recently delineated diagnostic criteria for PD-MCI [10]. These criteria indicate a two-step process with level I (possible PD-MCI) based on abbreviated assessment and level II diagnosis based on comprehensive neuropsychological evaluation permitting MCI subtyping [10], but they need to be validated, as well as the proposed neuropsychological scales and tests. A very recent study explored these criteria in a group of PD patients and the accuracy of three neuropsychological screening tests and found that none of them provided good combined sensitivity and specificity for PD-MCI [11]. For most of the neuropsychological tests, translation and validation across different languages and cultures are lacking, and this may represent a problem when assessing PD-MCI with level I criteria and a possible source of error when transferring data from a given population/language to other ones.

The present study was aimed to explore the sensitivity and specificity of the Italian versions of three neuropsychological tests for level I diagnosis of PD-MCI, namely, the Mini Mental State Examination (MMSE) [12], the Montreal Cognitive Assessment (MoCA) [13], and the Addenbrooke's Cognitive Examination Revised (ACE-R) [14], for all of which an Italian translation and validation exist [15–18]. Data from the three screening neuropsychological tests were compared to those from full neuropsychological testing (level II) [10], which represent the *gold standard* for MCI diagnosis.

2. Materials and Methods

2.1. Subjects. Our population sample was a group of 100 consecutive Italian PD patients. The study was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2001 and approved by local ethics committee. All patients gave signed informed consent prior to inclusion in the study. Inclusion criteria were (1) diagnosis of PD based on the UK PD Brain Bank Criteria [19]; (2) absence of PD-D [4]; (3) no other possible causes for cognitive impairment (e.g., delirium, stroke or cerebrovascular disease, head trauma, metabolic abnormalities, and adverse effects of medication); (4) no other PD-associated comorbid conditions (e.g., marked motor impairment, severe or unpredictable motor fluctuations and/or dyskinesia, severe anxiety, excessive daytime sleepiness, or psychosis) that may have significantly influenced cognitive testing [10].

Depression was assessed with the Beck Depression Inventory II (BDI-II) [20] with a cutoff of 14 for the presence of mild depression and a cutoff of 28 for severe depression [21]. Depression was not considered an exclusion criterion, except if severe (i.e., patients with a BDI-II score >28 were excluded), because it may be found in around 35% of PD patients [22] and including PD patients with mild to moderate depression would have resulted in a more real-life scenario. The severity of PD motor symptoms and related impairment and disability was measured with the Modified Hoehn and Yahr Staging Scale [23] and the Unified Parkinson's disease rating scale [24]. Total daily levodopa equivalent dose was calculated for each patient [25].

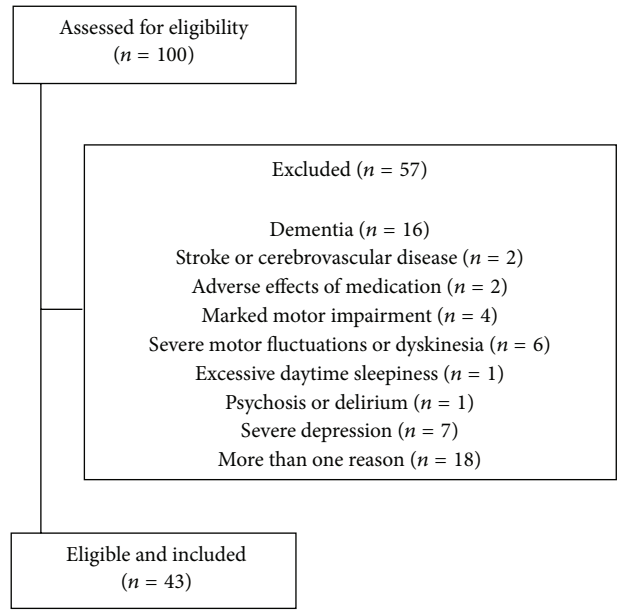

Figure 1: Flow diagram of the study and reasons for patients' exclusion.

After screening for inclusion criteria (Figure 1), 43 patients (27 males, 16 females, mean age 68.2 ± 9.2, range 44–88; mean education 8.5 ± 2.9 years, range 4–13) were included in the study. Demographic and clinical characteristics of patients are reported in Table 1.

2.2. Neuropsychological Assessment. All patients underwent the Italian versions of MMSE, MoCA, and ACE-R and a full neuropsychological testing, which were performed by different expert neuropsychologists, who were blinded to each other's results, on separate days at a similar time of the day, and with the patient in the ON state. Given overlapping items, the order of administration of the three screening tests was pseudorandom to avoid bias in performance related to fatigue, learning, or other effects secondary to order [11]. Since the ACE-R contains all the items of the MMSE, the common items were not administered twice. The time taken for administering each screening test and full neuropsychological testing was measured in each patient.

Full neuropsychological testing included at least two types of neuropsychological testing for each of the five following cognitive domains [10]. *Attention and working memory* were examined with four tests, namely, digit span, a subtest of the Wechsler memory scale [26], interference memory task (10 sec and 30 sec) based on the Brown-Peterson paradigm [27, 28], and trail making test (TMT) part A [29]. *Executive function* was explored with four tests, namely, TMT part B [29], frontal assessment battery [30], phonemic fluency test, and clock drawing test, the latter two being subtests of the short neuropsychological examination version 2 (ENB-2) [31]. *Language* was examined with four tests, namely, the short form of the Boston naming test [32] and three specific subtests of the neuropsychological examination of aphasia [33]. *Memory* was explored with four tests, namely, Rey's auditory verbal learning test (immediate recall, delayed

Table 1: Demographic and clinical characteristics of the patients.

Pt	Sex	Age (y)	School (y)	Duration (y)	H-Y (1–5)	Treatment and daily dosage	Depression (yes/no)
1	F	44	12	5	1	PRX 4.5 mg, RAS 1 mg	No
2	M	46	8	15	3	LD 600 mg, APO 36 mg, PRX 3 mg	Yes
3	M	51	13	10	2.5	LD 1150 mg	No
4	F	52	11	14	2	APO 84 mg, CAB 9 mg	No
5	F	56	13	11	2.5	LD 500 mg, APO 48 mg, PRX 4.5 mg	Yes
6	F	57	13	10	2	LD 600 mg, APO 52 mg	No
7	M	60	12	8	3	LD 500 mg	Yes
8	M	60	8	20	3	LD 750 mg	Yes
9	M	61	8	5	1	RAS 1 mg	Yes
10	M	61	13	21	2.5	LD 950 mg	No
11	F	63	10	4	1.5	PRX 3 mg	Yes
12	F	64	5	2	1.5	LD 400 mg	Yes
13	F	65	5	10	2.5	LD 700 mg, PRX 1.5 mg, RAS 1 mg	No
14	F	67	13	10	2	LD 1000 mg, PRX 4.5 mg	No
15	M	67	10	5	1	LD 400 mg	No
16	M	67	8	1	1	None	Yes
17	M	68	8	3	1.5	LD 400 mg	Yes
18	M	68	8	22	2.5	LD 975 mg	Yes
19	M	68	10	21	3	LD 1250 mg	Yes
20	M	68	8	23	2.5	LD 1150 mg	No
21	M	69	8	24	3	LD 950 mg	Yes
22	M	69	5	4	3	LD 850 mg	No
23	M	70	10	24	4	LD 1200 mg	Yes
24	F	70	3	10	1.5	LD 800 mg	No
25	M	72	8	4	1	LD 350 mg, ROP 8 mg	No
26	F	72	12	12	2.5	LD 550 mg, APO 42 mg	No
27	M	72	8	12	2.5	LD 1250 mg	No
28	F	73	5	5	1	LD 250 mg, SEL 10 mg	No
29	M	73	13	7	3	LD 1250 mg, ROT 10 mg	No
30	M	74	8	4	3	LD 700 mg, PRX 3 mg	No
31	M	75	8	6	3	LD 600 mg, ROP 16 mg	No
32	M	75	5	3	1	ROP 16 mg, SEL 10 mg	No
33	M	75	5	20	3	LD 1100 mg, ROP 12 mg	No
34	M	75	5	10	2.5	LD 800 mg, PRX 4.5 mg	Yes
35	F	75	5	5	2	LD 300 mg, ROP 16 mg	No
36	M	76	8	20	2.5	LD 1150 mg, PRX 3 mg	No
37	M	76	6	10	2	LD 900 mg, PRX 3 mg	No
38	M	76	5	25	3	LD 1250 mg	No
39	F	76	8	8	2	LD 1000 mg	Yes
40	M	76	13	11	2	LD 750 mg	Yes
41	F	79	5	4	2	LD 300 mg	No
42	F	83	5	4	2	LD 500 mg	Yes
43	F	88	4	1	1.5	LD 400 mg	No
Average		**68.2**	**8.3**	**10.5**	**2.2**		
SD		**9.3**	**3.0**	**7.3**	**0.8**		

Pt: patient; school: education (years); duration: disease duration (years); H-Y: Modified Hoehn and Yahr Staging Scale (range 1–5); SD: standard deviation; APO: apomorphine; CAB: cabergoline; LD: levodopa (dosage corrected according to the eventual use of COMT-inhibitors); PRX: pramipexole; RAS: rasagiline; ROP: ropinirole; ROT: rotigotine; SEL: selegiline.

Table 2: Characteristics of patients, according to the diagnosis and subtype of PD-MCI (MDS Task Force level II criteria).

	No PD-MCI ($n = 21$)	PD-MCI ($n = 22$)	p	Single-domain PD-MCI ($n = 8$)	Multiple-domain PD-MCI ($n = 14$)	p
Age	67.5 ± 11.2	68.9 ± 7.2	n.s.	65.5 ± 7.7	70.8 ± 6.2	n.s.
Sex (M/F)	12/9	15/7	n.s.	7/1	8/6	n.s.
School (y)	8.7 ± 3.1	8.3 ± 2.8	n.s.	9.3 ± 2.6	7.6 ± 2.8	n.s.
Duration (y)	7.8 ± 5.3	12.8 ± 8.1	0.03	13.1 ± 8.6	11.4 ± 8.1	n.s.
H-Y (1–5)	1.9 ± 0.7	2.5 ± 0.6	0.014	2.3 ± 0.8	2.6 ± 0.5	n.s.
UPDRS-III (0–108)	23.3 ± 8.9	30.2 ± 8.4	0.02	27.5 ± 10.2	31.5 ± 9.0	n.s.
Treatment						
LD (yes/no)	17/4	20/2	n.s.	7/1	13/1	n.s.
DA (yes/no)	12/9	7/15	n.s.	2/6	5/9	n.s.
MAO-I (yes/no)	4/17	1/21	n.s.	0/8	1/13	n.s.
Total LED (mg)	821 ± 413	889 ± 394	n.s.	893 ± 439	888 ± 384	n.s.
Depression (yes/no)	8/13	9/13	n.s.	3/5	6/8	n.s.

School: education (years); duration: disease duration (years); H-Y: Modified Hoehn and Yahr Staging Scale (range 1–5); UPDRS-III: Unified Parkinson's Disease Rating Scale part III (range 0–108); LD: levodopa; DA: dopamine agonist; MAO-I: monoamine oxidase inhibitors; LED: levodopa equivalent dose (daily).

recall) [34], and two prose recall subtest (immediate recall, delayed recall) derived from ENB-2 [31]. *Visuospatial function* was examined with two tests, namely, Benton's judgment of line orientation [35] and the geometrical figures copying test, a subtest of the mental deterioration battery [36].

The impairment on basic activities of everyday life (BADL) and instrumental activities of everyday life (IADL) was explored with specific questionnaires [37, 38].

2.3. PD-MCI Diagnosis. The diagnosis of PD-MCI was made according to the MDS Task Force level II criteria [10]. They included (1) gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant or observed by the clinician, consisting of at least 1 item of the IADL scale; (2) cognitive deficits that are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present, as documented by normal BADL scale; (3) impairment in at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain (single-domain PD-MCI) or one impaired test in two different cognitive domains (multiple-domain PD-MCI). Impaired performance on a neuropsychological test was defined as a score that was at least 1.5 standard deviations (SDs) below the age-adjusted mean from normative data [11]. According to the MDS Task Force criteria, significant decline on serial cognitive testing or from estimated premorbid level may be used instead of normative data [10], but we did not use these alternative criteria, because the former would have required repeated full neuropsychological testing with the risk of learning bias and because of the difficulties found in applying the latter (see Section 4) [11].

2.4. Statistical Analysis. All tests were carried out with the IBM SPSS version 20.0 and the Stata 11.0 statistical packages. The normality of variable distribution was analyzed with the Skewness-Kurtosis test. Continuous variables were explored with ANOVA and post hoc t-test with Bonferroni's correction. Homogeneity of variance was analyzed with Levene's test. The data were transformed (logarithmic transformation) before submitting them to ANOVA in case of an inequality in the variances. The nonparametrical Mann-Whitney U test was applied in case the distribution was not normal. Pearson's χ^2 test with Yates' correction for continuity was applied to dichotomous variables. Sensitivity and specificity of the MMSE (raw score and score corrected for age, sex, and education), MoCA (raw and corrected score), and ACE-R were calculated across all possible cutoff scores below which an individual would be classified as having PD-MCI. The area under the receiver-operator characteristics (ROC) curve (AUC) was calculated and compared across the three tests and the AUC 95% confidence intervals (CIs) were generated. $p < 0.05$ (two-tailed) was taken as the significance threshold for all the tests.

3. Results

According to the MDS Task Force level II criteria [10], PD-MCI was diagnosed in 22 patients (51%). Eight out of the 22 (36%) PD-MCI patients were classified as single-domain MCI, with five of them showing impairment in executive function and three with impaired memory. The other 14 patients (64%) were classified as multiple-domain MCI. Among multiple-domain MCI cases, attention and working memory was impaired in 9 patients, executive function in 14, memory in 8, language in 2, and visuospatial function in 1. Demographic and clinical variables according to the presence or absence of MCI and the MCI subtype (i.e., single-domain versus multiple-domain) are reported in Table 2. Disease duration was significantly longer in patients with MCI (12.8 ± 8.1 years) than in those without MCI (7.8 ± 5.3 years, $p = 0.03$; Table 2). PD motor and impairment scales were more severely impaired in MCI group (H-Y: 2.5 ± 0.6; UPDRS-III: 30.2 ± 8.4) than in patients without MCI (H-Y:

1.9 ± 0.7, p = 0.014; UPDRS-III: 23.3 ± 8.9, p = 0.02; Table 2). The other variables did not differ between the two groups. None of the demographic and clinical variables significantly differed according to the MCI subtype (Table 2).

3.1. Comparison between the Screening Tests. The ROC curves for the three screening tests (raw and corrected data) are illustrated in Figure 2. The AUC was 0.84 (95% CI: 0.72–0.97) for the MMSE (raw data), 0.88 (95% CI: 0.78–0.98) for the MMSE (corrected data), 0.80 (95% CI: 0.66–0.93) for the MoCA (raw data), 0.79 (95% CI: 0.66–0.93) for the MoCA (corrected data), and 0.81 (95% CI: 0.68–0.94) for the ACE-R. None of the pair-wise comparisons between AUC estimates were statistically significant.

The sensitivity and specificity of the three tests for detecting PD-MCI across different cutoff scores are reported in Tables 3 and 4.

3.2. Screening Cutoff Values. For raw MMSE data, the lowest cutoff value with sensitivity >0.80 was 29.5 (sensitivity = 0.96, specificity = 0.62). When using corrected MMSE data, the lowest cutoff value with sensitivity >0.80 was 28.6 (sensitivity = 0.86, specificity = 0.71). For raw MoCA data, the lowest cutoff value with sensitivity >0.80 was 24.5 (sensitivity = 0.82, specificity = 0.67). When analyzing corrected MoCA data, the lowest cutoff value with sensitivity >0.80 was 25.5 (sensitivity = 0.82, specificity = 0.67). For ACE-R, the lowest cutoff value with sensitivity >0.80 was 86.0 (sensitivity = 0.82, specificity = 0.67).

3.3. Diagnostic Cutoff Values. For raw MMSE data, the highest cutoff value with specificity >0.80 was 28.5 (sensitivity = 0.73, specificity = 0.81). When examining corrected MMSE data, the highest cutoff value with specificity >0.80 was 28.0 (sensitivity = 0.73, specificity = 0.81). For raw MoCA data, the highest cutoff value with specificity >0.80 was 21.5 (sensitivity = 0.55, specificity = 0.90). When using corrected MoCA data, the highest cutoff value with specificity >0.80 was 22.5 (sensitivity = 0.55, specificity = 0.86). When analyzing ACE-R findings, the highest cutoff value with specificity >0.80 was 77.5 (sensitivity = 0.59, specificity = 0.81).

3.4. Timing for Administering Screening Tests and Full Neuropsychological Testing. The average time for the administration of the screening tests was 7.8 ± 1.4 min for MMSE, 12.3 ± 3.2 min for MoCA, and 18.4 ± 2.9 min for ACE-R. Full neuropsychological testing required 52.3 ± 7.1 min.

