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Abstract: Cognition and gait appear to be closely related. The chronological interplay between cognitive decline and gait dysfunction is not fully understood. The aim of the present prospective study is investigating whether the dysfunction of specific gait parameters, during specific task and medication conditions, may predict subsequent cognitive impairment in Parkinson's disease (PD). We evaluated cognition and gait in 39 Parkinsonian patients at an initial assessment and after three years. Cognitive performance was evaluated with a neuropsychological battery designed to assess memory, executive/attention, and visuospatial domains. Gait was investigated using a gait analysis system during both the off and on states in the following conditions: 1) normal gait; 2) motor dual task; and 3) cognitive dual task. We used regression models to determine whether gait predicts subsequent cognitive dysfunction.
Overall, the cognitive test scores were stable over time with the exception of the executive/attention scores, whereas all gait parameters declined. The step length during the cognitive dual task during the on state at the initial evaluation was the only significant predictor of executive/attention domain dysfunction at follow up. The results were confirmed when executive/attention dysfunction at the initial assessment evaluation was included in the regression model as a covariate. Our longitudinal study offers additional insight into the progression of gait dysfunction, and its chronological relationship with cognitive dysfunction in PD patients. In particular, the present study indicates that step length during a cognitive task when on medication is an independent predictor of future executive/attention decline.

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Dear Editor,

On behalf of my co-authors, I am hereby submitting a research article entitled "Step Length Predicts Executive Dysfunction in Parkinson Disease: A Three-year Prospective Study" by Amboni et al., for publication in Journal of Neurology.

Our longitudinal study offers additional insight into the progression of gait dysfunction, its longitudinal response to dopaminergic treatment over time and, more importantly, its chronological relationship with cognitive decline in PD patients. Here, we demonstrate for the first time that gait, particularly step length during cognitive dual task on medication, could predict subsequent executive/attention decline in PD.

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We believe that this research article will be of interest to the wide readership of Journal of Neurology.

All authors have read and approved the version of the paper being submitted. These data have not been published elsewhere nor are they under consideration by any other publication. I state that no ghost writing by anyone not named on the author list must be included.

Looking forward to hearing from you,

Yours sincerely,

Dr. Marianna Amboni, MD, PhD
Step Length Predicts Executive Dysfunction in Parkinson’s Disease: A Three-year Prospective Study

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Abstract
Cognition and gait appear to be closely related. The chronological interplay between cognitive decline and gait dysfunction is not fully understood. The aim of the present prospective study is investigating whether the dysfunction of specific gait parameters, during specific task and medication conditions, may predict subsequent cognitive impairment in Parkinson’s disease (PD).
We evaluated cognition and gait in 39 Parkinsonian patients at an initial assessment and after three years. Cognitive performance was evaluated with a neuropsychological battery designed to assess memory, executive/attention, and visuospatial domains. Gait was investigated using a gait analysis system during both the off and on states in the following conditions: 1) normal gait; 2) motor dual task; and 3) cognitive dual task. We used regression models to determine whether gait predicts subsequent cognitive dysfunction.
Overall, the cognitive test scores were stable over time with the exception of the executive/attention scores, whereas all gait parameters declined. The step length during the cognitive dual task during the on state at the initial evaluation was the only significant predictor of executive/attention domain dysfunction at follow up. The results were confirmed when executive/attention dysfunction at the initial assessment evaluation was included in the regression model as a covariate.
Our longitudinal study offers additional insight into the progression of gait dysfunction, and its chronological relationship with cognitive dysfunction in PD patients. In particular, the present study indicates that step length during a cognitive task when on medication is an independent predictor of future executive/attention decline.
Introduction

Cognitive dysfunction is common in Parkinson’s disease (PD), even in the early stages, and it manifests as impairments in executive, attention, memory, language and visuospatial function [1,2]. Progression to dementia (PDD) is a complex and heterogeneous phenomenon [3]. PDD has been associated with increased disability, institutionalization with a consequent increase in health care costs [4] and ultimately higher mortality [5]; thus, the recognition of biomarkers for cognitive decline is crucial for the identification of a PD subpopulation at a higher risk of worse disease progression [6].