4. Discussion

We have explored the sensitivity and specificity of the Italian versions of three screening tests for recognizing PD-MCI in comparison to full neuropsychological testing. Our data documented that the performances of the three tests were similar and that they could achieve a limited trade-off between sensitivity and specificity, with a slight advantage of MMSE and the use of corrected data.

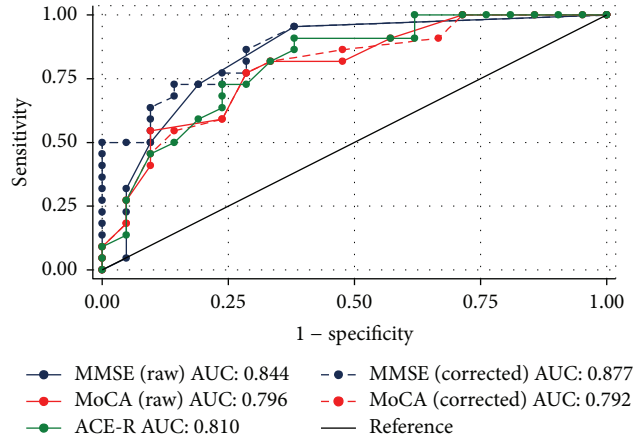

Figure 2: Receiver-operator characteristics (ROC) curves for the three screening tests (raw and corrected data).

The screening tests we examined were chosen because, to the best of our knowledge, they were the only ones with the availability of a validated Italian version at the time when the study was designed. None of them could reach combined sensitivity and specificity >0.80 at any cutoff value. The analysis of ROC curves for the screening scales showed a larger AUC and the best sensitivity-specificity profile for the corrected MMSE score. In particular, a cutoff of 28.6 resulted in sensitivity = 0.86 and specificity = 0.71, while a cutoff of 28.0 was associated in sensitivity = 0.73, and specificity = 0.81. The other scales performed slightly worse, but the difference between the ROC curves was not significant.

A number of previous studies compared different screening tests for assessing cognitive functions and/or early cognitive deficit in PD patients [5, 39], with conflicting results in terms of the best profile of sensitivity and specificity between them. The use of MMSE as a screening instrument in PD has been challenged because it does not specifically test subcortical executive function, which is impaired early in PD patients [40]. Some studies documented that MMSE has low sensitivity in detecting MCI and cognitive impairment in PD [41, 42], in particular when compared to MoCA [39, 43–45]. At variance, other authors reported that MMSE might be useful in detecting cognitive deterioration in early PD [46]. Data on the use of ACE-R as a screening tool for PD-MCI are controversial [47], but a previous version was found to be a good test for evaluating MCI [48] and dementia [49, 50] in PD patients. A reason for these discrepancies might be that ACE-R includes an assessment by domains and its abilities may not be completely comparable to that of MMSE and MoCA, which represent true screening scales. Moreover, MMSE and ACE-R share some common items, and the total points of ACE-R (100 points) differ from that of MMSE and MoCA (30 points). However, the comparison of AUCs instead of cutoffs should have avoided the difference in total points among screening tests to represent a bias.

Comparison between the present results and those from most of previous studies is however difficult, because only a few of them used a comprehensive neuropsychological

Table 3: Sensitivity and specificity of MMSE and MoCA for detecting PD-MCI at different cutoff values.

Cutoff	Sensitivity	Specificity
	MMSE	
Raw data		
<24.5	0.05	0.95
<25.5	0.23	0.95
<26.5	0.32	0.95
<27.5	0.50	0.90
<28.5	0.73	0.81
<29.5	0.96	0.62
Corrected data		
<22.5	0.05	1.00
<23.2	0.09	1.00
<23.7	0.14	1.00
<24.3	0.18	1.00
<25.0	0.27	1.00
<25.2	0.32	1.00
<25.4	0.36	1.00
<25.7	0.41	1.00
<26.0	0.46	1.00
<26.2	0.50	1.00
<26.3	0.50	0.95
<26.4	0.50	0.91
<26.6	0.55	0.91
<26.8	0.59	0.91
<27.0	0.64	0.91
<27.2	0.68	0.86
<27.6	0.73	0.86
<28.0	0.73	0.81
<28.4	0.77	0.76
<28.6	0.86	0.71
<29.4	0.95	0.62
	MoCA	
Raw data		
<15.0	0.05	1.00
<16.5	0.09	1.00
<17.5	0.18	0.95
<19.0	0.27	0.95
<20.5	0.41	0.90
<21.5	0.55	0.90
<22.5	0.59	0.76
<23.5	0.77	0.71
<24.5	0.82	0.67
<25.5	0.82	0.52
<26.5	0.91	0.33
<27.5	1.00	0.29
<28.5	1.00	0.14
<30.0	1.00	0.00
Corrected data		
<16.0	0.05	1.00
<17.5	0.09	1.00
<18.5	0.18	0.95
<20.0	0.27	0.95
<21.5	0.46	0.90
<22.5	0.55	0.86
<23.5	0.59	0.76
<24.5	0.77	0.71
<25.5	0.82	0.67
<26.5	0.86	0.52
<27.5	0.91	0.33
<28.5	1.00	0.29
<29.5	1.00	0.05

MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; PD-MCI: mild cognitive impairment in Parkinson's disease.

Table 4: Sensitivity and specificity of ACE-R for detecting PD-MCI at different cutoff values.

Cutoff	Sensitivity	Specificity
<62.5	0.05	1.00
<66.5	0.09	1.00
<69.5	0.14	0.95
<73.5	0.27	0.95
<75.5	0.46	0.90
<76.5	0.50	0.86
<77.5	0.59	0.81
<78.5	0.64	0.76
<80.0	0.68	0.76
<82.5	0.73	0.76
<84.5	0.73	0.71
<86.0	0.82	0.67
<87.5	0.86	0.62
<89.0	0.91	0.62
<90.5	0.91	0.43
<91.5	0.91	0.38
<92.5	1.00	0.38
<93.5	1.00	0.29
<94.5	1.00	0.24
<95.5	1.00	0.19
<96.5	1.00	0.14
<97.5	1.00	0.09
<98.5	1.00	0.05
<100.0	1.00	0.00

ACE-R: Addenbrooke's Cognitive Examination Revised; PD-MCI: mild cognitive impairment in Parkinson's disease.

evaluation and standard criteria to detect and diagnose MCI. A couple of recent studies applied the new MDS criteria for MCI and yielded contrasting results, in that one documented limited sensitivity-specificity profile for both MMSE and MoCA [11], while the other reported high sensitivity of MoCA for predicting PD-MCI [51].

Other neuropsychological scales, such as the Mattis dementia rating scale [48, 52, 53], the Cambridge cognitive assessment [54], the cognitive linguistic quick test [55], the PD cognitive rating scale [56], and the SCOPA cognition [57], have been demonstrated to be helpful in exploring early cognitive decline in PD [10], but the absence of an Italian version impeded their exploration as a screening tool for PD-MCI in our PD patients sample. What is more, the long administration time of these scales (i.e., up to 25–45′) is not suitable for a screening procedure in the clinical setting.

Our data favor the correction for age, sex, and education when scoring MMSE, in that corrected MMSE data yielded a larger AUC and slightly better sensitivity-specificity profile than raw ones. At variance, correcting MoCA did not change the performance of the test. However, pair-wise statistical comparisons between ROC curves did not show any significant difference between them. In the clinical setting, MMSE correction is reasonable especially for older and less educated patients.

We recorded the time taken for administering the three screening scale, and this variable favored the MMSE (7.8 ± 1.4 min) compared to the MoCA (12.3 ± 3.2 min) and the ACE-R (18.4 ± 2.9 min). According to these combined figures (i.e., similar sensitivity-specificity profile, shorter time of administration), it is reasonable to prefer the use of MMSE in the setting of a busy clinic.

A number of factors may contribute to cognitive dysfunction in PD patients and lead to a false positive diagnosis of PD-MCI. All the possible contributing factors were considered and our strict inclusion criteria, which resulted in the exclusion of approximately half of the patients, should have reduced this bias. Drugs with possible effect on cognition represented an exclusion criterion, and the total LED was similar between patients with and without MCI. As a consequence, pharmacological effects should not have influenced our findings. Depression has been documented to be more frequent in PD-MCI patients in comparison to those without MCI [58], but this was not the case in our sample. We excluded only patients with severe depression according to the BDI-II, because mild to moderate depression is a common feature of PD and exclusion of all depressed patients might have resulted in a non-real-life scenario. We may argue that depression should not have been a bias factor in the present study.

PD patients with MCI had significantly longer disease duration and more severe motor impairment and disability, according to the H-Y and UPDRS-III scales. This finding is in accordance with some previous reports [58] but in contrast with other ones [11]. Differences in the sampling of PD patients across different studies, depending on different settings (e.g., primary care versus referral centre) or different populations, are the most likely reasons for this discrepancy.

The analysis of MCI subtypes indicated a prevalence of multidomain PD-MCI in comparison to single-domain. This finding is in accordance with previous reports using new MDS criteria [11, 59]. We could not document any difference in clinical variables between single- and multidomain PD-MCI patients, but the small samples might have impeded the recognition of small differences between the two groups. In accordance with previous studies [5, 7], we documented a high prevalence of executive alterations in our PD sample. This finding may stem from the use of four tests for this cognitive domain, which may have resulted in a higher likelihood of falling in two of them [60]. However, this potential bias effect seems not to be major, because the upper limit (maximum probability) for detecting impairment on a test was found to stabilize at two tests in the executive functions domain and did not increase with three or four tests [60].

When applying the MDS level II diagnostic criteria for PD-MCI [10], impairment on a neuropsychological test was defined as a score that was at least 1.5 SD below the age-adjusted normative data [11]. We avoided the use of the alternative criterion of a significant decline on serial cognitive testing [10], because of the lack of previous neuropsychological testing in the majority of our patients. For what concerns the other alternative criteria of a decline from estimated premorbid level [10], this was also not used for a number of reasons. They include the lack of any indication on how to use tests of premorbid intellectual functioning [10], the absence of a validated Italian version of the Wechsler test of adult reading [10], and the previous evidence of the ineffectiveness of the Italian version of the alternative national adult reading test for the estimation of premorbid reading ability [61]. In a previous study, the number of patients diagnosed as PD-MCI with level II criteria varied consistently (i.e., from 33% to 79%) by applying different criteria for impairment on a neuropsychological test [11], and this might represent an important source of uncertainty when applying level II criteria. Similarly, varying cutoff values for single tests had a large influence on the percentage of PD-MCI patients in the same population [62].

Limitations of the present study include the small sample and the high prevalence of PD-MCI. MCI was found in 51% patients in our PD sample, while cross-sectional studies documented that the prevalence of MCI ranges from 20 to 30% in PD [42, 58]. However, our sample is too small to provide a good approximation of the prevalence of the condition in the general population, and there may have been some bias due to the strict selection criteria. The present data should be confirmed in a larger PD patients group before generalizing our conclusions.

Another limitation is the absence of follow-up data. Serial testing of PD-MCI patients documented that a similar proportion of them might either progress to PD-D or revert to normal cognition (i.e., approximately 20%) after one year [63]. Reasons for this apparently paradoxical finding might include comorbidities, measurement errors, learning effects due to repeated neuropsychological testing, and improved cognition after initiation of symptomatic treatment [63], in addition to suboptimal treatment of motor symptoms at the time of first testing, motor fluctuations, or drug side effects.

BADL and IADL were evaluated with questionnaires [37, 38] that are not PD-specific, because, to the best of our knowledge, there is no Italian version of any disease-specific scale, such as the Parkinson's disease cognitive functional rating scale [64]. We think that this point does not represent a major bias, because the questionnaires were used to group

patients as having PD-MCI or not and not to quantitatively measure impairment on BADL and IADL.

5. Conclusions

Our data might be helpful in the clinical and the neurorehabilitation setting, because cognitive impairment is common in PD, PD-MCI may progress to PD-D, and both these conditions may have a negative impact on function, quality of life, and caregiver burden [43]. Identification and intervention at the earliest stage of PD-MCI is a crucial unmet need for the overall care of PD patients [10]. MMSE might represent a good tool for screening cognition throughout all stages of PD, because of the short time of administration and the sensitivity-specificity profile comparable to those of MoCA and ACE-R. Follow-up serial testing might be necessary in case of confounding factors. Complete neuropsychological testing, however, still represents the *gold standard* for a diagnosis of PD-MCI.

Future studies should better explore the reliability of level I and level II MDS criteria for MCI and incorporate biomarkers of cognitive dysfunction [2, 10].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Balance Dysfunction in Parkinson's Disease: The Role of Posturography in Developing a Rehabilitation Program

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Balance dysfunction (BD) in Parkinson's disease (PD) is a disabling symptom, difficult to treat and predisposing to falls. The dopaminergic drugs or deep brain stimulation does not always provide significant improvements of BD and rehabilitative approaches have also failed to restore this condition. In this study, we investigated the suitability of quantitative posturographic indicators to early identify patients that could develop disabling BD. Parkinsonian patients not complaining of a subjective BD and controls were tested using a posturographic platform (PP) with open eyes (OE) and performing a simple cognitive task [counting (OEC)]. We found that patients show higher values of total standard deviation (SD) of body sway and along the medio-lateral (ML) axis during OE condition. Furthermore, total and ML SD of body sway during OE condition and total SD of body sway with OEC were higher than controls also in a subgroup of patients with normal Berg Balance Scale. We conclude that BD in Parkinsonian patients can be discovered before its appearance using a PP and that these data may allow developing specific rehabilitative treatment to prevent or delay their onset.

1. Introduction

Parkinson's disease (PD) is one of the most common neurological disorders and balance dysfunction (BD) is a common feature [1]. BD is a highly disabling symptom, difficult to treat, and predisposing patients to unexpected falls [2]. The uses of dopaminergic drugs or deep brain stimulation do not provide significant improvements of BD, probably due to a neuropathological process spreading towards nondopaminergic pathways [3].

Moreover, previous studies have demonstrated that treatment with levodopa increases postural sway in patients with advanced PD [4]. BD is characterized by alterations of postural control strategies during standing tasks responding to an unexpected destabilizing perturbation or performing voluntary movements [5]. From the stage 2 Hoehn and Yahr Scale [6], Parkinsonian patients stand with an increasingly narrow stance and stooped posture [7]. The increased muscle tone in flexor muscles and an impaired proprioception, modifying the sense of position, contribute to this posture [8], which leads to a displacement of the body center of mass over the base of support [7]. Because of that, Parkinsonians in quiet stance show an alteration of the physiological postural sways consisting of higher velocity and frequency compared to healthy controls [7]. Since medical and surgical treatments do not have beneficial effects on these symptoms, it is necessary to look for other intervention strategies.

There is an increasing body of evidence, confirmed by systematic reviews [9, 10], that physical therapy interventions can improve BD of people with PD [3]. Unfortunately, the small number and the limited quality of the included trials call for more research in order to clarify the real impact of exercise on balance. A large cohort of rehabilitation interventions have been proposed for BD: exercises programs with balance training components [9], external cueing training [11], treadmill training [12], training with external perturbations [1], progressive resistance exercise [13], hydrotherapy [14], dance [15], and movement strategy training [16]. Nevertheless, the optimal design and delivery of programmes remain unclear [3].

Postural sway can be abnormal in persons with PD before the onset of clinical BD symptoms [17]. This fact has important implications because probably exists the possibility to identify, quantify, and treat BD in patients who do not complain of postural instability. Posturography has been recognized as a useful technique to assess balance in PD [18]. The aim of our study is to investigate the utility of the quantitative posturographic indicators in the assessment of balance in PD patients not complaining of BD in order to develop a tailored rehabilitation treatment specifically addressing its prevention.

2. Methods

2.1. Participants. We enrolled, at the Department of Parkinson's Disease and Brain Injury Rehabilitation of Moriggia-Pelascini Hospital, Gravedona ed Uniti, Italy, twenty-nine PD patients not complaining of BD. Patients were diagnosed according to the UK Brain Bank criteria [19] and were evaluated by a neurologist specialized in movement disorders. Twelve controls matched for age and sex were recruited from our database of volunteers.

The inclusion criteria were (i) stage 2.5–3 according to the Hoehn and Yahr Scale, (ii) stable pharmacological treatment for the last 8 weeks, and (iii) Mini-Mental State Examination (MMSE) >25.

Exclusion criteria were (i) focal brain lesions, (ii) disabling drug-induced dyskinesias, (iii) disturbing tremor, and (iv) vestibular/visual dysfunction limiting balance. Patients included in stage 3 H&Y should not complain of BD in spite of impaired postural reflexes objectively found at the pull test.

All patients and controls underwent a posturography at 9 AM and during the medication ON state (in case of PD patients).

Unified Parkinson's Disease Rating Scale (UPDRS) was assessed in PD patients, while the Berg Balance Scale (BBS) [20] was assessed in both groups before posturography. The BBS is a 14-item test designed to measure the balance of older adults by assessing their performance of specific functional tasks. Each task is scored from 0 to 4, for a maximum of 56 points. A score of 41–56 is associated with a low fall risk, 21–40 with a medium fall risk, and 0–20 with a high fall risk [21].

The study design and protocol were approved by the local Scientific Committee (Moriggia-Pelascini General Hospital, Gravedona ed Uniti, Como) and were in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki, 1967). A complete explanation of the study protocol was provided to and written informed consent was obtained from all patients before the participation in the study.

2.2. Posturographic Platform. PD patients and controls were tested using a posturographic platform (PP) (Prokin 254 (Pro-Kin Software Stability), TecnoBody S.r.l., Dalmine, 24044 Bergamo, Italy), according to standardized methods [22]. The PP is a force platform with a flat and regular surface fixed to four force-transduction systems. The related set of signals is sent to a computer for offline analysis and is used to detect the position of the center of pressure (CoP). The CoP represents the point of application of forces exchanged between feet and ground. The CoP area is an index of the effectiveness of the tonic postural system in keeping the center of gravity closer to the intermediate position of balance.

Patients and controls were required to stand still on a force plate with their feet positioned comfortably within a box defined by dimensions equal to their foot length. They were instructed to look straight ahead at a screen surface placed 80 cm away and to keep arms comfortably at their sides during the stances in a normal forward-facing position, with eyes focused on a stationary target. Each participant performed two standing tests, each epoch lasting 30 seconds. Using the PP as a visual feedback, patients were asked to maintain a cursor sensitive to the displacement of the center of gravity, within a target located in the center of the screen. The standard deviation (SD) of body sway [total and along the anteroposterior (AP) and mediolateral (ML) axis] was calculated and expressed in mm. Total SD of body sway was defined as the mean error of the CoP on the x-y directions with respect to the trunk axis. In addition, we analyzed the statokinesigram, which is the layout of a line connecting the different positions of the CoP. Statokinesigram is not a geometrical figure and in order to quantify the dispersion of the successive CoP we used the area of the body sway: this is the area ellipse (measured in mm^2) containing 90% of the sampled positions of the CoP. These measurements were obtained in two conditions: with open eyes (OE) and performing a simple cognitive task [counting (OEC)].

Subsequently, the posturographic data were analysed on the basis of the BBS values.

2.3. Statistical Analysis. The normality of the distribution of all variables was assessed by the Shapiro-Wilk statistic, supported by visual inspection. Descriptive statistics of continuous variables are reported as mean ± SD. Between-group comparisons for continuous data were assessed with unpaired t-test or with Mann-Whitney U-test in case of violation of the normality assumption. Comparisons for categorical variables were carried out by the chi-square test or Fisher's exact test when appropriate. The association between pairs of variables was assessed by the Pearson correlation coefficient. To assess the association between BBS values and measurements obtained from PP, multiple regression analysis was used, with BBS as dependent variable and posturographic parameters as predictors. Nonsignificant variables were eliminated by a backward elimination procedure at the 0.15 significance

Table 1: Demographic and clinical characteristics of patients and controls.

Variable	All patients ($N = 29$)	Controls ($N = 12$)	p value*	Patients at low risk of fall ($N = 23$)	p value†
Sex (M/F)	12/17	3/9	0.480	10/13	0.463
Age (years)	69.2 ± 8.8	66.5 ± 6.3	0.322	67.8 ± 8.5	0.649
Weight (kilograms)	75.8 ± 10.4	73.4 ± 9.6	0.48	75.9 ± 11.3	0.52
Height (centimeters)	173.7 ± 8.2	172.6 ± 9.0	0.69	174.4 ± 7.3	0.51
Education (years)	10.06 ± 4.8	10.5 ± 5.4	0.80	10.1 ± 4.7	0.86
Disease duration (years)	10.6 ± 5.2			11.2 ± 5.0	
UPDRS III	18.6 ± 5.5			18.1 ± 5.7	
Side of disease onset (L/R)	18/11			12/11	
L-DOPA equivalent (mg/day)	742.2 ± 336.4			792.2 ± 340.8	

* p value for the comparison between all patients and controls.
† p value for the comparison between patients at low risk of fall and controls.
UPDRS III: Unified Parkinson's Disease Rating Scale, part III, ON state.

Table 2: Values of BBS and posturographic parameters observed in patients and controls.

Variable	All patients ($N = 29$)	Controls ($N = 12$)	p value*	Patients at low risk of fall ($N = 23$)	p value†
BBS	46.3 ± 8.4	54.3 ± 1.7	0.002	49.6 ± 4.5	0.002
AP SD OE (mm)	5.7 ± 3.0	5.9 ± 2.9	0.852	5.4 ± 2.3	0.596
ML SD OE (mm)	5.3 ± 2.6	3.4 ± 0.8	0.019	4.8 ± 2.3	0.050
Area ellipse OE (mm^2)	601.6 ± 581.6	373.5 ± 202.2	0.195	510.0 ± 446.9	0.324
Total SD OE (mm)	15.1 ± 14.1	3.0 ± 1.6	0.005	14.1 ± 14.5	0.013
AP SD OEC (mm)	5.7 ± 3.8	5.4 ± 1.6	0.813	5.5 ± 3.7	0.957
ML SD OEC (mm)	4.8 ± 3.4	3.3 ± 1.3	0.172	4.5 ± 3.5	0.283
Area ellipse OEC (mm^2)	477.1 ± 493.2	321.4 ± 179.7	0.297	385.7 ± 376.4	0.583
Total SD OEC (mm)	13.1 ± 13.6	3.5 ± 2.1	0.020	14.0 ± 14.3	0.017

* p value for the comparison between all patients and controls.
† p value for the comparison between patients at low risk of fall and controls.
BBS: Berg Balance Scale; UPDRS III (ON state): Unified Parkinson's Disease Rating Scale III; OE: open eyes; OEC: open eyes counting; AP SD OE: anteroposterior standard deviation of trunk sway with open eyes; ML SD OE: mediolateral standard deviation of trunk sway with open eyes; Total SD OE: total standard deviation of trunk sway with open eyes; AP SD OEC: anteroposterior standard deviation of trunk sway with open eyes counting; ML SD OEC: mediolateral standard deviation of trunk sway with open eyes counting; Total SD OEC: total standard deviation of trunk sway with open eyes counting.

level. A p value <0.05 was considered statistically significant. When multiple comparisons were carried out, the Bonferroni correction was applied. Accordingly, when couples of comparisons were considered, the significance level was set to 0.025. All analyses were carried out using the SAS/STAT statistical package, release 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

Demographic and clinical characteristics of patients and controls are shown in Table 1.

The values of BBS and the posturographic parameters observed in patients and controls are reported in Table 2.

Due to some skewness, several posturographic variables did not fully satisfy formal Shapiro-Wilk test for normal distribution, but violations to the normality assumption were not marked. All results obtained from parametric tests were therefore checked using also nonparametric statistics, which consistently yielded superimposable results.

As expected, BBS values were lower in PD patients compared to controls ($p = 0.002$) (Figure 1). Statistical analysis revealed significant differences in the SD of body sway between PD patients and controls. In particular PD patients showed higher values of total SD of body sway during OE ($p = 0.005$) (Figure 2) and OEC ($p = 0.020$) and along the ML axis with OE ($p = 0.019$) (Figure 3), while values along the ML axis in the OEC condition showed a trend toward higher values, but the difference did not reach statistical significance ($p = 0.172$).

Area ellipse with OE and OEC was not significantly different across groups ($p = 0.195$ and $p = 0.297$, resp.).

Focusing on the subgroups of PD patients with low risk of falls according to BBS score (BBS >40, $N = 23$), the values of ML and total SD of trunk sway with OE and total SD of trunk sway with OEC were higher than controls, with Bonferroni corrected statistical significance reached only for the last two comparisons ($p = 0.050$, $p = 0.013$, and $p = 0.017$, resp.).

The same variables were significantly higher than in controls also selecting only PD patients with BBS values

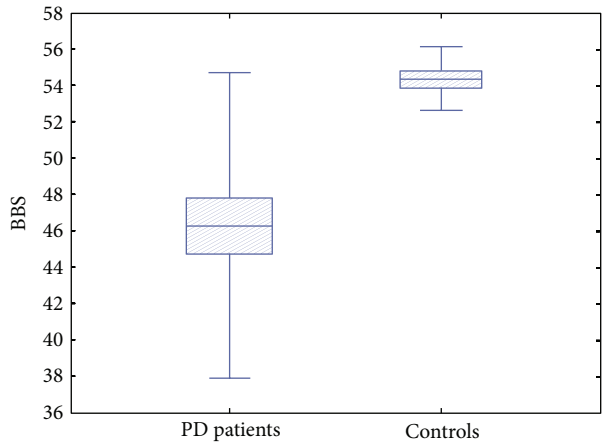

Figure 1: Berg Balance Scale values in PD patients compared to controls. *As expected, BBS values were lower in PD patients compared to controls.*

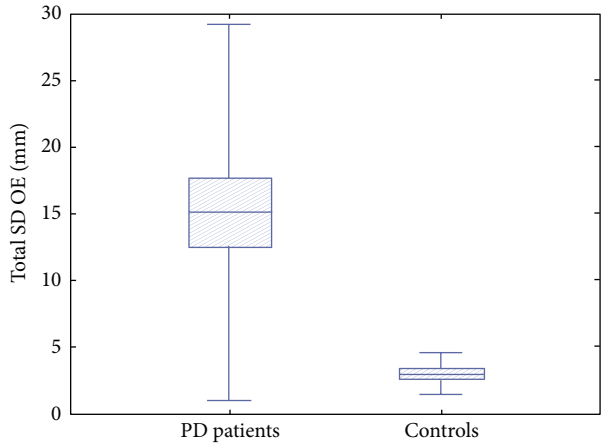

Figure 2: Total standard deviation of trunk sway with open eyes in PD patients with respect to controls. *PD patients showed higher values of total standard deviation (SD) of trunk sway with open eyes (OE) with respect to controls.*

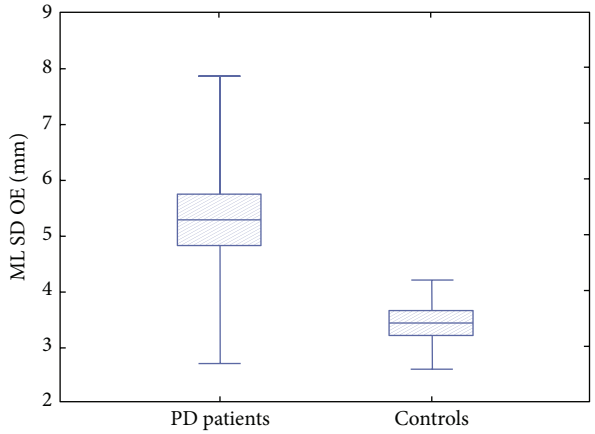

Figure 3: Mediolateral standard deviation of trunk sway with open eyes in PD patients with respect to controls. *PD patients showed higher values of mediolateral (ML) standard deviation (SD) of trunk sway with open eyes (OE) with respect to controls.*

comparable to controls ($N = 11$ patients with BBS > 51) (borderline significant $p = 0.029$ for ML SD of trunk sway with OE, $p = 0.012$ for total SD of trunk sway with OE, and $p = 0.019$ for total SD of trunk sway with OEC). The results of correlation analysis are listed in Tables 3(a) and 3(b) for PD patients and controls, respectively. While no association was found between BBS scores and posturographic variables in controls, in PD patients a significant negative correlation between BBS scores and ML SD of the trunk with OE ($r = -0.49$, $p = 0.007$) and with the area ellipse with OEC ($r = -0.53$, $p = 0.004$) was observed. In order to gain some insight into this finding, we performed further correlation analysis considering first the subgroup of patients at medium risk of falls (BBS ≤ 40) and then the group of patients with BBS values similar to controls (BBS ≥ 51). The finding of a strong association in the first case and of no association in the second case suggests the possibility of a ceiling effect for higher BBS values.

As expected, many posturographic parameters were significantly correlated with each other, with several values of Pearson correlation coefficient > 0.80. No significant correlation was found between posturographic parameters and disease severity as evaluated with UPDRS.

Finally, the backward variable selection procedure in multiple regression analysis revealed that ML SD of body sway with OE was an independent predictor of BBS ($p = 0.007$).

4. Discussion and Rehabilitation Perspectives

4.1. Posturographic Findings. The main finding of our study is that, in comparison to a control group of healthy people, PD patients not complaining of BD have higher values of total SD of body sway and along the ML axis during OE condition. Total and ML SD of body sway during OE condition and total SD of body sway with OEC were higher than controls in a subgroup of Parkinsonians with low risk of falls and also in those patients with normal BBS values. Since neither disease duration nor disease severity evaluated by UPDRS were correlated with posturographic values, we can hypothesize that these are specifically related to balance control disruption and not to global disease severity, showing a high sensitivity of these posturographic parameters to early balance disturbances in PD patients not complaining of BD.

Poor balance is a typical characteristic of PD. This has already been demonstrated in advanced PD, but our data stress the need to diagnose these alterations as early as possible in order to establish a specific rehabilitative treatment. As a matter of fact, our finding of relatively higher measurements in total body sway in Parkinsonians not complaining of BD means that balance control in PD is affected even in absence of clinical signs or subjective symptoms. Our study seems to indicate that the higher body sway results mainly from increased oscillations in ML axis. Previously, increased sway in ML direction has been associated with falls in a number of conditions including PD [23]. On the contrary, several authors found that balance in the ML axis is preserved in Parkinsonians and this should explain why their gait is typically narrow-based [24] and why

Table 3: (a) Results of correlation analysis (correlation matrix for PD patients). (b) Results of correlation analysis (correlation matrix for controls).

(a)

	Age	BBS	UPDRS III	AP SD OE	ML SD OE	Area ellipse OE	Total SD OE	AP SD OEC	ML SD OEC	Area ellipse OEC	Total SD OEC
Age	1.00	−0.46 ($p = 0.011$)	0.28 ($p = 0.145$)	−0.08 ($p = 0.679$)	0.32 ($p = 0.089$)	0.05 ($p = 0.778$)	−0.35 ($p = 0.060$)	0.22 ($p = 0.259$)	0.31 ($p = 0.107$)	0.40 ($p = 0.037$)	−0.41 ($p = 0.029$)
BBS	−0.46 ($p = 0.011$)	1.00	−0.37 ($p = 0.050$)	−0.13 ($p = 0.502$)	−0.49 ($p = 0.007$)	−0.32 ($p = 0.093$)	−0.11 ($p = 0.562$)	−0.27 ($p = 0.153$)	−0.30 ($p = 0.110$)	−0.53 ($p = 0.004$)	0.07 ($p = 0.711$)
UPDRS III	0.28 ($p = 0.145$)	−0.37 ($p = 0.050$)	1.00	0.04 ($p = 0.824$)	0.20 ($p = 0.309$)	0.19 ($p = 0.343$)	0.02 ($p = 0.906$)	0.16 ($p = 0.408$)	0.30 ($p = 0.117$)	0.30 ($p = 0.129$)	−0.06 ($p = 0.746$)
AP SD OE	−0.08 ($p = 0.679$)	−0.13 ($p = 0.502$)	0.04 ($p = 0.824$)	1.00	0.44 ($p = 0.016$)	0.86 $p < 0.001$	0.14 ($p = 0.476$)	0.46 ($p = 0.012$)	0.22 ($p = 0.256$)	0.37 ($p = 0.051$)	−0.13 ($p = 0.517$)
SD ML OE	0.32 ($p = 0.089$)	−0.49 ($p = 0.007$)	0.20 ($p = 0.309$)	0.44 ($p = 0.016$)	1.00	0.79 $p < 0.001$	0.04 ($p = 0.849$)	0.67 $p < 0.001$	0.80 $p < 0.001$	0.74 $p < 0.001$	−0.02 ($p = 0.898$)
Area ellipse OE	0.05 ($p = 0.778$)	−0.32 ($p = 0.093$)	0.19 ($p = 0.343$)	0.86 $p < 0.001$	0.79 $p < 0.001$	1.00	0.13 ($p = 0.518$)	0.71 $p < 0.001$	0.58 $p < 0.001$	0.63 $p < 0.001$	−0.11 ($p = 0.583$)
Total SD OE	−0.35 ($p = 0.060$)	−0.11 ($p = 0.562$)	0.02 ($p = 0.906$)	0.14 ($p = 0.476$)	0.04 ($p = 0.849$)	0.13 ($p = 0.518$)	1.00	−0.06 ($p = 0.745$)	−0.15 ($p = 0.423$)	−0.01 ($p = 0.974$)	0.86 $p < 0.001$
AP SD OEC	0.22 ($p = 0.259$)	−0.27 ($p = 0.153$)	0.16 ($p = 0.408$)	0.46 ($p = 0.012$)	0.67 $p < 0.001$	0.71 $p < 0.001$	−0.06 ($p = 0.745$)	1.00	0.57 ($p = 0.001$)	0.89 $p < 0.001$	−0.17 ($p = 0.392$)
ML SD OEC	0.31 ($p = 0.107$)	−0.30 ($p = 0.110$)	0.30 ($p = 0.117$)	0.22 ($p = 0.256$)	0.80 $p < 0.001$	0.58 $p < 0.001$	−0.15 ($p = 0.423$)	0.57 ($p = 0.001$)	1.00	0.79 $p < 0.001$	−0.13 ($p = 0.485$)
Area ellipse OEC	0.40 ($p = 0.037$)	−0.53 ($p = 0.004$)	0.30 ($p = 0.129$)	0.37 ($p = 0.051$)	0.74 $p < 0.001$	0.63 $p < 0.001$	−0.01 ($p = 0.974$)	0.89 $p < 0.001$	0.79 $p < 0.001$	1.00	−0.12 ($p = 0.550$)
Total SD OEC	−0.41 ($p = 0.029$)	0.07 ($p = 0.711$)	−0.06 ($p = 0.746$)	−0.13 ($p = 0.517$)	−0.02 ($p = 0.898$)	−0.11 ($p = 0.583$)	0.86 $p < 0.001$	−0.17 ($p = 0.392$)	−0.13 ($p = 0.485$)	−0.12 ($p = 0.550$)	1.00

BBS: Berg Balance Scale; UPDRS III: Unified Parkinson's Disease Rating Scale, part III; OE: open eyes; OEC: open eyes counting; AP SD OE: anteroposterior standard deviation of trunk sway with open eyes; ML SD OE: mediolateral standard deviation of trunk sway with open eyes; Total SD OE: total standard deviation of trunk sway with open eyes; AP SD OEC: anteroposterior standard deviation of trunk sway with open eyes counting; ML SD OEC: mediolateral standard deviation of trunk sway with open eyes counting; Total SD OEC: total standard deviation of trunk sway with open eyes counting.