Cognition and gait in PD appear to be closely related in a complex fashion [7]. Early studies showed that the postural instability and gait difficulties (PIGD) phenotype represents a risk factor for cognitive impairment and later dementia [8,9]. In addition, the PIGD phenotype was selectively associated with executive and visuospatial dysfunctions [10], an association that is also present in newly diagnosed PD patients [11]. More recently, we have shown that dysfunctions in specific gait parameters that are poorly responsive to levodopa and highly sensitive to dual-task conditions are associated with mild cognitive impairment (MCI), and visuospatial impairment is strongly associated with instability in PD patients [12]. These findings support the hypothesis that dopa-resistant gait components and cognitive dysfunction might share common nondopaminergic network dysfunction [13].

The temporal interplay between gait dysfunction and cognitive decline remains incompletely understood. Verghese and colleagues [14] have previously indicated that quantitative gait measures may predict future risk of cognitive decline and dementia in non-demented older adults without PD. More recently, a longitudinal population-based study in elderly subjects without PD concluded that a slow gait speed precedes cognitive decline, whereas baseline cognition is not associated with later changes in gait speed [15]. On the other hand, some studies have reported that cognition could predict gait changes in older adults (for a review, see [16]). Very recently Rochester at al. [17] have found that low cerebrospinal fluid β-amyloid 1-42 predicts future decline in gait characteristics. These complex and biunivocal relationships open the issue of reverse causality -the reversion between cause and effect- between gait and cognition suggesting again their complex and not disentangled relationship.
To date, only one study has longitudinally evaluated the interplay between quantitative gait parameters and cognition in patients with PD and has found that gait is more sensitive than cognition in predicting decline in specific cognitive domain in early PD [18]. These findings support the idea that gait impairment antedates cognitive dysfunction in PD. As a consequence, gait may represent a reliable, low-cost, noninvasive surrogate biomarker of cognitive decline [6,15].

There is robust evidence [7] that gait changes during the performance of another task (dual task), particularly a highly demanding task, strongly support the hypothesis that shared higher-order neural networks are involved in the simultaneous performance of 2 tasks. This is the rationale why dual task procedures are widely used to demonstrate a strong interaction between gait and cognition. Due to the direct relationship between the grade of cognitive impairment and the magnitude of gait deterioration during the performance of a concurrent task, walking under dual task is more sensitive than simple gait to cognitive decline.

The aim of the present prospective study of a PD cohort is to investigate whether the dysfunction of specific gait parameters -during specific dual tasks and medication conditions- may predict subsequent cognitive impairment. To this aim, we first characterize the progression of gait and cognition separately, in order to generate the prerequisite for the subsequent speculative approach on the temporal relationship between them.

**Patients and Methods**

**Study design and population**

This is a 3-year prospective study. The study population consisted of 43 PD patients referred to the Movement Disorders Unit of the Institute for Diagnosis and Care Hermitage-Capodimonte of Naples, Italy. At the initial evaluation, all patients fulfilled the diagnostic criteria for PD established by the United Kingdom Parkinson’s Disease Society Brain Bank [19]. No patient had been reconsidered for a diagnosis other than PD during the 36-month interval between the two evaluations. The inclusion and exclusion criteria of the original cohort are described elsewhere [12]. Briefly, at the initial assessment, the inclusion criteria were as follows: 1) age 45 years or older; 2) Hoehn & Yahr (H&Y) score ≤3; 3) disease duration <10 years; and 4) antiparkinsonian treatment at a stable dosage during the previous 4 weeks. The exclusion criteria were as follows: 1) dementia according to the clinical diagnostic criteria for Parkinson’s disease dementia [20]; 2)
clinically significant comorbidities, including other neurologic disorders, orthopedic diseases, or cardiovascular/respiratory diseases; 3) major depression according to the DSM-IV criteria for current major depression; 4) anticholinergic or neuroleptic treatment; or 5) brain surgery. The local Ethics Committee approved the study, which was performed in accordance with the Declaration of Helsinki.