(b)

	Age	BBS	AP SD OE	ML SD OE	Area ellipse OE	Total SD OE	AP SD OEC	ML SD OEC	Area ellipse OEC	Total SD OEC
Age	1.00	−0.68 ($p = 0.016$)	0.05 ($p = 0.874$)	0.21 ($p = 0.515$)	0.06 ($p = 0.841$)	−0.01 ($p = 0.986$)	−0.31 ($p = 0.330$)	0.08 ($p = 0.811$)	−0.24 ($p = 0.462$)	−0.04 ($p = 0.891$)
BBS	−0.68 ($p = 0.016$)	1.00	−0.10 ($p = 0.753$)	−0.38 ($p = 0.227$)	−0.18 ($p = 0.574$)	0.19 ($p = 0.546$)	−0.16 ($p = 0.625$)	−0.22 ($p = 0.500$)	−0.07 ($p = 0.834$)	0.07 ($p = 0.827$)
AP SD OE	0.05 ($p = 0.874$)	−0.10 ($p = 0.753$)	1.00	−0.06 ($p = 0.849$)	0.91 $p < 0.001$	0.28 ($p = 0.382$)	0.38 ($p = 0.218$)	−0.11 ($p = 0.732$)	0.06 ($p = 0.841$)	0.32 ($p = 0.314$)
SD ML OE	0.21 ($p = 0.515$)	−0.38 ($p = 0.227$)	−0.06 ($p = 0.849$)	1.00	0.31 ($p = 0.321$)	−0.04 ($p = 0.903$)	0.36 ($p = 0.250$)	0.56 ($p = 0.060$)	0.42 ($p = 0.176$)	−0.25 ($p = 0.442$)
Area ellipse OE	0.06 ($p = 0.841$)	−0.18 ($p = 0.574$)	0.91 $p < 0.001$	0.31 ($p = 0.321$)	1.00	0.30 ($p = 0.340$)	0.58 ($p = 0.047$)	0.20 ($p = 0.528$)	0.30 ($p = 0.336$)	0.31 ($p = 0.328$)
Total SD OE	−0.01 ($p = 0.986$)	0.19 ($p = 0.546$)	0.28 ($p = 0.382$)	−0.04 ($p = 0.903$)	0.30 ($p = 0.340$)	1.00	0.45 ($p = 0.144$)	0.63 ($p = 0.030$)	0.65 ($p = 0.022$)	0.70 ($p = 0.011$)

(b) Continued.

	Age	BBS	AP SD OE	ML SD OE	Area ellipse OE	Total SD OE	AP SD OEC	ML SD OEC	Area ellipse OEC	Total SD OEC
AP SD OEC	−0.31 ($p = 0.330$)	−0.16 ($p = 0.625$)	0.38 ($p = 0.218$)	0.36 ($p = 0.250$)	0.58 ($p = 0.047$)	0.45 ($p = 0.144$)	1.00	0.68 ($p = 0.014$)	0.88 $p < 0.001$	0.43 ($p = 0.165$)
ML SD OEC	0.08 ($p = 0.811$)	−0.22 ($p = 0.500$)	−0.11 ($p = 0.732$)	0.56 ($p = 0.060$)	0.20 ($p = 0.528$)	0.63 ($p = 0.030$)	0.68 ($p = 0.014$)	1.00	0.90 $p < 0.001$	0.41 ($p = 0.184$)
Area ellipse OEC	−0.24 ($p = 0.462$)	−0.07 ($p = 0.834$)	0.06 ($p = 0.841$)	0.42 ($p = 0.176$)	0.30 ($p = 0.336$)	0.65 ($p = 0.022$)	0.88 $p < 0.001$	0.90 $p < 0.001$	1.00	0.45 ($p = 0.142$)
Total SD OEC	−0.04 ($p = 0.891$)	0.07 ($p = 0.827$)	0.32 ($p = 0.314$)	−0.25 ($p = 0.442$)	0.31 ($p = 0.328$)	0.70 ($p = 0.011$)	0.43 ($p = 0.165$)	0.41 ($p = 0.184$)	0.45 ($p = 0.142$)	1.00

BBS: Berg Balance Scale; OE: open eyes; OEC: open eyes counting; AP SD OE: anteroposterior standard deviation of trunk sway with open eyes; ML SD OE: mediolateral standard deviation of trunk sway with open eyes; Total SD OE: total standard deviation of trunk sway with open eyes; AP SD OEC: anteroposterior standard deviation of trunk sway with open eyes counting; ML SD OEC: mediolateral standard deviation of trunk sway with open eyes counting; Total SD OEC: total standard deviation of trunk sway with open eyes counting.

they have few balance problems moving sideways [25]. In this regard, patients are still able to ride a bicycle, which is an activity that requires a coordinated interplay between rhythmic pedaling and maintaining balance in the ML plane, even in the face of severe walking difficulties [26]. By contrast, ML balance impairment can be observed in patients with atypical parkinsonisms [27] and an augmented body sway in the ML axis could help in the differential diagnosis between PD and atypical parkinsonisms [27].

Kerr et al. found that future PD fallers had not ML but AP greater postural sway when standing on a firm surface compared to nonfallers [28]. In our study, we made a comparison between PD patients without subjective BD and healthy controls, whereas in Kerr's paper the comparison is between parkinsonians fallers and nonfallers: thus, the populations taken into account are different (e.g., such patients presented freezing of gait in the cited paper). The differences found in these previous studies could indicate that there is an extensive and continuous spectrum of alterations involving both the AP and the ML balance control systems. Thus, the existence of a predominant alteration in the ML axis does not exclude a concomitant or subsequent pathological involvement of the mechanism that controls the AP body sway.

S. L. Mitchell et al. found an increase in ML sway in quite stance in Parkinsonian subjects as compared to age-matched controls. ML posturographic measures were also associated with poor performance on clinical measures of balance. For these authors, the increase in ML sway may reflect an attempt to maintain stabilizing movements during quiet stance, in order to compensate for the impaired movement in the AP direction. This notion supports the idea that ML instability could be a posturographic marker of functional balance impairment in PD [29].

The most important finding of our study is that the higher ML sway found in PD patients not complaining of BD may indicate a subclinical index of impaired balance. The maintenance of stability in ML direction requires active control, while the AP stability requires passive control [30]. In quite stance, AP balance is under ankle (plantar/dorsiflexor) control, whereas ML balance is under hip (abductor/adductor) control [31]. Both ankle and hip strategies contribute to the net balance control in different way [31]. In the ML direction, the two strategies reinforce, whereas in the AP direction the ankle mechanism must cancel most of the inappropriate contribution by the hip load/unload mechanism [31]. Basal ganglia, in particular the substantia nigra and its projections to the upper dorsal brainstem, help to optimize muscle tone for the balance control. This mechanism is disrupted in PD. As a consequence, an increased stiffness in ankle muscles in Parkinsonians has been demonstrated [32], which can explain higher sway in ML axis with a poor activation of muscles facilitating the AP sway, thus favoring nonphysiological ML oscillations.

Finally, we found that the OE condition is only slightly better than the OEC in differentiating between groups. It is known that the PD patients have more difficulties compared to healthy subjects in performing dual task. Performing a cognitive (like counting) or motor task during standing increases postural sway, particularly in PD patients. However, switching from quiet stance to concurrent task conditions in which subject's attention is diverted showed similar rates of change in both control and PD patients [33]. It can indicate that there is no significant contribution from attentional strategies in maintaining balance in PD. Further, our findings with OEC can be explained considering that postural sway increases in this condition also in healthy individuals.

4.2. Implications for Balance Rehabilitation in PD. The finding of a pathological total and ML body sway in PD patients not complaining of BD indicates the possibility of using posturography in order to develop a specific rehabilitation program for balance disorders.

It is possible to use different strategies to counteract the total and ML pathological sway. Clinicians could use exercises associated with cues or feedback (visual and/or auditory) in order to improve the mechanisms directed to this goal [34, 35].

PD is typically an asymmetrical disease. Previous studies using posturography have shown that balance control, which is an intuitively symmetrical task, can also be asymmetrically affected in PD [36]. This aberrant control determines that one leg produces more force than the other one in order to keep the body upright. The upright position in quiet stance, the mechanisms of balance control, and the gait initiation are correlated with each other. Indeed, gait initiation involves motor asymmetry, because the step leg must be unloaded, thereby introducing an asymmetric ML weight distribution [37]. Since we found an alteration in the ML balance control system in Parkinsonians not complaining of BD, we argue that the altered weight distribution between the two sides of the body can contribute to the increase in ML body sway in PD. The ability to transfer body weight from one leg to the other is a basic aspect of human locomotion. The transfer requires postural adjustments, necessary for both the gait and the maintenance of balance [38]. An asymmetric force between the left and the right leg can determine asymmetry in balance control in PD [39]. Thus, a balance rehabilitation program can also include a weight-shift training to improve the asymmetry in the body sway, as already demonstrated in chronic stroke patients [38].

Impaired proprioception is another contributing factor to chronic BD in PD [40]. It is known that quiet standing predominantly depends on somatosensory processing, with proprioception as the principal component [41]. Basal ganglia neurons have many proprioceptive receptive fields and this explain why proprioceptive deficits may contribute to the impaired postural and balance control in PD. Proprioceptive dysfunction in PD has been shown to be responsible for postural instability not only impairing adaption to a changing base-of-support [42], but also reducing the perception of trunk and surface orientation and postural sway in stance. These factors can partially explain why Parkinsonian patients show smaller limits of stability [43] and higher ML sway in our and in other previous studies in PD [44]. On this basis, we suggest that also a proprioceptive-motor training rehabilitation program can significantly influence balance and produce improvements in BD.

Furthermore, as previously argued, the AP balance control mechanism can be also impaired when ML abnormal sway is present. As a matter of fact, PD patients lack the modification of postural muscle synergies required to forward displace their CoP, indicating high stiffness in ankle muscles [45]. Ankle mechanisms dominate during normal stance, especially in the AP plane [46], and the increased ankle muscle stiffness contributes to balance control impairment. Kinematics showed a reduction of the range of motion in the hip, knee, and ankle joints [47]. Since the ankle plays an important role in AP balance control, a rehabilitation strategy should include stretching exercises intended to minimize the stiffness of the ankle. Moreover, narrow stance, that is typical in PD, decreased the role of the ankle and increased the role of hip mechanisms in the AP plane [46]. Therefore, in order to maintain physiological dynamic between the AP and the ML mechanisms of balance control, clinicians should immediately intervene to broaden the base of support of patients with focused exercises.

We argue that BD in Parkinsonian patients can be disclosed before the appearance of symptomatic manifestations using PP. We believe that a specific early rehabilitation treatment aimed at acting on altered ML balance control mechanism has to include (i) stretching exercises intended to minimize the stiffness of the ankle, (ii) a weight-shift training program, to improve the asymmetry in balance control, (iii) a proprioceptive-motor training, (iv) interventions to broaden the base of support, and (v) a balance training based on visual and auditory feedback.

4.3. Study Limitations. This study has some limitations: in order to correlate the posturographic data with the clinical outcome and to determine their prognostic value, a prospective study should be designed, performing the posturography in a cohort of early PD patients and then checking the occurrence of clinical balance troubles through the disease evolution. Furthermore, it could be useful to perform also a retrospective assessment on PD subjects divided into two groups of fallers and nonfallers. Another criticism derives from the observation that the measurements of postural stability during static and dynamic tasks have some limitations when used in a clinical setting, because patients' self-perceived risk of falling seems more reliable than objective evaluations of BD [48]. However, this may be misleading in PD patients in light of their awareness and wrong priority problems [49].

5. Conclusions

We have demonstrated the high sensitivity of quantifiable posturographic parameters in detecting balance disruption in PD patients not complaining of BD. These results are consistent with the literature and confirm the alteration of the complex mechanism of balance control in PD. We believe that the clinical utilization of these parameters can be useful to identify PD patients at risk of disabling BD. The obtained data can represent a possible starting point to develop specific rehabilitation treatments for balance dysfunction and BD in PD.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

The Parkinsonian Gait Spatiotemporal Parameters Quantified by a Single Inertial Sensor before and after Automated Mechanical Peripheral Stimulation Treatment

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This study aims to evaluate the change in gait spatiotemporal parameters in subjects with Parkinson's disease (PD) before and after Automated Mechanical Peripheral Stimulation (AMPS) treatment. Thirty-five subjects with PD and 35 healthy age-matched subjects took part in this study. A dedicated medical device (Gondola) was used to administer the AMPS. All patients with PD were treated in off levodopa phase and their gait performances were evaluated by an inertial measurement system before and after the intervention. The one-way ANOVA for repeated measures was performed to assess the differences between pre- and post-AMPS and the one-way ANOVA to assess the differences between PD patients and the control group. Spearman's correlations assessed the associations between patients with PD clinical status (H&Y) and the percentage of improvement of the gait variables after AMPS ($\alpha < 0.05$ for all tests). The PD group had an improvement of 14.85% in the stride length; 14.77% in the gait velocity; and 29.91% in the gait propulsion. The correlation results showed that the higher the H&Y classification, the higher the stride length percentage of improvement. The treatment based on AMPS intervention seems to induce a better performance in the gait pattern of PD patients, mainly in intermediate and advanced stages of the condition.

1. Introduction

The most typical gait pattern of Parkinson's disease (PD) is a short-stepped shuffling gait. It is characterized by reduced stride length and walking speed [1, 2]. These gait disorders worsen progressively, as the disease advances, and are related to the risk of falling among the Parkinsonians [3]. Therefore, it is not surprising that gait impairment in PD is the major contributor to decreased patients' quality of life [4].

The management of PD was traditionally centered on drug therapy, with levodopa being its "gold standard" treatment [5]. Several studies have demonstrated the ability of levodopa to decrease stride length and improve walk speed [6]. However, as the disease progresses, chronic levodopa treatment can be associated with response decrease and with development of motor complications, including wearing-off episodes and dyskinesia [5].

To reduce these motor fluctuations, new treatments based on peripheral stimulation of the sensory-motor system, called bottom-up stimulation, have been inspiring new rehabilitation approaches in PD [7, 8]. Recently, new approaches have been developed to recover the gait impairment such as the Automated Mechanical Peripheral Stimulation (AMPS) treatment [9, 10]. The AMPS is delivered by a dedicated device, known as Gondola (Gondola Medical Technologies SA, Switzerland), and consists in the application of a pressure

via rounded stimulation tips in the four areas to be stimulated (two in each foot, which are the head of the big toe and the first metatarsal joint).

Stocchi et al. [9] evaluated the change in gait and the clinical status of 18 patients with PD after 6 sessions of a treatment based on AMPS. The study results indicate that the AMPS treatment has positive effect on bradykinesia and allows the improvement of walking velocity. Furthermore, AMPS has a positive effect on the step and stride length and on walking stability, measured as the increase in stride length and the reduction of double support time during walk. These results are consistent, and the results of improvement were measured via clinical scales.

Also recently, Galli et al. [10] evaluated a group of PD patients before and after AMPS evaluated with the Timed Up and Go (TUG) test, a widely used clinical performance-based measure of fall risk, measured with inertial sensors. The AMPS treatment improves the walking stability and seems to reduce the risk of falls in patients with PD. After the AMPS patients performed the TUG test faster and improved some kinematic parameters as the velocity to stand up from a chair and to sit down.

Based on these findings, the current study aims to evaluate the impact of the AMPS in functional abilities, measured with gait spatiotemporal parameters based on a single inertial wearable sensor. Recently, wireless inertial sensing devices are being developed also for the assessment of spatial-temporal parameters in unobstructed environment outdoors, thus overcoming the typical limitations of measurements in indoor laboratory settings. Several applications in the rehabilitation and recovery of patient mobility have been already reported by using these devices [11–14], more specific in patients with PD [5, 15–17].

The aim of this study was to assess and to quantify if the AMPS is capable of promoting changes on spatiotemporal parameters of PD gait. More specifically, this paper aims to assess the associations of the patients' clinical status with the percentage of improvement of the gait variables (stride length, velocity, cadence, and propulsion) after AMPS. The hypothesis of this study is that the AMPS stimulation improves the spatiotemporal gait of patients with PD, and the more compromised the patient is, the more benefits he/she will have after the bottom-up rehabilitation.

2. Methods

2.1. Participants. The Parkinson group (PD) consisted in 35 patients affected by Parkinson's disease. PD was diagnosed based on clinical criteria [18, 19], dopamine transporter (DaT) scans, and/or magnetic resonance imaging. All these patients are similar in terms of disease duration and are free of peripheral sensory neuropathy and other disorders based on their reported histories, symptoms, physical examinations, and clinical tests. Patients with liver, kidney, lung, or heart diseases, diabetes, or other causes of autonomic dysfunction were not included in the study.

The characteristics of the considered subjects are summarized in Table 1. The control group (CG) consisted in 35 healthy adults with the average characteristics in Table 1.

Table 1: Anthropometric characteristics.

Variables	Parkinson	Control group	P
Age (years)	68.15 ± 6.83	66.27 ± 6	0.419
Body mass (kg)	74.8 ± 12.54	73.22 ± 11.45	0.147
Height (cm)	162.73 ± 13.04	164.81 ± 10.10	0.315
H&Y	3.27 ± 1.09	—	—
UPDRS III	30.1 ± 10.4	—	—
Disease duration (years)	10.2 ± 6.3	—	—

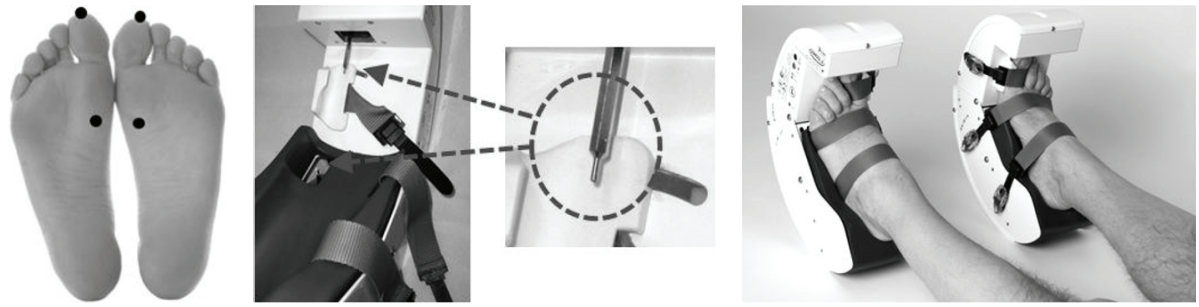
The study has been approved by the Ethics Research Committee of the IRCCS San Raffaele Institute. The trial was registered online at ClinicalTrials.gov (identifier number NCT01815281). All procedures were explained to the participants and were carried out with their adequate understanding, after receiving their written informed consent.

2.2. Experimental Procedures. During all intervention PD patients were in off phase, after an overnight withdrawal of all anti-Parkinsonian treatments.

2.2.1. The Automated Mechanical Peripheral Stimulation (AMPS). The treatment consists in the application of a pressure via rounded stimulation tips in four specific target areas in patient's feet (Figure 1(a)). To perform this mechanical stimulation, a dedicated medical device (Gondola, Gondola Medical Technologies, Lugano, Switzerland) was used to deliver the AMPS (Figure 1(b)). The system consists of feet supports (left and right) with electrical motors which activate two actuated steel bars with a 2 mm diameter; the motor-activated stimulators apply a mechanical pressure in two specific areas of each foot: on the head of the hallux, left and right, and on the 1st metatarsal joint, left and right.

Before treatment, the device needs to be adjusted to the patient's feet (Figure 1(c)): an inner sole of the correct size is inserted in each unit (left and right) to accommodate the feet; then the feet are inserted in the two units and tied up, using three straps per foot; after that, correct length steel bars are mounted on the axis of the electrical motors. The next step consists in positioning the motors that are mounted on adjustable platforms in order to make the steel bars interact with the areas to be stimulated (head of the hallux and first metatarsal joint of both feet). Once the device is adjusted, the excursion of the four motors (which work independently from each other) is programmed (using a remote control), aiming to apply the correct pressure stimulation on each area. The pressure of stimulation, always applied in a range of 0.3–0.9 N/mm^2, is set for each subject upon appearance of the monosynaptic reflex in the Tibialis Anterior muscle by the detection of a liminaris contraction while applying pressure in the contact areas.

Once the pressure value has been set using this procedure, the value is recorded to administer the AMPS. This preparatory procedure requires approximately 10 minutes.



(a) (b) (c)

Figure 1: The device used for the AMPS treatment: (a) the specific points of feet stimulation; (b) the two moving steel bars; (c) patient positioning.

The treatment consists in 4 cycles; one cycle includes a stimulation of the 4 target areas requiring 24 seconds, whereas the overall 4-cycle treatment lasts for a total of 96 seconds. During the AMPS treatment, patients lay down (Figure 1(c)). At the end of the AMPS stimulation, both units of the device are removed from the feet of the patient; this final action is very easy and fast (less than 1 minute). This link shows images of a pre- and post-AMPS patient's gait (https://www.youtube.com/watch?v=deHFpt5gk3A&feature=youtu.be).

2.2.2. The Inertial Sensor. The single inertial sensor is a wireless inertial sensing device (GSensor, BTS Bioengineering S.p.A., Italy) which provides acceleration along three orthogonal axes: anteroposterior, mediolateral, and superoinferior. Acceleration data were transmitted via Bluetooth to a PC and processed using dedicated software (BTS G-STUDIO, version: 2.6.12.0).

The portable GSensor consists in a wireless network of inertial sensors for human movement analysis. The sensors are controlled by a data logger unit (up to 16 elements), a ZigBee radio type communication. Each sensor is sized 62 mm × 36 mm × 16 mm, weighs 60 g, and is composed of a 3-axis accelerometer (max range ± 6 g), a 3-axis gyroscope (full scale ± 300°/s), and a 3-axis magnetometer (full scale ± 6 gauss). This sensing device is calibrated with the gravitational acceleration immediately after its manufacturing process. Only one sensor was used during this work. It was attached to the subjects' waists with a semielastic belt, covering the L4-L5 intervertebral space. The acceleration was analyzed about the three orthogonal anatomical axes: the anterior-posterior, mediolateral, and vertical axes.

The reference coordinate frame had the z-axis oriented to the front, x-axis oriented vertically upward, and y-axis orthogonal to the other two, towards the right. This motion analysis was performed with a sensitivity for the F4A accelerometer of 3G and a sampling frequency of 50 Hz. Acceleration data were transmitted via Bluetooth to a PC and processed with the use of dedicated software (BTS G-STUDIO, version: 2.6.12.0), which automatically provides the parameters described next.

All study participants were asked to walk at a self-selected speed along a pathway. Then, from the collected acceleration signals, the following typical spatial-temporal gait parameters were obtained:

(i) Stride length [m], the distance between two consecutive heel strikes of the same foot.

(ii) Stride length/height [%], the stride length normalized by subject height.

(iii) Speed [cm/s], the average instantaneous speed within the gait cycle as integration of acceleration.

(iv) Cadence [strides/min], the number of strides in a minute.

(v) Propulsion [m/s^2], the anterior-posterior acceleration peak during the lower limb swing phase.

2.3. Statistical Analysis. For statistical analysis, the data were first tested for normality with the Kolmogorov-Smirnov test. Because all the behavioral data exhibited normal distributions, parametric statistics were applied. The one-way ANOVAs ($\alpha < 0.05$) were applied to compare the anthropometric data (i.e., age, body mass, and height) between the PD group and the CG. Furthermore, this test was applied to compare the differences between the right and the left lower limbs of the PD group and the CG. Once no significant differences were found between the right and left limbs, the left limb was selected to represent the CG and PD bodies for all gait variables comparisons.

Then, the described parameters were computed for each participant and for each trial, and significant values and standard deviations of all indexes were calculated for each group. After verifying that the parameters were normally distributed by means of Kolmogorov-Smirnov test, the one-way ANOVA for repeated measures ($\alpha < 0.05$) was performed to assess the differences between pre- and post-AMPS; also, the one-way ANOVA for independent measures ($\alpha < 0.05$) was performed to assess the differences between PD before and after AMPS and control group.

Next, Spearman's correlations ($\alpha < 0.05$) were used to assess the associations between the Hoehn & Yahr (H&Y) [20] patient with PD clinical status and the percentage of improvement of the gait variables (stride length, velocity, cadence, and propulsion) after AMPS. The interpretation of

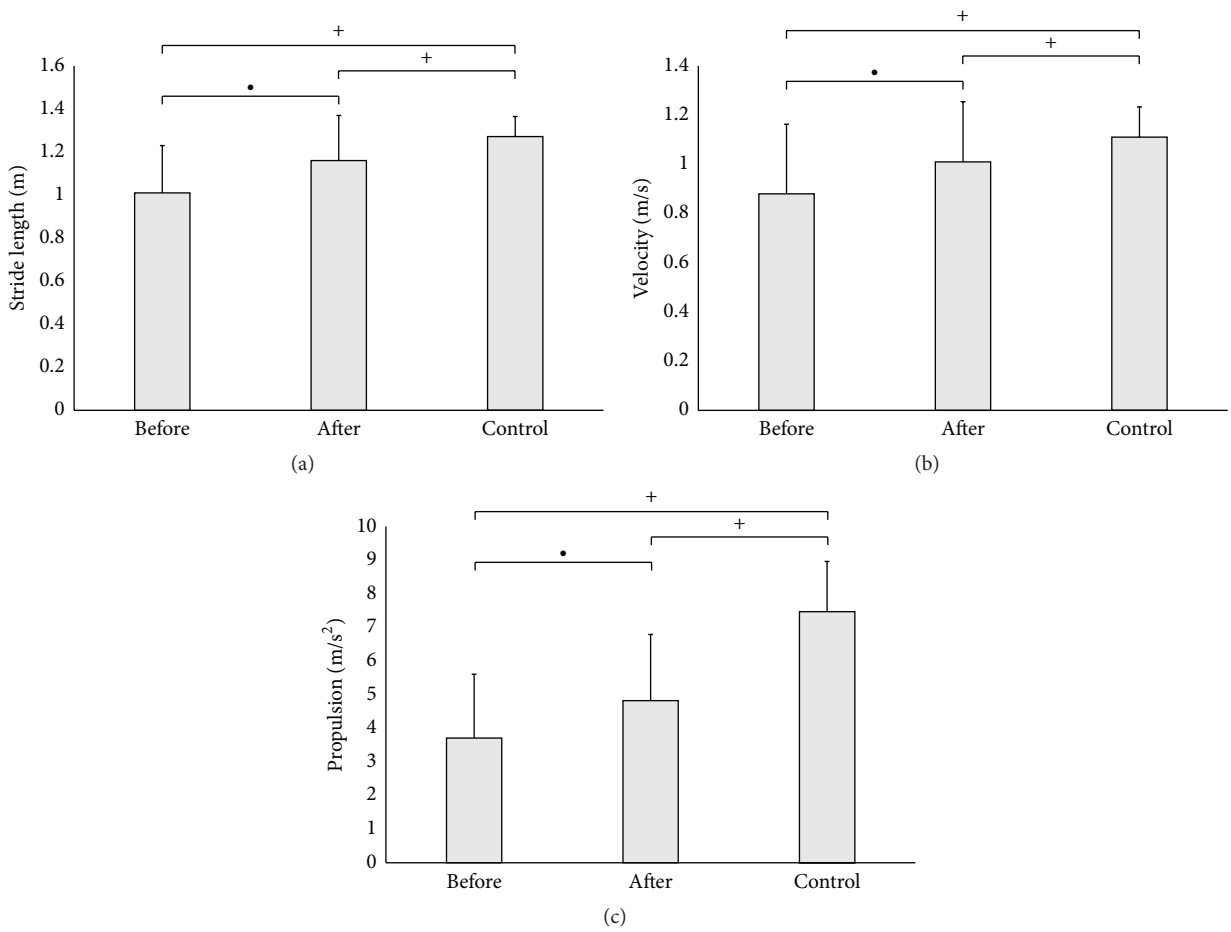


Figure 2: Significance and standard deviation of gait spatiotemporal parameters before and after AMPS: (a) stride length; (b) velocity; and (c) propulsion. • = $P < 0.05$ between pre- and post-AMPS; + = $P < 0.05$ between PD and control group.

the correlation degree is as follows: 0.9 to 1 indicated a very high correlation; 0.7 to 0.9 indicated a high correlation; 0.5 to 0.7 indicated a moderate correlation; 0.3 to 0.5 indicated a low correlation; and 0 to 0.3 indicated little to no correlation. All tests were two tailed. SPSS (version 19, IBM, Armonk, New York, United States) was used to perform all statistical analyses.

3. Results

Figure 2 illustrates the spatiotemporal gait parameters results before and after AMPS. The patients with PD post-AMPS treatment presented longer stride length (Figure 2(a)); higher gait velocity (Figure 2(b)); and higher propulsion (Figure 2(c)).

For the 35 PD patients evaluated; 57.14% had H&Y stage 4; 20% had H&Y stage 3; 5.71% had H&Y Stages 2 and 5; 8.57% had H&Y Stages 1 and 5; and 8.57% had H&Y stage 1. Figure 3 illustrates a significant and high positive correlation observed between the clinical status of the PD patients (H&Y) and the stride length percentage of improvement after AMPS ($\rho = 0.733$; $P = 0.013$). The more compromised the PD patient, the higher the percentage of the stride length improvement after AMPS intervention.

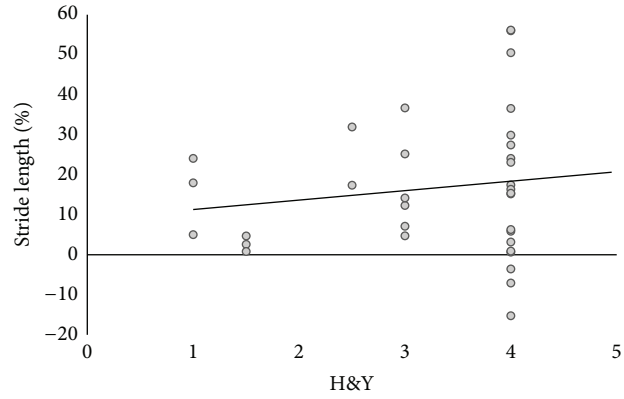


Figure 3: Correlation observed between the PD clinical status (H&Y) and the stride length percentage of improvement (stride length %) after AMPS.

4. Discussion

The aim of this study was to evaluate the effect of AMPS treatment in PD subjects using a single inertial sensor to quantify the gait spatiotemporal parameters. Supporting our

hypothesis, this study's results indicated that the AMPS stimulation improves the spatiotemporal gait parameters (stride length, walking velocity, and propulsion) of patients with PD and showed high correlation between the patient clinical status (H&Y) and the stride length percentage of improvement after AMPS.

Before AMPS, the spatiotemporal data acquired by a single inertial sensor were in accordance with previous studies [5], and the PD patients in the off stage of levodopa presented lower stride length and slower walking than the aged matched control groups.

Notwithstanding remaining in the "off medication" state, after one intervention with AMPS the PD group had an improvement of 14.85% in the stride length; 14.77% in the gait velocity; and 29.91% in the gait propulsion. The AMPS treatment seems to generate a more stable walking pattern in PD patients, reducing the well-known gait impairment that is typical of Parkinson's disease, mainly in off stages. Stocchi et al. [9] and Galli et al. [10] support these findings.

Moreover, the results of this study give a new insight of the AMPS as an effective therapy for the well-being of PD patients that helps improving their dynamic balance, especially in compromised clinical status patients. The correlation results show that the more severe the impairment of the PD patient, the higher the percentage of stride length improvement induced by the AMPS intervention.

The study has some limitations. The relatively small number of participants studied resulted in limited strength of the statistical findings. However, it documents the use of a new approach for the PD patient rehabilitation: the AMPS treatment applied via dedicated portable device.

5. Conclusion

The treatment based on AMPS induces a better performance in the gait pattern of PD patients. The obtained results showed that the AMPS treatment represents a promising rehabilitation. The results indicated that PD patients may be potential beneficiaries of the AMPS treatment once they face many neuromotor deficits, mainly in intermediate and advanced stages of the disease. These results are in agreement with our previous study done by a multifactorial quantitative laboratory. Moreover, the wearable devices are able to detect the typical motor fluctuations of PD patients after off levodopa and to document and quantify improvements following rehabilitation techniques such as the AMPS treatment.