**Clinical and cognitive evaluations**

All subjects were evaluated, both initially and after three years, using a detailed assessment that included demographic, clinical and anthropometric data as previously described [12]. In addition, they completed the Mini Mental State Examination (MMSE) and an extensive neuropsychological battery comprising the following tests: (1) the Rey auditory 15-word learning test, immediate recall and delayed recall [21] for the episodic memory domain; (2) the Frontal Assessment Battery [22], Stroop color-word test [23], Phonological verbal fluency [21], and Ten Point Clock test [24] for the executive/attention domain; and (3) the Spatial (Corsi’s block tapping) span [25], Constructional apraxia test [25], and Raven’s 47 Progressive Matrices [21] for the visuospatial domain. The test scores were corrected for current normative values. All neuropsychological tests were administered to the patients during the pharmacological on state, according to the Movement Disorders Society Task Force guidelines [26].

**Gait analysis procedures**

Both at the initial and follow up evaluation, gait was assessed with an opto-kinematic system (Qualisys®, Sandvålen, Sweden) equipped with a set of 6 infrared cameras, a ProReflex Motion Capture Unit (MCU, CCD technology, 240 Hz sampling rate) and dedicated data acquisition software (Qualisys Track Manager®, QTM).

Given that there are no consistent findings on which dual task is more sensitive to cognitive decline, we employed two common dual task procedures that require the involvement of different cognitive networks. In particular, the motor dual task (walking while carrying a tray with two glasses filled with water) is primarily mediated by the fronto-parietal networks, whereas the cognitive dual task (walking while serially subtracting 7s starting from 100) is predominantly mediated by the frontal working memory networks. In addition, in the present study, the
evaluation of gait was performed both with and without dopaminergic medication to better assess
the progression and the relationship of symptoms, such as gait and cognition, that are increasingly
underpinned by non-dopaminergic components over time. Based on the previously described
rationale, patients’ gait was assessed in both off and on states and during three experimental
conditions (each performed twice): 1) normal gait (normal walking, Gait-off and Gait-on); 2) motor
dual task (Mot-off and Mot-on); and 3) cognitive dual task (Cog-off and Cog-on). Prior to each trial,
all participants were instructed to walk at their normal pace, at their usual speed and were not
provided with specific instructions regarding prioritization (walking or task) during the dual task
conditions. Any freezing of gait episodes recording was excluded from the analysis, due to the high
interference of this phenomenon on gait variables. Furthermore, for each subject, we have
excluded from the analysis both the turning and the approaching to the end recordings in order to
analyze only the straightway walking. The straight trajectory was 8 meters performed twice for
each condition; thus, there were 16 meters per condition. Further details regarding the gait
analysis, medication condition and walking parameters have been extensively described elsewhere
[12]. Based on their significant association with cognition [12], specific gait parameters were
included in the present study: the normalized step length (step length x 100/body height), swing
time, single/double support ratio, normalized velocity (gait velocity x 100/body height) and step
length variability.

Statistical analysis
Because the distribution of variables could not be assumed to be approximately normal, clinical
data, cognitive test scores and gait variables at the initial assessment and the follow up
appointment were compared using non-parametric tests, namely, the Wilcoxon test. Similarly, the
Wilcoxon test was used to evaluate the levodopa responsiveness by comparing the gait parameter
variation from the off to on state at both the initial and follow up evaluations.
In order to quantify patients performance on each cognitive domain, cognitive tests scores were
first transformed into z-scores according to published methods [27]; then, performance on each
cognitive domain for each subject was expressed as a composite score obtained by averaging the
standardized scores of the tests that loaded on the specific cognitive domain (i.e., memory,
executive/attention, or visuospatial).
A cognitive domain was considered impaired if its composite score was at least 1.5 standard deviations below the expected age and education-corrected mean z score of the specific cognitive domain [27].