Conflict of Interests

In this work, there were no commercial relationships that might lead to conflict of interests.

Authors' Contribution

All authors have read and agreed with all the contents of this paper.

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Review Article

Living with Parkinson's and the Emerging Role of Occupational Therapy

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Parkinson's disease is a chronic and increasingly complex condition, demanding multidisciplinary management. Over the last twenty years or so, alongside the growth of specialist services and healthcare teams specifically developed for people with Parkinson's, occupational therapy has grown in recognition as a treatment option, especially since evidence of its efficacy is now slowly emerging. The purpose of this work is to outline the role of occupational therapy clinical practice in the management of people living with Parkinson's disease and its emergent evidence base, combined with details of current occupational therapy philosophy and process, as applicable to occupational therapy practice for people with Parkinson's. The Canadian Practice Process Framework is used to structure this overview and was selected because it is a well-recognized, evidence-based tool used by occupational therapists and encompasses the core concepts of human occupation and person-centred practice. The framework employed allows the flexibility to reflect the pragmatic occupational therapy intervention process and so enables the illustration of the individually tailored approach required to accommodate to the complex pathology and personal, domestic, and social impacts, affecting the functioning of Parkinson's disease patients on a daily basis.

1. Introduction

Parkinson's disease (PD) develops in an insidious and increasingly complex manner and, until a cure is devised, must be endured by affected individuals for the remainder of their life spans. Although progressive by nature, Parkinson's is not of itself terminal; hence, over the often prolonged time span of the condition, numerous domains of every day function including motor and nonmotor performance are affected. In addition to numerous characteristic symptoms, the manifestation of the disease is influenced by environmental conditions, often fluctuates through the day, over the course of the disease, and is expressed in a highly individualised manner [1]. An occupational therapy process aims to address all of these issues, since the core of occupational therapy (OT) is *human occupation*, defined as "doing culturally meaningful work, play or daily living tasks, in the stream of time and, in the context of one's physical and social world" [2]. Systematic Cochrane reviews published in 2001 and 2007 [3, 4] concerning OT and Parkinson's found insufficient evidence to support or refute the value of OT for people with Parkinson's. However, national guidelines such as The National Parkinson's Disease Guidelines published in the UK in 2006 included a recommendation that OT is available *as required* to people with Parkinson's from the time of their diagnosis [5].

This overview explores the philosophy and evolution of the OT role specifically in the management of people with Parkinson's from the unique perspective of the two authors, who have a combined 47 years' professional experience of working with people living with Parkinson's (and related movement disorders). Recently published, robust and rigorous randomised controlled trials (RCTs), along with earlier non-peer reviewed, published sources that synthesised and translated basic research evidence into clinical practice, and more recent evidence-based Parkinson's specific guidance for OTs are also presented. This emergent evidence base

underpins and demonstrates the role of OT and its value, in terms of health related quality of life benefits of OT for people with Parkinson's and in some cases for their care givers as well.

A patient-centred, top-down approach, which is initially focused on functional performance problems, is fundamental to OT assessment and intervention, as noted by Neistadt [6] as this approach helps to immediately identify functional performance problems of concern to patients and focus an OT's attention quickly on those impairments that are causing functional difficulties. Two well-established models employed to underpin OT practice support this mode of clinical reasoning and working practice, namely, the *Occupational Therapy Intervention Process Model* [7] and the *Canadian Practice Process Framework* (CPPF) [8]. These models can be applied to any medical diagnosis, including PD, and the CPPF has been selected to structure our content.

2. Canadian Practice Process Framework

The CPPF is evidence-based and encompasses the core concepts of *occupation* and *patient-centred practice*. Also incorporated are key concepts concerning *enablement* and an *occupation-based* focus, and additionally the CPPF takes into account the following contexts: *societal, clinical practice, the frame of reference*, and *the actual process*, as represented by eight action points which will be explored here and are listed below [8]:

(1) Enter/Initiate.
(2) Set the stage.
(3) Assess/evaluate.
(4) Agree objective and plans.
(5) Implement plan.
(6) Monitor/modify.
(7) Evaluate outcome.
(8) Conclude/exit.

2.1. The Frame of Reference, Societal, and Practice Context. The underlying clinical reasoning of an occupational therapist, dealing with PD patients, should be focused on facilitating performance of personally meaningful everyday occupations and addressing issues that interfere with their performance. Reasons for impaired or unsatisfactory performance can include stage of the disease, environmental restrictions, both physical and social, drug regimes, motivational issues, fatigue, depression, cognitive impairments, and motor symptoms such as freezing, plus other motor impairments. As every individual experiences Parkinson's in their own unique manner, it is not standard practice to limit OT interventions by focusing on prescribed goals and symptoms or according only to the stage of the disease. Disease specific staging models such as the 5-point Hoehn and Yahr scale (H&Y) [9, 10] offer a simple snapshot of functional impairment and disability [10]. In addition to awareness of the stage of the disease, OT intervention must also consider personal concerns, abilities, and goals. Therefore, OTs must utilise both conceptual models and models of practice simultaneously. Conceptual models support clinical reasoning about PD patients and their occupations and environments [11]. Meanwhile, to enable OTs to intervene tangibly, on a practical and pragmatic level, models of practice help OTs to promote beneficial changes in PD patients' daily activities, engagement in meaningful occupations, and to participate more fully in their physical environments. Conceptual models used by occupational therapists working with patients with PD include the Model of Human Occupation [2], the Person Environment Occupation (PEO) model [12], the Canadian Model of Occupational Performance-Enablement (CMOP-E) [13], and others. Frames of reference and practice models are connected, because frame of reference will change [8] with the demands of "Parkinson's patient-occupational therapist" interactions; thus frames of reference and practice models are combined to support the clinical practice process.

OT intervention strategies designed specifically for people with Parkinson's are often based on teaching the use of cognitive and sensory attentional strategies. Such coping strategies can be taught to interested patients to aid almost any daily task such as getting dressed more easily and undertaking safer and easier transfers and mobility around the home. This approach was first suggested in 1997 by a multidisciplinary team based in Melbourne, Australia, in their pioneering book: *Parkinson's Disease: A Team Approach* [14]. The role of OT in the management of people with Parkinson's disease was also reported in 1998 by an OT based in the UK [15]. Subsequently, a meta-analytic review published in 2001 by a team in the United States evaluated the effectiveness of occupational therapy-related treatments for people with Parkinson's disease and concluded that whilst further evidence was called for, the team reported that "to provide effective occupational therapy intervention, it is necessary to draw on research evidence" and suggested their own review as "a source of evidence for occupational therapists who treat clients with Parkinson's disease" [16].

Since publication in 2006 of the UK National Institute for Clinical Excellence (NICE) Clinical Guidelines for Parkinson's Disease, there has been a growing trend for using rehabilitation as an adjunct to pharmacological and surgical treatments, with an emphasis on the importance of multidisciplinary management of this highly complex and multidimensional condition. The 2006 NICE recommendation specifically addressing the role of OT for people with Parkinson's [5] highlights the need for consideration during OT assessment of work, family, leisure, transfers, mobility, personal self-care (such as eating and drinking, washing, and dressing), environmental safety, motor function, and cognitive function and recommended provision of appropriate OT interventions in these domains. NICE's 2006 recommendation for OT [5] was based on just 2 small scale and rather dissimilar group therapy RCTs [17, 18], yet the role of OT was given additional weight by the expert guideline development group [5]. However, NICE (2006) does not offer advice for OTs about *how* to work specifically with people who have Parkinson's, yet clinical experience shows that standard, generic OT approaches yield little benefit with this particular group of patients. The often paradoxical and counterintuitive responses of people with Parkinson's to generic OT interventions may be due to the complex neurological causes underlying the functional

impairments experienced by these particular patients. In 2003 following a 2-wave national survey of around 160 OTs in the UK, Deane and colleagues had already suggested the need for postgraduate training for occupational therapists, who had acknowledged some of the unique challenges of treating Parkinson's patients a few years before publication of the 2006 NICE guidelines [19, 20]. To support OTs working with people with PD, Parkinson's UK (a national charity) and the College of Occupational Therapists collaborated to develop the *Occupational Therapy for People with Parkinson's Best Practice Guidelines* published in 2010 in the UK (and available since then online), based mainly on basic scientific findings, expert opinion, and clinical experience and subsequently peer reviewed and ratified by over 30 OTs [21].

Occupational therapists, working with people who have PD, should have access to knowledge and skills specifically concerning Parkinson's and be aware of resources and developments in this area of OT practice. The findings of an online survey published in 2011 about the views and experiences of OT of 230 people living with PD in 4 European countries (Norway, Slovenia, Sweden, and the UK) demonstrate that participants had numerous concerns regarding daily functioning and OT was considered as an important and highly valued intervention by the 54% of the survey participants who had received an OT service since their diagnosis of Parkinson's [22]. According to Sturkenboom et al. [23, 24], a recent high quality RCT and subsequent economic evaluation of OT in The Netherlands involving 191 community dwelling Parkinson's patients and 180 care givers led to measurable improvements in self-perceived performance in daily activities (as shown by improved scores on the COPM used as a primary, patient-centred outcome), without adding to overall healthcare costs. As a 2 to 1 randomisation method was employed, 124 participants received 10 weeks of individualised home-based OT intervention and 67 controls had only usual medical care. Sturkenboom et al. [23, 24] show that OT enabled "smart spending" of healthcare funds yielding personally significant gains in domains which have a direct influence on quality of life. Furthermore, OT led to positive cost-effective support for caregivers of people with PD [24]. There is also evidence published in 2010 from a groundbreaking RCT conducted in the United States suggesting that people with PD ($n = 117$) benefit in terms of their health related quality of life from self-management rehabilitation delivered in a group setting, at 3 intensities, and at 2 levels and according to disease stage, by a team of OT, physiotherapy, and speech therapists experienced in working with Parkinson's [25]. Most gains were demonstrated in terms of activities of daily living (ADL) when patients identified more concerns with ADL and mobility at the initial assessment stage [25]. The same research group published a systematic review in 2014 of interventions used by OTs with Parkinson's patients in which the 3 broad categories of OT intervention evaluated were (a) exercise or physical activity, (b) environmental cues, stimuli, and objects; and (c) self-management and cognitive-behavioural strategies. Moderate to strong evidence was found for task-specific, targeted physical activity training—on motor performance, postural stability, and balance. Evidence of moderate quality also demonstrated positive effects on motor control of external supports used during functional mobility or other movement activities. In addition, moderate evidence was found to support individualized interventions focused on promoting participant wellness and personal control by means of cognitive-behavioural strategies, to improve targeted domains of quality of life [26]. This adds support to Rao, also based in the United States, whose 2010 update of OT and Parkinson's [27] also demonstrated benefits for people with PD in terms of mobility and health related quality of life. Very recent evidence employing neurorobitcs and gaming technology (exergaming) for rehabilitation (with origins dating back to 2002), applicable to people with all neurological conditions, including PD, has been published [28–32] adding further depth and a new dimension to this evolving field of clinical practice. Further evidence about how OTs can use these novel approaches for the benefit of people with PD will no doubt emerge in the near future.

As a part of the OT assessment process, meaningful information about the patients' home and working environments as well as social and community support opportunities is gathered. PD patients' knowledge and experiences should be explicitly integrated into the process of evidence-based clinical decision-making in occupational therapy [16]. Personal strengths might include attributes, abilities, values, and beliefs, both spiritual and cultural [11]. Strengths and challenges may also be identified by the involvement and support of "significant others" in the patients' life, especially during H&Y stages 2–5 of the disease. Within this initial stage of the OT process, the OT must also search for, identify, and provide reliable information that empowers patients and enables their families to become knowledgeable about their condition before engaging in therapeutic interventions. The methods and key elements of this OT process will now be detailed in the following 8-point action plan.

2.2. Eight Action Points

2.2.1. Enter/Initiate. Based on a healthcare or social care referral or by private contract, an OT process is initiated and an occupational therapist would initially consider their own professional competencies and experiences to work with patients with PD and if indicated may decide not to continue the OT process [8]. Generally though an OT will proceed to identify potential/actual occupational issues. Evidence available to date suggests that OT intervention is most often required in the intermediate to advanced stages of Parkinson's equivalent to H&Y stages 3–5 [33–35], whereas it is likely to be of benefit to introduce OT earlier (H&Y stages 1 and 2) as a form of secondary prevention [22, 23, 36]. Standard healthcare practice lags behind this ideal, however, as seen, for example, from a Dutch survey of healthcare for people with Parkinson's, which revealed that only 9% of the PD population received OT consultation [37].

2.2.2. Set the Stage. The person-centred nature of OT acknowledges the individual as the central element of the treatment process [38]. Thus, OT intervention will be most effective when methods to identify those occupational issues that are most important to PD patients are employed.

The Canadian Occupational Performance Measure (COPM) [39] was designed to identify an individual's perceptions of his or her performance in daily activities over time. The COPM is a standardized, semistructured interview tool that is cost-effective, easy to administer, and sensitive to change [1]. It has been used widely in OT research, and in a recent study by Sturkenboom et al. [23] where COPM was used as a primary outcome measure it showed good sensitivity and ability to capture the efficacy of community OT for people with PD. While conducting a COPM interview, an OT will ask a patient with PD to identify the activities that are difficult to perform in the domains of self-care, productivity, and leisure [6]. Further to this, a person with PD will be asked to identify up to five of their highest priority problems and to rate his or her performance and level of satisfaction in each of these activities. The occupational therapist listens to the PD patient's story within the context of their personal, physical, and social environment. Use of COPM assists a person with PD to identify those daily tasks that he/she wants to do, needs to do, or is expected to do, but can not or that are not performed to a satisfactory level for the individual [11]. This approach presents the unique concerns of OT [40], thus ensuring efficiency and promoting increased effectiveness of OT intervention with PD patients, and also captures the unique domain/focus of occupational therapy [7]. Other examples of approaches to engage a PD patient in the OT process could be by standard interview using structured, semistructured, or open interview methods, or by using Goal Attainment Scaling.

2.2.3. Assess/Evaluate. Some assessment scales utilised by OTs in their clinical practice with Parkinson's patients are disease specific and have been devised only for use in PD; other scales such as COPM are applicable to a wide range of medical conditions and have been validated for PD. During the OT assessment process, it is important to evaluate those impairments (motor and nonmotor symptoms) that have an impact on the performance of meaningful everyday tasks that the patient has identified, for example, by using the COPM. Impaired attributes may include challenges related to changes in manual dexterity, coordination and handwriting, visuospatial perception, cognitive skills, stamina (fatigue), mood (depression), motivation, pain, motor symptoms, and/or motor complications. According to concerns identified, there are several assessment scales that can be used to explore these domains further, including the Jebsen Test of Hand Function [41], modified by Jones and Harrison [42], which is a reliable and valid test of hand function. According to Jones and Harrison [42], Jebsen's Test of Hand Function can detect neurological deficit and measure changes in the severity of this deficit. Other useful assessments that may be used by OTs in their assessment process include the Parkinson fatigue scale [43], the Beck Depression Questionnaire [44], the Rivermead Behavioural Memory Test [45], and the Visual Analogue scale for the measurement of pain severity. There are several other assessment tools that can be used through this process. For example, when assessing ADL, The New Unified Parkinson's Disease Rating Scale ADL section can be employed [46] although it is important to note that the ADL section of this scale contains the mixture of impairment and disability-related items [47]. The Assessment of Motor and Process Skills (AMPS) is a performance-based, valid, and reliable measure of ADL, with no ceiling and floor effects [7]. AMPS can only be administered if the PD patient is able to engage in activities, and it is therefore not valid for those with extreme motor fluctuations or those in the later stage of Parkinson's disease [1]. For assessing driving ability in people with Parkinson's disease, Webster's Rating Scale differentiated between safe and unsafe drivers [48]; road testing however is probably the most sensitive assessment method, although driving ability also correlates well with ability on simulator testing. EuroQol is a valid and reliable measure of quality of life; in addition the PDQ 39 is another reliable and valid tool for measuring health related quality of life for those with Parkinson's disease [49].

Latest advances in robot-based and sensor-based measures are becoming increasingly available for OTs assessing temporal and spatial domains of bodily movement. For example, Parkinson's KinetiGraph (PKG) automatically records movement and can be worn continuously over 6 to 10 days during activities of daily living, so that, by using an accelerometer, movement data can be gathered in an automated manner to assesses bradykinesia and dyskinesia [50]. Another example of this leading edge approach is reported by Williams et al. [32] who explored freezing of upper limbs using sensors.

2.2.4. Agree Objectives and Plan. Occupational therapist and PD patient's expectations should be focused towards the same achievable functional goals. It is important to negotiate goals that are specific and measurable and that can be achievable in the time frame available for intervention.

2.2.5. Implement Plan. Intervention by an OT is individually tailored to each patient, resulting in an intervention plan that has personal relevance and meaning for the person and their family, and is therefore patient-centred [13]. OTs aim to maintain independence, confidence, and safety, in the performance of daily tasks and activities in all areas of life, for as long as possible. PD patients can benefit from OT from the time of diagnosis if daily tasks are problematic as shown by recent evidence [23, 34] that supports the value of OT in early stages of the disease. The role for OT as Parkinson's progresses increases. For example, as scores on the H&Y scale increase, especially when wearing-off problems, on-off fluctuations, dyskinesias, falls, and freezing are becoming more evident, it is important for OTs to educate Parkinson's patients about how to adapt their everyday routines and personal lifestyle, in order to optimise functional ability and health related quality of life.

The following types of treatment intervention [7] related to the H&Y stages could be used in the long-term management of Parkinson's disease (Table 1).

Acquisitional occupation is targeted towards the restoration of impaired skills [7] and is most relevant for the early stages of PD (relevant to H&Y stages 1–3). It relates to training/maintaining Parkinson's patients' quality of daily occupations.

Table 1: OT treatment intervention modes as related to the Hoehn and Yahr scale [9].

Hoehn and Yahr stage	OT treatment intervention modes [7]
Stage 1	Acquisitional occupation, restorative occupation, and occupation-based education programs
Stage 2	Acquisitional occupation, restorative occupation, occupation-based education programs, and adaptive occupation
Stage 3	Acquisitional occupation, restorative occupation, occupation-based education programs, and adaptive occupation
Stage 4	Adaptive occupation, restorative occupation, acquisitional occupation, and occupation-based education programs
Stage 5	Adaptive occupation, occupation-based education programs

Restorative occupation is targeted toward restoration of impaired personal factors (daily routines, values, and habits) and impaired bodily functions (motor, fatigue, balance, and motivation) [7]. Robot-assisted arm training is less studied in Parkinson's, yet it offers another promising tool for improving upper limb function in this condition [29]. Furthermore, the use of exergaming technology such as Nintendo Wii and Xbox Kinect are novel intervention tools that are increasingly being employed by OTs and other therapists within neurorehabilitation services [28, 30, 31]. These novel exergaming tools are used to facilitate different types of exercise, with the aim of improving balance and reaction times. Exergaming devices have the added advantage that they can be used both in institutions and in the home setting [30, 31].

Adaptive occupation [7] is targeted toward adapted methods of performing daily occupations; interventions also include the introduction of aids and equipment and environmental adaptations. After analysis of PD patients' functioning and of their physical environment, the OT suggests methods and or equipment for safe, effective, and confident performance. This process could include teaching methods that help PD patients to perform daily occupations independently and in the most satisfying way that their residual ability allows, or the provision of hand rails, adapting bathroom facilities, installation of a stair lift, adapting the kitchen, supply of handwriting devices, adaptation of clothing, and so forth. Adaptive occupation is relevant to H&Y stages 2–5. As even in the advanced (H&Y = 5) stage, OT interventions can be devised to improve comfort, dignity, and enjoyment of leisure time.

Occupation-based educational programs delivered by OTs [7] involve implementation of workshops, lectures, or other educational programs for Parkinson's patients and/or their close relatives or care givers, related to the nature of Parkinson's, occupational issues, and other psychological and social concerns. These may include organisation or contributions by OTs to programs for newly diagnosed PD patients, patients at H&Y stages 2 and 3, and even patients in H&Y stages 4 and 5. Additionally, separate educational sessions or programs for relatives or care givers are available in some places.

Acquisitional, restorative, and adaptive occupation may be based on approaches that employ attentional strategies, cognitive and sensory cueing techniques, and conductive education methods, which will be outlined below.

Conductive education originally developed for use with children affected by cerebral palsy usually employs group-based exercises using rhythmically facilitated practice of basic movements, which are required for daily living tasks, and is applicable to PD patients [51]. This approach is used, for example, to improve handwriting, gait, and other forms of movement control.

Cueing techniques using a personalised selection from a wide variety of cognitive and sensory stimuli can aid preparation for and performance of personal, domestic, and community activities by people living with PD [52]. In an international collaboration with many leading authorities in the field, a book entitled *Rehabilitation for Movement Disorders* (including Parkinson's disease) was published in 2013 and edited by Iansek and Morris. This work translated basic laboratory-based research from a wide array of high-tech, brain imaging studies (e.g., fMRI, SPECT, and PET) [52]. Iansek and Morris suggest in the introductory section of their book that the use of attention, combined with specific cognitive processes and sensory cues, allows a person with PD (or their care giver) to exploit alternative short motor loops (that can be engaged for survival) and thus may enable access to available neural pathways, structures, and neurotransmitters to enable improved performance [52]. Cues appear to "bypass" the underactive basal ganglia (or autopilot system) and to thus elicit and enhance the performance of functional activities by employing alternative "manual control" mechanisms [52]. In an interesting RCT also from Morris's Australian team, external cues and attentional strategies aimed to improve size, speed, and movement sequence were also found to have a positive effect on ADL performance [53]. Applying and building on these findings in relation to handwriting, which is often a great frustration for people with Parkinson's, OTs can also be informed by a well conducted yet small RCT of Micrographia by Oliveira et al. [54] from the UK who showed back in their 1997 publication, that both external visual and auditory cues draw attention to the goal of writing bigger and thus encourage the patient to write less automatically, with the beneficial effect of increasing amplitude of handwriting. Two further handwriting studies published in 2005 and 2007 [55, 56] also showed that motor performance can be aided by the cognitive/sensory strategy of prior prereading of a word, or by seeing a word semantically related to the expected motor performance. Thus seeing the word "Reach" on a prompt card, for example, or saying the word "Reach" stimulates the neural networks responsible for the performance of a reaching task.

Motivational Interviewing may also be practised within an OT process to promote adherence to a treatment plan. A review by O'Halloran et al. [57] looked at the use of Motivational Interviewing amongst people with chronic health conditions and demonstrated that approximately 75% of the studies examined demonstrated a beneficial effect, regardless of whether the problems being addressed were psychological or physiological. The same authors argue that Motivational Interviewing is not limited in any way to counselling of a small group of selected clients but can be used in the treatment of a broader area of diseases that, to some extent, are influenced by behaviour, and go on to suggest that this is a method with an important potential effect, from which patients may very well benefit [57].

2.2.6. Monitor/Modify. It is important to monitor and modify the OT intervention process at frequent points during a course of OT sessions. To fully engage each PD patient, it is beneficial to follow their personal agenda of key concerns, and working collaboratively with the patient is critical to the success of the OT intervention process. As applicable, an OT intervention plan is reviewed, redesigned, and adjusted according to progress in addressing personally relevant goals. Often, as issues are resolved or an acceptable management approach has been established, new priorities arise and the OT must therefore anticipate and monitor new concerns and goals through ongoing evaluation.

2.2.7. Evaluate Outcome. Evaluation can identify whether the OT process has facilitated attainment of goals, development of life skills, and adaptation to the progression of the disease. Thus, evaluation assists the process of healthy occupational adaptation for the PD patient. According to the assessments, evaluation, and goal setting methods used to establish the OT process, repeated measures can be undertaken as a course of OT progresses and in particular, as an episode of care nears conclusion.

2.2.8. Conclude/Exit. The therapist and the PD patient will need to communicate about the conclusion of the OT process as an episode of care ends. Because self-management is promoted throughout the rehabilitative process, dependence on the OT is not encouraged or is contained. Often people with Parkinson's will return for further goal-focused courses of OT intervention as their symptoms change, the condition progresses, or other comorbidities or life events necessitate another course of OT intervention. Following each episode of OT care, a written or oral report is provided for patients and is shared if appropriate with other multidisciplinary team members. People with Parkinson's and their families or care givers should be provided with adequate information for transfer to other supportive services and for reentry to OT as required.

3. Summary

The CPPF has been used here to demonstrate how Parkinson's patients who engage in an OT intervention process are enabled through a flexible, individually tailored approach to accommodate to the complex pathology and functional impacts they face in living with PD. As an OT intervention proceeds, it must be adjusted to each Parkinson's patient's current needs, and thus it is useful to use relevant contexts and stages from the eight action points outlined above. In concordance with Davis et al. [8], this way of reasoning about the OT process has been employed to make it possible for some less observable aspects of OT practice to be made explicit. The growing evidence base presented here also shows that referral for OT assessment and intervention is relevant for Parkinson's patients willing to engage in a suitably tailored course of OT intervention, at any stage of the condition (H&Y stages 1–5).

4. Conclusion

The role of OT for people with Parkinson's, ideally delivered within the context of a multidisciplinary healthcare team, is now becoming well established. High quality research to build on the firm foundations explored here would be of particular interest in establishing more details about the effects of OT intervention. Studies of OT (and other rehabilitation therapies) used to address functional concerns about activities of daily living before commencement of anti-Parkinson's medications would be of particular interest. Establishing the value of OT, using a Parkinson's specific approach as outlined here and specific studies focused on the short-, medium-, and long-term value of OT, for example, commenced in the early (H&Y stages 1-2) stages of Parkinson's, would also add to the small but rapidly growing evidence base concerning rehabilitation of people with PD. This information may be of particular use to OTs facing the many challenges of their Parkinson's patients. Furthermore those diagnosed with Parkinson's at a younger age and others who wish to find nonpharmacological ways to delay or minimise reliance on anti-Parkinson's medications may also benefit by increased understanding of the value of participation in intermittent episodes of OT intervention.

Conflict of Interests

The authors have no conflict of interests to disclose.

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Review Article

Action Observation and Motor Imagery: Innovative Cognitive Tools in the Rehabilitation of Parkinson's Disease

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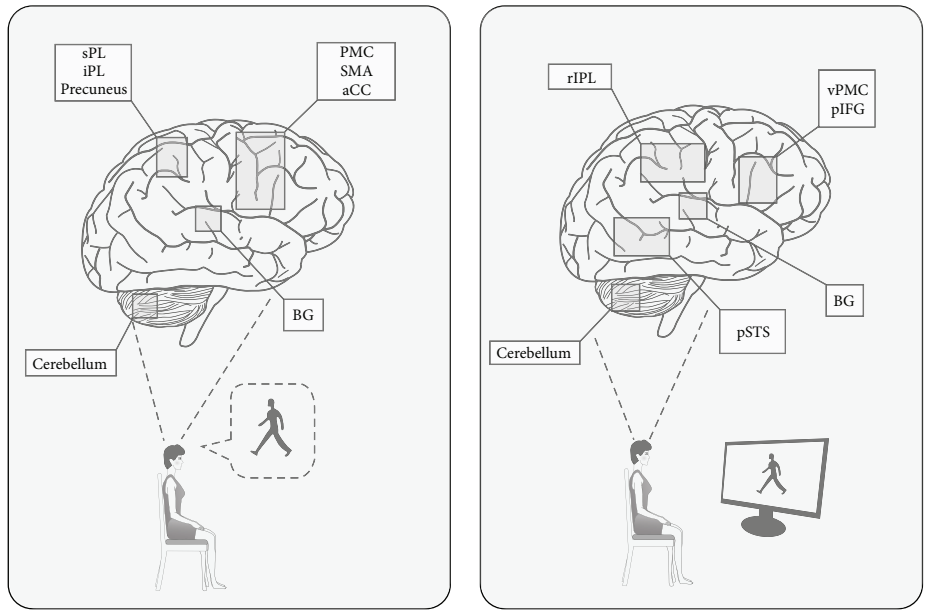
Parkinson's disease (PD) is characterized by a progressive impairment of motor skills with deterioration of autonomy in daily living activities. Physiotherapy is regarded as an adjuvant to pharmacological and neurosurgical treatment and may provide small and short-lasting clinical benefits in PD patients. However, the development of innovative rehabilitation approaches with greater long-term efficacy is a major unmet need. Motor imagery (MI) and action observation (AO) have been recently proposed as a promising rehabilitation tool. MI is the ability to imagine a movement without actual performance (or muscle activation). The same cortical-subcortical network active during motor execution is engaged in MI. The physiological basis of AO is represented by the activation of the "mirror neuron system." Both MI and AO are involved in motor learning and can induce improvements of motor performance, possibly mediated by the development of plastic changes in the motor cortex. The review of available evidences indicated that MI ability and AO feasibility are substantially preserved in PD subjects. A few preliminary studies suggested the possibility of using MI and AO as parts of rehabilitation protocols for PD patients.

1. Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by motor and nonmotor symptoms. Since no known cure exists, the management of PD is traditionally based on symptomatic treatment with drug therapy (levodopa being considered the "gold standard") or with neurosurgical approaches (Deep Brain Stimulation, DBS). However, even with optimal medical or surgical management, patients with PD still experience a progressive deterioration of their autonomy with increasing difficulties in daily living activities and in various aspects of mobility such as gait, transfers, balance, and posture. For this reason, there has been increasing recourse to the inclusion of rehabilitation therapies as an adjuvant to pharmacological and neurosurgical treatment with the aim of maximizing functional ability and minimizing secondary complications.

A recent meta-analysis of physiotherapy interventions [1] provided evidence of short-term, small but significant and clinically important benefits for walking speed and balance in PD patients. However, formal comparison of different techniques could not be performed and there was insufficient evidence to support one specific physiotherapy intervention [2]. The latter reviews pointed out the need for more adequate trials and for the development of innovative approaches demonstrating a longer-term efficacy and better cost-effectiveness of physiotherapy in PD. Traditionally, physiotherapy was based on physical practice to improve motor abilities (such as muscular strength, gait, or coordination); however, the new guidelines highlighted that physiotherapy for PD needs to maximise quality of movement and functional independence by means of a tailored intervention linked to the stage of the disease progression.

With regard to physiotherapy interventions, several approaches aim to teach patients using compensatory attentional/cognitive strategies that may rely on the recruitment of alternative motor circuits. Indeed, it has been demonstrated that both cueing strategies (based on the use of external



(a) Motor imagery (b) Action observation

Figure 1: The human brain activity during motor imagery (a) and action observation (b). (a) shows brain areas activated during kinesthetic and visual motor imagery. The pattern of activity includes the following regions: ventral and dorsal part of the premotor cortex (PMC); supplementary motor area (SMA); anterior Cingulate Cortex (aCC); superior Parietal Lobule (sPL) and inferior Parietal Lobule (iPL); precuneus; basal ganglia (BG); and cerebellum. (b) shows the complex brain network ("mirror neuron system") involved in action observation: ventral premotor cortex (vPMC), posterior part of the Inferior Frontal Gyrus (pIFG), rostral part of the Inferior Parietal Lobule (rIPL), and posterior Superior Temporal Sulcus (pSTS).

stimuli associated with the initiation and facilitation of a motor activity) and attentional strategies (such as instructions which rely on cognitive mechanisms of motor control and are internally generated) are able to improve walking performance by using alternative pathways unaffected by PD [3]. In this sense, motor imagery (MI) and action observation (AO) are two training techniques that have recently gained attention as a promising rehabilitation tool for patients with neurological disorders [4–6].

The aim of this perspective review was to show that both motor imagery (MI) and action observation (AO) represent two innovative rehabilitation approaches that are feasible in Parkinson's disease (PD) and potentially able to induce significant benefits. Here we briefly summarized the basic mechanisms underlying MI and AO, their role in motor learning, and possible abnormalities in patients with PD. Further, we reviewed the available evidences supporting the use of MI and AO in the rehabilitation of Parkinsonian subjects.

2. Motor Imagery and Motor Learning

Motor imagery (MI) is a cognitive process in which a subject imagines that he is performing a movement without actually doing it and without even tensing the muscles (Figure 1(a)). It is a complex, self-generated, dynamic state during which the representation of a specific motor action is internally activated without any motor output [7, 8]. MI has been categorized as external (visual) and internal (kinesthetic) and the perspective the person uses to imagine can be either the first or the third person. The "first-person" perspective is related either to the person's view of the imagery contents or to its kinesthetic sensation, while the "third-person" perspective is the visual imagery of scenes outside the person.

Jeannerod and Decety [9] suggested that MI would represent the result of conscious access to the intention to move, suggesting that conscious motor imagery and unconscious motor preparation are likely to share common mechanisms. Indeed, a large body of evidence suggests that imagined and executed actions share the same neural structures recruiting overlapping brain regions (i.e., premotor cortex, anterior cingulate, inferior Parietal Lobule, and cerebellum) [10, 11], although MI is thought to reflect mainly the process of movement preparation, with reduced involvement of end-stage movement execution related processes [12, 13].

Besides the overlap in neural activation between imagery and execution there are also similarities in the behavioural domain. For instance, the time to complete an imagined movement is known to be similar to the time needed for actual execution of that movement [14]. This phenomenon is known as mental isochrony. Decety et al. [15] studied subjects who were instructed to either actually perform or mentally simulate a leg exercise. Heart rate and respiration rate were measured in both conditions. The results showed that the heart rate and respiration rate began to increase not only during actual exercise but also in the mental condition where no work at all was produced. These findings have led to a theoretical position termed the "simulation hypothesis"

suggesting that movement execution and MI are driven by the same basic mechanisms [16].