To assess the gait capacity at the initial evaluation to predict cognitive decline at the follow up assessment, logistic regression procedures were performed; cognitive decline at follow up (impaired/unimpaired) was set as the dependent variable, and gait parameters at the first evaluation were set as predictors; in addition, to explore whether initial gait was able to predict independently later cognitive decline, we entered in the adjusted models also cognitive performance at the initial assessment. Given the high number of gait variables, a preliminary exploratory non-parametric correlation analysis (Spearman) was performed to assess the associations between gait variables at the initial evaluation and cognitive measures at follow up [28]; only gait variables that attained a significant correlation (p<0.05) with cognitive measures were included in the subsequent logistic regression analyses, which included three models: 1) Partial (each significant gait variable entered separately in the model); 2) Partially adjusted (each significant gait variable, controlled for age, disease duration and cognitive performance at the initial evaluation, entered separately in the model); and 3) Fully adjusted (all significant gait variables, controlled for age, disease duration and cognitive performance at the initial evaluation, entered in a stepwise forward model with selection criterion: p<0.10).

Finally, where applicable, to determine the best cutoff value of a significant gait variable at the initial evaluation in the prediction of cognitive outcome at follow up, Receiver Operating Characteristic (ROC) curves were used, and the coordinates of the curves were visually inspected to identify cut points with the best sensitivity and specificity, presented here as percentages (%).

Independent variables included in the logistic regression analyses were tested for multicollinearity. The multicollinearity diagnostics (VIF) were all less than 5, indicating an assumption of reasonable independence among variables. Significance was set at p=0.05. Computation was supported by the Statistical Package for the Social Sciences (SPSS 16.0) and Stata MP 14.1.

Results

Clinical and cognitive progression evaluation

Of the 43 subjects enrolled at the initial evaluation, 39 subjects were re-evaluated at the 36-month
follow up. A flow diagram of the study with the cognitive category of patients (normal cognition, MCI and dementia) is presented in Fig 1.

When the clinical features at the initial and follow up evaluations were compared, the PD patients exhibited significant worsening on the H&Y stage, Gait-Questionnaire and UPDRS part I, II, III during off (Table 1). The comparison of the cognitive tests scores and z-scores indicated a significant worsening over time on the executive/attention domain, whereas there was no significant change in the memory or visuospatial domains (Table 2).

**Progression of gait impairment**

When the gait measures at the initial and follow up evaluations were compared, the PD patients exhibited a significant worsening of all gait parameters during each condition during both the off and on states (i.e., Gait-off, Gait-on, Mot-off, Mot-on, Cog-off, and Cog-on) with the only exception of the step length variability during the Mot-off condition. In particular, the PD patients displayed a reduction in the normalized step length, swing time, single/double support ratio and normalized velocity, whereas the step length variability was increased (Fig 2).

**Levodopa responsiveness of gait variables over time**

At the initial evaluation, the PD patients exhibited a significant response to levodopa in all gait variables during each condition (i.e., normal gait, motor and cognitive tasks) with the exception of the step length variability (Fig 3). In particular, levodopa significantly increased the normalized step length, swing time, single/double support ratio and normalized velocity, whereas it did not decrease the step length variability. At the follow up assessment, the PD patients retained a significant response to levodopa on all gait variables in each study condition again with the exception of the step length variability (Fig 3).

**Gait at the initial evaluation as a predictor of subsequent cognitive decline**

An exploratory Spearman’s rank correlation analysis was conducted among the executive/attention domain z-scores at follow up (the only cognitive domain that declined over time) and all gait parameters at the initial evaluation. Exploratory univariate analyses indicated weak but significant positive correlations between the executive-attention domain z-scores at...
follow up and the following gait parameters at the initial evaluation: normalized velocity Gait-off, normalized step length Gait-on, normalized velocity and single/double support Cog-off normalized step length Cog-on (see Supplementary data).

We conducted logistic regression models setting executive/attention domain dysfunction at follow up as the dependent variable and the previously described gait parameters as predictors. The logistic regression models indicated that the normalized step length Cog-on at the initial evaluation was the only significant determinant of executive/attention domain dysfunction at the follow up assessment, even after entering executive/attention domain dysfunction at the initial assessment as a categorical covariate and age and disease duration as continuous covariates (Table 3). The Hosmer-Lemeshow goodness-of-fit test supported the validity of the model.