On the basis of all these data, it is reasonable to think that, like motor execution, MI training can induce improvements in motor performance and thus in motor learning processes.

Pascual-Leone et al. [17] showed that during 5 days of training of a musical performance both MI and motor execution resulted in an increase in performance although the motor execution group outperformed the motor imagery group. Interestingly, the MI group demonstrated the same training effect as the motor execution group after only one additional execution session. Further, MI has been demonstrated to modify the actual speed of execution of body movements [18]; the authors investigated the effect of changing MI speed on actual movement duration over a 3-week training period. Participants mentally performed a series of body movements faster or slower than their actual execution speeds. The fast MI group's actual times decreased on subsequent performance. The effect of MI on actual speed execution supports the ideomotor theory because anticipation of sensory consequences of actions is mentally represented. The beneficial effects of mental practice on the physical performance have been suggested to rely on the close temporal association between motor rehearsal and actual performance. In the same vein, Avanzino et al. [19] showed that motor imagery is able to improve the performance of repetitive finger opposition movements more than the motor practice alone. Further, when subjects performed MI, they speeded up the movement by modifying different kinematic aspects of finger opposition movements, thus suggesting that motor imagery was able to significantly improve movement speed by inducing a modification in the specific motor program.

At the basis of motor performance improvement induced by MI is that the same cortical-subcortical network, active during motor execution, is engaged in MI [9, 10]. In accordance with that, it has been demonstrated that motor imagery training leads to the development of neuroplasticity in the primary motor cortex (M1), as it affected transcranial magnetic stimulation induced plasticity in M1 [20].

3. Motor Imagery in Parkinson's Disease

The ability of people with PD to efficiently imagine movements is still controversial. Abnormal performance on motor imagery tasks was initially suggested in patients with PD using different approaches, including behavioural, electrophysiological (transcranial magnetic stimulation, TMS, and movement-related potentials, MRPs), and functional imaging studies.

Tremblay et al. [21] investigated the facilitation of motor evoked potentials (MEPs) to TMS during action imagination. Corticomotor facilitation was defective in medicated PD patients thus supporting the hypothesis of an impaired motor preparation associated with basal ganglia dysfunction in PD. Cunnington et al. [22] reported that MRPs, recorded during motor imagery of an externally paced sequential button-pressing task, were present but significantly reduced in amplitude and abnormally prolonged in PD. However, the preparatory-phase associated with motor imagery was mainly impaired in patients with more severe Parkinsonian symptoms and not in early-stage PD. Consistent with this finding, a PET study by the same authors [23] showed that imagined movements of PD patients in the "off" condition were associated with reduced activation of specific cortical areas (including the anterior cingulate and the right dorsolateral prefrontal cortex, DLPFC) but also with compensatory activation of additional areas (ipsilateral premotor and inferior parietal cortex).

Although brain activation during MI is abnormal in Parkinsonian subjects [24], the possible occurrence of compensation during MI was documented in PD using fMRI [25]: in strongly lateralized PD patients, MI of the most-affected hand recruited additional resources in extrastriate visual areas (and their connections with premotor cortex). Conversely, the inhibition by repetitive TMS (theta burst stimulation) of the right extrastriate body area abolished in PD patients but not in healthy subjects the compensatory effect on MI [26].

These studies basically highlighted functional changes in the activation of corticostriatal circuits in relation to the imagery of motor tasks in PD subjects, further supporting general abnormalities of motor planning in this condition. Indeed, the motor corticostriatal circuit seems to be engaged during motor imagery. In PD patients implanted for DBS it has been shown that imagination of a simple, repetitive movement significantly reduced the neuronal firing rate of GPi neurons [27]. Similarly, oscillatory beta activity in the region of the subthalamic nucleus (STN) was modulated to the same extent during motor execution and imagination [28]. Stimulation of the STN was also demonstrated to change PET activation during actual or imagined movements in PD [29].

Altogether, experimental results support preserved MI ability in PD, but with different patterns of cerebral activity [30]. In keeping with this hypothesis, recent contributions suggested a substantially normal efficiency of MI processes in PD. Heremans et al. [31] used an extensive imagery ability assessment battery to test 14 PD patients and 14 normal subjects. They found that physical execution was slowed to the same extent as MI, indicating that the slowness of MI reflects the bradykinesia inherent to PD rather than an inability to correctly perform it. These authors [32] also investigated whether the quality of MI could be improved by external cueing. The presence of visual cues significantly reduced the patients' bradykinesia during MI and increased their imagery vividness.

The influence of pharmacological (levodopa) treatment was also investigated: the vividness of MI was not different between the "on" and "off" conditions or between PD and controls [33]. These results suggest that although levodopa has been suggested to normalize brain activity in several cortical areas (including the supplementary motor area), PD patients are able to imagine similarly to older adults when both "on" and "off" anti-Parkinson medication. A recent study by Maillet et al. [34] showed that "kinesthetic" motor imagery abilities are preserved in PD patients and can be further improved by training.

Finally, we recently used MI to investigate time processing abilities (time estimation and reproduction) in PD patients [35]: a similar behaviour was observed during imagery task and in the execution task. Likewise, Conson et al. [36] demonstrated a parallel impairment between motor and mental simulation mechanisms in PD patients. To further support the ability of Parkinsonian patients to mentally simulate physical activities, MI was also used during fMRI to investigate locomotion related brain activity in PD [37, 38].

We may conclude that MI ability is substantially preserved in PD subjects (particularly in the mid and early stage), although it might be "slow" in comparison to healthy controls. In particular, it is likely that PD patients may use a compensatory "third-person" strategy rather than using MI from a "first-person" perspective. The studies, therefore, support the possible use and implementation of motor imagery training in the rehabilitation of patients with PD.

Although MI ability was extensively investigated in PD, very few studies have tested the possibility of using MI as part of rehabilitation protocols for PD patients (see Table 1).

The combination of MI and physical practice was compared to physical therapy alone in a randomized-controlled (RC) trial [39]. Both groups practiced callisthenic exercises, functional task, and relaxation exercises. However, the experimental group (treated with both imagery and real practice) exhibited faster performance of motor sequences (reduced bradykinesia). Interestingly, the implementation of MI allowed higher gains in the mental subsets of the Unified Parkinson's Disease Rating Scale (UPDRS).

On the other hand, Braun et al. [40] compared mental practice with relaxation embedded in standard physiotherapy and did not find any significant difference in walking performance and related outcome measures. Finally, a recent RC single-blinded trial [41] investigated autogenetic training (AT) based on visual imagery. When used as an adjunct to physical therapy, AT proved more effective than physical therapy alone in improving motor performances (UPDRS motor section) in 66 PD patients.

4. Action Observation and Motor Learning

It is widely accepted that the observation of actions performed by others activates in the brain the same neural structures used for the actual execution of the same actions. The neurophysiological basis of "action observation" (AO) (Figure 1(b)) is represented by the discovery of mirror neurons in the monkey cerebral cortex [42, 43] that discharge during both the execution of goal-directed actions and the observation of other individuals performing similar actions. The definition of "mirror neuron system" (MNS) comprises the cerebral areas containing mirror neurons and evidences with the use of TMS and functional imaging (fMRI) suggested that an MNS is also present in the human brain [44].

In humans during AO the excitability of the motor cortex is enhanced [45] and the 15–25 Hz EEG activity is suppressed [46]. AO, therefore, is able to recruit specific areas in the frontal and parietal lobes similarly to what happens during motor execution. Such effect is maximal when the observed actions are familiar and belong to the motor repertoire of the observers. The MNS has been shown to be also involved in "imitation" within a circuit involving the inferior Parietal Lobule, the Inferior Frontal Gyrus, and the premotor cortex [47].

Indeed, treatment with AO is essentially based on the principle that "imitation" of movement implies motor observation, motor imagery, and actual execution of movements. Patients are requested to observe and imitate specific actions in order to restore the structures normally activated in the actual execution of those actions [6].

It has been proposed that this mechanism linking observation and action forms the basis by which we understand the actions of others: by mapping the representation of observed actions onto motor systems, observers gain knowledge of those actions by "internally" executing them [48]. From that idea, it has been widely demonstrated that the system linking observation and action can facilitate motor learning [49].

Several studies have consistently shown that AO is an effective way to learn or enhance the performance of a specific motor skill. In a seminal study, participants (required to perform a reaching task in a novel environment) performed better after observing a video depicting a person learning to reach in the same novel environment, than participants who observed the same movement in a different environment [49]. Bove and coworkers [50] showed that the observation of repetitive finger opposition movements at a frequency different from the spontaneous tempo induced changes that closely resembled the observed rhythms and that were long-lasting. Notably, the observation-execution interval had a significant effect on learning: the larger the interval between observation and the first movement execution was, the weaker the effect on the rate of execution of finger movements was. Indeed, it has been proposed that the motor memory of behavioural aspects of an observed rhythmical action can be formed only when movements are promptly executed after video observation [51]. For instance, when AO and physical practice were applied simultaneously it was shown that this combination was more effective to induce both plastic changes in M1 and motor performance improvements than physical practice and AO alone [52–54].

It is postulated that the cortical regions that underlie active motor learning also play a role in motor learning induced by observation. Indeed, passive observation of motor actions induces cortical activity in the primary motor cortex (M1) of the onlooker, which could potentially contribute to motor learning [45]. This facilitation during action observation has been consistently documented and appears to be muscle dependent rather than direction dependent, temporally coupled with the observed action, causally linked to activity in premotor cortex, and dynamically modulated. Recently it has been showed that 30 minutes of repeated thumb movement observation induced neuroplastic changes (LTP, long-term potentiation) in the primary motor cortex, similar to what is seen after physical practice [55]. This result provided some indication as to the underlying neurophysiological mechanism related to the behavioural gains achieved through action observation and suggested that an extended period of action observation may be sufficient to induce LTP in the primary motor cortex.

Table 1: Summary table of studies on rehabilitation with "motor imagery" or "action observation" in Parkinson's disease.

Citation	Groups	Age (years)	Duration (years) H&Y	Type of intervention	Dose of intervention (m/d/w)	Results	FU
Tamir et al. (2007) [39]	Exper. = 12 PD	67.4 ± 9.7	7.4 ± 3.1 2.29 ± 0.4	Combination of imagery + PT	>60/2/12	Significant improvements for the Exper. group in TUG time (decrease 2.5 sec.), getting up from supine (decrease 1.5 sec.), and 360-degree turn. Significant improvement in UPDRS mental section (from 2.1 to 1.2 points).	No
	Control = 11 PD	67.4 ± 9.1	7.8 ± 4.5 2.31 ± 0.4	Only PT		No parallel changes in the control group.	
Braun et al. (2011) [40]	Exper. = 25 PD	70.0 ± 8.0	5.2 ± 5.0 Most < 3	PT + imagery	60/1/6	No significant differences between the groups. General trend in favour of Exper. group.	No
Ajimsha et al. (2014) [41]	Exper. = 32 PD	61.4 ± 2.6	3.0 ± 0.6 2-3	Autogenic training	60/5/8	Significantly greater improvement of UPDRS motor section in the Exper. group after training (51.78% versus 35.24%) and at FU (30.82% versus 21.42%).	12 weeks
	Control = 33 PD	60.8 ± 2.1	3.1 ± 0.5 2-3	PT			
Pelosin et al. (2010) [66]	Exper. = 10 PD with FOG	68.8 ± 4.1	11.6 ± 4.9 2.1 ± 0.3	Action observation + PT	60/3/4	Significant improvement in both groups of motor performance (UPDRS-III, TUG, 10 M-WT) and quality of life (PDQ-39) after training and at FU. FOG-Q and number of FOG episodes significantly reduced in both groups after training, but only in Exper. group at FU.	4 weeks
	Control = 10 PD with FOG	70.2 ± 6.8	9.5 ± 3.7 2.2 ± 0.3	Landscape observation + PT			
Buccino et al. (2011) [67]	Exper. = 7 PD	68 (59–80)	7 (5–19) 3 (2.5–4)	Action observation + PT	—	Significantly greater improvements in Exper. group for UPDRS and FIM scores.	No
	Control = 8 PD	73.5 (67.5–76.5)	9 (5.5–13.5) 1.7 (1.5–2.3)	PT only			

PD = Parkinson's disease, H&Y = Hoehn and Yahr stage, PT = physical therapy, TUG = time-up-and-go test, UPDRS = Unified Parkinson's Disease Rating Scale, FOG = Freezing of Gait, 10 M-WT = 10-meter walking test, FOG-Q = Freezing of Gait Questionnaire, FIM = Functional Independence Measure Scale, FU = follow-up, and PDQ-39 = Parkinson's Disease Questionnaire.

5. Action Observation in Parkinson's Disease

Although the MNS is present in healthy humans, it is still unclear whether it is efficiently working also in PD.

Two studies in PD patients implanted for DBS [56, 57] showed that AO was accompanied by bilateral reduction of the beta oscillatory activity in the STN and of cortico-STN coherence. The occurrence of changes that mimic those observed during actual movement (including the medication effect) suggests that the MNS is reflected in the basal ganglia activity and that it is operating also in PD patients. Further, it has been proposed that the STN might be involved in inhibiting the tendency to carry out the observed action [58].

An original study [59] investigated the effect of viewing action-relevant stimuli (object or finger movements) on reaction-time responses of healthy subjects and PD patients. Both groups produced faster responses when the observed movement matched the direction of their response, but PD subjects lacked specificity for finger movements. Tremblay et al. [21] showed in PD that MEP amplitudes increased during active imitation but not during observation. However, training with Wii Fit was able to improve corticomotor excitability during observation [60]. Castiello et al. [61] made a kinematic analysis of grasping movements after watching a model performing the same movement. PD patients showed AO-related facilitation only when the model was a Parkinsonian subject thus postulating an impaired effectiveness of AO due to damaged basal ganglia function. The latter studies, therefore, would suggest abnormal AO in PD.

On the contrary, Albert et al. [62] using a movement interference task (horizontal/vertical arm or dot movements) found no difference between healthy controls and PD patients (in the "off" condition) thus suggesting that AO system is normally effective in PD. In addition, we recently demonstrated [63] that a single session of AO could reduce bradykinesia of finger movements in PD by improving spontaneous pace. Such effect was still present 45 minutes later only in the "on" condition thus suggesting that the dopaminergic state influences AO ability in PD.

Altogether, available evidences suggest that AO can modify the speed and accuracy of actions in PD, though it is not clear how PD can affect "imitation."

Several studies investigated treatment with AO for motor rehabilitation of subacute and chronic stroke [53, 64, 65]. On the other hand, very few evidences are available for rehabilitation of patients with PD (see Table 1).

We investigated [66] whether AO, combined with practicing the observed actions, was able to reduce Freezing of Gait (FOG) episodes in PD. Twenty patients entered a single-blind trial and underwent identical physical therapy training but were randomly assigned to the experimental (watching video clips showing specific strategies to circumvent FOG episodes) or control (watching video clips of static different landscapes) groups. The FOG Questionnaire score and the number of FOG episodes were significantly reduced in both groups after the training period, but at follow-up examination (4 weeks after the end of the intervention), a significant reduction in the number of FOG episodes was observed only in the experimental group. This study suggested that AO has a positive additional effect on recovery of walking ability in PD patients.

A pilot RC study investigated the effectiveness of rehabilitative treatment with AO in 15 (Hoehn and Yahr: 2-3) subjects with PD [67]. Individuals in the case group improved significantly more than controls on the UPDRS and the Functional Independence Measure (FIM) scale.

6. Conclusions

PD is thought to reflect the dysfunction of circuits interconnecting frontal cortical areas and basal ganglia as a result of the degeneration of the nigrostriatal pathway. Although the pathophysiological mechanisms underlying motor impairment are still uncertain, neurophysiological and neuroimaging studies have been consistent with a deficit in the cortical network subserving movement preparation which translates clinically into cardinal symptoms associated with slowing of motor executions (bradykinesia) and difficulties in action initiation (akinesia).

The dysfunction of the motor cortical network in PD is witnessed by the reduced activation in areas such as the supplementary motor area (SMA) and the primary motor cortex, during performance of motor tasks. However, a compensatory cortical reorganization can be achieved by modulating cortical plasticity through peripheral feedback and sensorimotor integration. Such compensatory reorganization underlies the potential mechanism of rehabilitation interventions.

MI and AO are novel, physiologically well grounded, approaches in neurorehabilitation. Both have the potential to be applied in the rehabilitation of people with PD, though with some limitations. Further research and large, well-designed, RC trials are required to definitely support their efficacy. In addition, it is likely that action representation can be potentiated by concomitant approaches such as cueing [32] or proprioceptive stimulation [68]. It should also be pointed out that although MI and AO are likely to partially share some common mechanisms they cannot be considered interchangeable [6]. MI is more demanding than AO depending on the individuals' capacity to imagine themselves performing specific actions. Further, the correct mental training during MI is difficult to be verified by the therapist. Treatment with AO, therefore, is simpler and more easily to be applied, though a number of details (time and intensity of training, first- or third-person presentation, and type of actions) need to be defined.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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