A ROC analysis was performed to identify the best cutoff value of the normalized step length Cog-on at the initial evaluation in the prediction of subsequent executive dysfunction. The analysis was significant (p=0.0044), and the area under the curve (AUC) was 0.743. According to the ROC analysis, the best cut-off value of the normalized step length Cog-on at the initial assessment in the prediction of executive/attention decline at follow up was ≤0.305 meters, which demonstrated good sensitivity (>83%) and weak specificity (58%).

**Discussion**

To our knowledge, this investigation represents the first prospective gait analysis study exploring the chronological interplay between gait during different medication conditions and cognitive dysfunction in patients with PD.

Here, we show that the reduction of step length under a cognitive dual task during the on state at the initial evaluation may predict later executive dysfunction in PD. In addition, this is the first study to assess the progression of gait component dysfunction in PD patients and their response to levodopa over time by directly comparing the on and off states. In this respect, we determined that the levodopa responsiveness of all examined gait parameters, with the exception of the step length variability, remained significant over time.

*Progression of PD: clinical evaluation, gait analysis and cognitive assessment*
Consistent with the natural progression of PD, all disease clinical measures (H&Y, Gait-Questionnaire and UPDRS) significantly worsened over time, with the exception of the UPDRS part III during the on state, in agreement with a recent longitudinal study [29]. In contrast, the comparison between the initial and follow up evaluations indicated that all gait parameters, in single and dual tasks and off and on states, significantly worsened over time. In particular, the PD patients exhibited a reduction in the spatio-temporal gait variables (step length, swing time, single/double time support ratio and velocity) and an increase in the step length variability. Taken together, these results may reflect two aspects that are not mutually exclusive: 1) UPDRS represents a gross measure of motor progression, which is predominately based on the assessment of appendicular symptoms, and tends to underrate axial symptoms; 2) a quantitative motion analysis is undoubtedly a more reliable tool than a clinical examination and is able to capture a wide spectrum of subclinical changes. In addition, these initial results support the common notion that appendicular symptoms tend to maintain a better response to levodopa compared with gait, which appears to deteriorate over time even under levodopa, as indicated by the direct comparison of gait variables between the initial and follow up evaluations during the on states (Fig 2).

In partial disagreement with our gait analysis results, a recent longitudinal study regarding early PD patients [30] indicated that gait variables remain stable over time with the exception of the step length and swing time. Nevertheless, the different follow up periods (36 months in our study vs. 18 months [30]) and the different mean disease durations of the enrolled patients (5.3 years in our study vs. 6.3 months [30]) may account for these differences.

Regarding the progression of cognitive impairment, overall cognitive performance declines with PD progression [31,32]. In our population, only executive dysfunction progressed during the 3-year interval between the first evaluation and the follow-up evaluation, whereas memory and visuospatial skills remained relatively stable. Few studies have evaluated cognition over time in PD patients and have reported discrepant results. Two longitudinal studies conducted on mid stage PD patients [33,34] indicated a clear decline in most cognitive domains, whereas recent studies [35-37] suggest that cognitive dysfunction may be stable or even revert to a normal cognition during early-mid stage PD. Potential explanations for these discrepancies include methodological differences among the studies (i.e., the choice and number of neuropsychological tests employed...
to measure cognitive functioning and the cutoffs used to define impairment [38], fluctuating
disease-related or unrelated comorbidities and learning effects as a result of repeated
neuropsychological testing.

**Levodopa responsiveness of gait parameters over time**

Previous studies have targeted gait parameter responses to levodopa in a cross-sectional fashion
[39,40]. Here, we longitudinally evaluated the effect of levodopa on walking features and showed
that the levodopa responsiveness of all examined spatio-temporal gait parameters remains stable
over time (Fig 3); however, these parameters significantly worsen when comparing the on states
between the initial and follow up assessments (Fig 2). Taken together, these findings support the
hypothesis that gait worsening in PD is underpinned by the progressive involvement of non-
dopaminergic networks [41,42]. Consistent with a recent gait analysis longitudinal study [30], we
show that spatial features of gait continue to respond to dopaminergic treatment, and in contrast,
we determined that temporal features also continue to respond. This discrepancy may be a result
of the differences in the methodology, which also encompass the way the levodopa response was
investigated. We directly compared gait parameters against time and pharmacological conditions,
whereas Galna and collaborators performed an indirect inference based on correlations between
the improvement of gait and the increase in the levodopa equivalent daily dose.

Finally, in agreement with several previous studies [30,43] and in contrast with other studies
[39,44,45], we determined that the gait variability (specifically, the step length variability)
responds less to levodopa, potentially because this gait parameter may be predominately
underpinned by the functioning of non-dopaminergic networks.

**Temporal interplay between gait and cognition in PD**

The regression models indicated that gait at the initial evaluation predicts cognitive dysfunction,
which thus supports the role of gait as a surrogate biomarker of cognitive impairment in PD
[6,18,46,47]. In particular, we determined that reduced normalized step length Cog-on at the first
assessment predicts executive dysfunction at follow up even in the latter statistical model
including the initial cognitive performance, suggesting an important role of this gait variable in
predicting executive cognitive decline. The predictive ability of this gait parameter on executive
dysfunction is further corroborated by its peculiar characteristics, namely, the concurrent task and the pharmacological state. In fact, a cognitive dual task is widely considered a proxy measure of frontal cognitive reserve [7]; furthermore, a suboptimal performance during the on state may indicate more non-dopaminergic network dysfunction in patients who subsequently develop executive decline compared with patients who are cognitively stable over time. Taken together, these findings suggest a double clue regarding the progression of executive dysfunction: 1) it would be predated by reduced frontal reserve that, if compensated during a single task, collapses under a challenging competition, such as the dual-task that so could represent a sensitizing tool; and 2) it would be, at least in part, underpinned by non-dopaminergic network dysfunction from the beginning of the pathological process.

The ROC analysis confirmed the potential predictive value of the normalized step length Cog-on at the initial evaluation on subsequent executive dysfunction, with good sensitivity and weak specificity for a cut-off of ≤0.305 meters. It is worth noting that our findings can tell nothing about causal mechanisms but they only support the notion that gait and cognition share neurochemical and pathological mechanisms that can express themselves in different symptoms, at different times of the disease course: from this perspective, one symptom, namely reduced step length Cog-on, would represent a predictor for the future development of the other one, that is executive dysfunction. Further studies with larger samples and longer follow ups are mandatory to better explore the diagnostic accuracy of this gait parameter. A very recent longitudinal study on early PD [18] has demonstrated that slower pace, higher gait variability and more unstable postural control may predict decline on fluctuating attention but not on executive function; in addition Morris and colleagues failed to find a sensitizing role for dual task. These discrepancies could be due to the different disease stage their cohort compared with ours (early vs mid stage), the different cognitive and gait protocol including the adoption of a defined-on in our study that possibly allows to better unmask true dopa-resistant gait characteristics.

Our study has some limitations. First, the absence of progression in a cognitive domain other than executive/attention didn’t allow us to investigate the ability of gait to predict dysfunction on more posterior cognitive domains, and longer follow up times are likely necessary to assess this issue. Second, we incorporated attention and executive function in a unique domain, and we didn’t assess language. Third, we acknowledge that because our cohort is composed of patients in
early/middle stages, some patients had mild cognitive decline at the initial assessment; nevertheless, the purpose of the present study was to identify potential motor markers of subsequent cognitive decline over time. We admit that a longitudinal study on newly diagnosed PD patients would be ideal to identify early markers of subsequent cognitive dysfunction. Finally, as a result of a regression model on a small sample size, although supported by other statistical tests (i.e. The Hosmer-Lemeshow test and the ROC curve analysis), the conclusions should be considered preliminary and should be confirmed with larger samples.

In conclusion, our longitudinal study offers additional insight into the progression of gait dysfunction, its response to dopaminergic treatment over time and, more importantly, its chronological relationship with cognitive dysfunction in PD patients. Here, we confirm that a quantitative gait analysis represents a sensitive tool to longitudinally monitor gait worsening; we show that levodopa responsiveness of gait variables continues to be significant over time, being the increase in the non-dopaminergic components responsible for the common label “levodopa resistant” applied to gait. Finally, we show that gait, particularly step length during a cognitive task on medication, predicts subsequent executive/attention dysfunction.

Full Financial Disclosures of all Authors:

MA, LI, AI, AF, RP, RR, MP, IL, PV, CV, MC, and GS have no financial disclosures to report; PB reports personal fees from Acorda, Union Chimique Belge, Zambon, grants from Abbvie, Biotie, and Zambon.

On behalf of all Authors, the corresponding author states that there is no conflict of interest.
REFERENCES


Figures legends:

**Figure 1.** Flow diagram of the patients enrolled at initial evaluation, lost and re-assessed at follow up.
MCI-, PD patients without mild cognitive impairment; MCI+, PD patients with mild cognitive impairment; PDD, PD patients with dementia.

**Figure 2.** Comparison analysis of PD patients at the initial and follow up evaluation on normalized step length, swing time, single/double support time ratio, velocity and step length variability. Gait, normal gait; Cog, cognitive dual task; Mot, motor dual task; off, in off state; on, in on state; ns, not significant; *P < .05; **P < .01; ***P < .001, ****P<.0001

**Figure 3.** Levodopa responsiveness of PD patients at the initial and follow up evaluation on normalized step length, swing time, single/double support time ratio, velocity and step length variability. Gait, normal gait; Cog, cognitive dual task; Mot, motor dual task; off, in off state; on, in on state; ns, not significant; *P < .05; **P < .01; ***P < .001, ****P<.0001
Assessed at the first evaluation (n=43)  
(24 MCI- and 19 MCI+)

Excluded (n=4)  
(1 MCI-, 3 MCI+)
- Two moved to another city  
- Two could not be contacted

Assessed at the 3-year follow up evaluation  
(n=39)

Analyzed (n=39)  
(19 MCI-, 18 MCI+, 2 PDD)
Figure 3: Graphs showing changes in various gait parameters with and without intervention.

- **Step length**
- **Swing phase**
- **Single/Double support ratio**
- **Velocity**
- **Step length variability**

Each graph compares data before (Initial Assessment) and after (Follow-up) intervention, with and without intervention (OFF/OFF, ON/ON). Statistical significance is indicated by asterisks (*) and ns (not significant).
Table 1. Demographic and clinical features of PD patients at initial evaluation and follow up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (mean± SD)</th>
<th>Follow up (mean±SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.28±6.7</td>
<td>67.25±6.6</td>
<td>NA</td>
</tr>
<tr>
<td>Gender (f/m)</td>
<td>8/31</td>
<td>8/31</td>
<td>NA</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.3±2.8</td>
<td>8.2±2.7</td>
<td>NA</td>
</tr>
<tr>
<td>H&amp;Y off</td>
<td>2.20±0.5</td>
<td>2.64±0.8</td>
<td>0.001</td>
</tr>
<tr>
<td>H&amp;Y on</td>
<td>1.64±0.4</td>
<td>2.18±0.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gait-Q</td>
<td>10.02±10.2</td>
<td>13.59±12.5</td>
<td>0.006</td>
</tr>
<tr>
<td>FOG-Q</td>
<td>6.28±5.9</td>
<td>7.69±6.5</td>
<td>0.06</td>
</tr>
<tr>
<td>UPDRS I</td>
<td>1.79±1.2</td>
<td>2.89±1.74</td>
<td>0.0001</td>
</tr>
<tr>
<td>UPDRS II</td>
<td>7.40±4.6</td>
<td>13.59±6.40</td>
<td>0.0001</td>
</tr>
<tr>
<td>UPDRS III off</td>
<td>23.00±6.4</td>
<td>25.61±7.94</td>
<td>0.009</td>
</tr>
<tr>
<td>UPDRS III on</td>
<td>11.10±4.7</td>
<td>12.23±5.99</td>
<td>NS</td>
</tr>
<tr>
<td>BDI</td>
<td>9.74±5.8</td>
<td>11.44±9.4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>26.67±4.36</td>
<td>26.50±4.19</td>
<td>NS</td>
</tr>
</tbody>
</table>

NA, not applicable; H&Y, Hoehn and Yahr; Gait-Q, Gait-questionnaire; FOG-Q, Freezing of gait-questionnaire; UPDRS, Unified Parkinson Disease Rating Scale; BDI, Beck Depression Inventory; BMI, Body Mass Index; NS, not significant
Table 2. Cognitive assessment of PD patients at initial evaluation and follow up

<table>
<thead>
<tr>
<th>Cognitive tests scores</th>
<th>Baseline (mean± SD)</th>
<th>Follow up (mean±SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mini-Mental State Examination</strong>*</td>
<td>27.11±1.97</td>
<td>26.82±2.37</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Episodic memory domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey 15 words immediate recall</td>
<td>38,32±7,28</td>
<td>37,70±9,76</td>
<td>NS</td>
</tr>
<tr>
<td>Rey 15 words delayed recall</td>
<td>8,30±2,26</td>
<td>8,43±2,29</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Executive/attention domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phonemic fluency</td>
<td>33,30±10,10</td>
<td>31,63±11,52</td>
<td>NS</td>
</tr>
<tr>
<td>Frontal Assessment Battery</td>
<td>13,95±2,12</td>
<td>12,92±3,38</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroop (color/word table)</td>
<td>19,92±5,03</td>
<td>17,90±5,62</td>
<td>0.03</td>
</tr>
<tr>
<td>Ten Point Clock Test</td>
<td>5,80±3,41</td>
<td>6,12±3,60</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Visuospatial domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial span</td>
<td>4,49±0,82</td>
<td>4,53±0,9</td>
<td>NS</td>
</tr>
<tr>
<td>Constructive apraxia</td>
<td>10,91±1,28</td>
<td>10,80±2,41</td>
<td>NS</td>
</tr>
<tr>
<td>Raven's 47 Progressive Matrices</td>
<td>26,41±4,82</td>
<td>25,2±5,96</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Cognitive z-scores</strong>#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory z-score</td>
<td>-0.37261 ± 0.68773</td>
<td>-0.21267 ± 0.813573</td>
<td>NS</td>
</tr>
<tr>
<td>Executive/attention z-score</td>
<td>-0.46290 ± 0.65960</td>
<td>-0.809244 ± 1.07810</td>
<td>0.01</td>
</tr>
<tr>
<td>Visuospatial z-score</td>
<td>-0.88398 ± 0.83937</td>
<td>-0.72378 ± 1.14423</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Screening evaluation
\# Based on the extensive cognitive evaluation
NS, not significant
Table 3. Regression models exploring association between gait variables at initial assessment and executive dysfunction at follow up

<table>
<thead>
<tr>
<th></th>
<th>Velocity Gait-off</th>
<th>Step length Gait-on</th>
<th>Velocity Cog-off</th>
<th>Single/double support Cog-off</th>
<th>Step length Cog-on</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b (SE)</td>
<td>p</td>
<td>b (SE)</td>
<td>p</td>
<td>b (SE)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Partial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive Dysfunction</td>
<td>5.75 (4.68)</td>
<td>0.21</td>
<td>20.18 (10.89)</td>
<td>0.06</td>
<td>6.84 (4.12)</td>
</tr>
<tr>
<td>at follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Partially Adjusted)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Executive Dysfunction</td>
<td>4.84 (5.16)</td>
<td>0.34</td>
<td>19.68 (11.62)</td>
<td>0.09</td>
<td>5.22 (4.47)</td>
</tr>
<tr>
<td>at follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3*</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(Fully Adjusted)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Executive Dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at follow up</td>
<td>23.41 (10.18)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Forward Stepwise
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