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An ambulatory persistence power curve: Motor planning affects ambulatory persistence in Parkinson's disease

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ABSTRACT

Background/objectives: When performing activity associated with walking, the amount of walking a person does often will depend on their plans. This study was designed to evaluate the relationship between motor planning and ambulatory persistence in participants with Parkinson's disease (PD) and to see if ambulatory persistence was related to the ability to perform activities of daily living (ADL). *Methods*: 20 individuals with idiopathic PD were recruited to perform the Trail making Test (a test of motor planning) and to wear a step activity monitor for 48 h. The measurement of persistence of an ambulatory event consisted of the number of steps taken during an event and an ambulatory event was defined as continuous ambulation (taking step) without pausing for 3 or more seconds. The resumption of taking step (ambulation) after 3 or more seconds counted as a new ambulatory event. UPDRS-motor and ADL scale were also obtained. *Analysis and results*: The cumulative percentage of the total ambulatory events at each number of steps was plotted for each subject which when plotted could be described as a sigmoid curve. We found that this sigmoidal curve defined by the equation $y = x^n/(k^n + x^n)$, fit the data well, where k represents a constant specific to each subject, x represents the number of steps during each ambulatory event, and y represents the projected percentage of movement events containing x number of steps or less. (Root Mean Square Error (RMSE) = 0.02, $R^2 = 0.98$). Trail making test part A was highly associated with the constant k ($R = -0.74$, $p < 0.001$). The constant k was also highly associated with the UPDRS ADL subscale ($R = -0.81$, $p = 0.0001$). A forward bivariate regression model including Part A of the Trail making test, and the UPDRS-ADL subscale predicted 66% of the variability of the constant k. The overall number of steps taken per day, and the UPDRS motor subscale did not contribute to the model. *Conclusions*: Defective motor planning in Parkinson's disease as measured by poor performance on a Trail making test is associated with a measurable alteration in ambulatory persistence, and altered ambulatory persistence, quantified by our proposed model parameter, correlates highly with the UPDRS ADL score. Thus, cognitive-motor planning defects might be a major source of disability in PD. We suggest that in future clinical practice gait tests can be used in order to quantify short-term planning ability in neurodegenerative diseases.

Currently, many studies evaluating gait of individuals with medical or neurologic disorders intensively evaluate ambulatory activity over short periods of time. For example, multiple studies in Parkinson's disease (PD) evaluate kinetics and kinematics of gait over short periods during intensive external observation [1,17,21]. Subjects in these studies are given instruction on the protocol, and conditions of ambulation are rigidly defined. The presence of external observers and instructions would be expected to provide a high degree of motivation to the subjects to perform at peak effectiveness. This type of evaluation cannot characterize internally motivated and internally planned aspects of gait, nor is prolonged measurement of ambulation possible. In disorders with frontal dysfunction internal direction of behaviors may be impaired. For example, in PD multiple authors suggest that self-initiation of prospectively directed behaviors is impaired in PD even as capacity to react habitually or in response to direction is unimpaired

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[4,8,22]. In this context, capacity to produce ambulatory behaviors in a highly motivating laboratory environment under direct observation is likely to be different from ambulation in a non-directed fashion at home, which might be more influenced by motor planning and capacity to internally generate behavior. To study internally generated aspects of gait, we focused on the length of time that individuals with PD ambulated before pausing (ambulatory train length) as a measure of goal directed behavior in our sample.

We studied the relationship between disease severity, cognition (particularly motor planning [1] and executive function), and ambulatory train length in our sample. PD is a slowly progressive neurologic disease that may impact gait on a number of levels, including alterations in capacity to ambulate related to rigidity, bradykinesia, or balance defects [23,24] related to the progressive dopaminergic deficit, and we hypothesized that these might influence ambulatory train length in our sample. Secondly, ambulatory train length might be related to cognitive and executive function. For example, individuals with PD have defects in motor planning and programming [10,13,18].

We used the Trail making test as a method to measure visual processing, motor planning, and other cognitive factors that might impact overground "trail making" in our sample. In the Trail making test, individuals must develop a strategy to move a pen as rapidly as possible to move from one target to another. The goal is to completely connect all targets as rapidly as possible. The score of the subject is the time (in seconds) needed to accomplish the test (so high number in scoring scale indicates poor performance). In Trail making test part A, individuals sequentially connect numbers (1–26) on a page, while in Trail making test part B, individuals must sequentially connect a series of numbers and letters (e.g. 1-A-2-B-3-C) and complete the same task. While Trail making test part A is felt to put a stronger focus on processing speed, visual tracking, and motor planning, Trail making test part B has been more strongly associated with higher level executive function including set shifting and cognitive flexibility [9,11,19,25]. We posited that individuals with poor performance on the Trail making test would similarly have poor performance with over ground "trail making", and would display a higher proportion of short ambulatory trains (few steps). As bradykinesia, rigidity, or gait disturbance might also affect the size and duration of ambulatory events, we also evaluated the relationship of disease severity (using the four elements of the Unified PD Rating Scale) on ambulatory train length.

To measure gait function in this study, we used microprocessor-linked step activity monitor. The CYMA step activity monitor (SAM) is able to measure and record whether one or more steps have occurred during a 3-s time period. Capacity of SAM to accurately measure steps has been shown in a number of studies that assessed patients with neurological diseases [2,3,14], including stroke [6,14,20]. Muscular dystrophy [15], and multiple sclerosis [16].

The purpose of our analysis was to extract characteristic features from gait data that would be able to describe sufficiently better than the UPDRS test the short-term motor planning and associate it with the quality of life of the patients, quantified by the ADL test.

Twenty individuals meeting the Brain Bank criteria [7] for idiopathic PD were randomly selected either by direct referral by a movement disorders neurologist or by selection from an IRB approved database of participants with PD who were interested in participating in clinical research. All subjects were assessed with the Mini-Mental Status and were excluded if they scored below 27. We also excluded individuals with significant orthopedic, cardiac, or pulmonary disease. All subjects were recruited from the University of Florida Movement Disorders Center or the affiliated North Florida/South Georgia VA Medical Center, and informed consent was obtained from all subjects. Demographics of the participants are displayed in Table 1.

Table 1
Demographics of sample.

Category	Value (±S.D.)
Age (Mean ± S.D.)	71 ± 11
Gender (M/F)	10/6
Disease specific measures	
Disease duration (years)	7.0 (±4.2)
UPDRS	
Total	49 (±21)
Mentation, behavior and mood (I)	3 (±3)
Activities of daily living (II)	13 (±7)
Motor examination (III)	29 (±11)
Complications of therapy (IV)	3 (±4)
Trail making test	
Trail making test part A	57 (±30)
Trail making test part B	188 (±143)

Sixteen of 20 recruited subjects were able to participate in the full evaluation, including home activity monitoring. Four subjects were excluded due to error (2 subjects) or unsuspected dementia (2 subjects). The placement of the SAM and performance of the Trail making Test, Parts A and B, were performed during a home visit. The calibrated step monitor was mounted just over the right lateral malleolus. To calibrate SAM we had each participant walk 30 feet. The time and number of steps required to walk this distance was recorded. The monitors were then read and re-calibrated until they were shown to record steps with an accuracy of at least 95%. Participants were instructed to wear the SAM for 2 days. The monitor was only removed during bathing and during sleep.

SAM is able to capture free-living ambulatory movements throughout the day in 3 s blocks. Approximately 28,800 data points (3 s blocks) were therefore available for analysis for each subject each day. A movement event was defined as a period, during the day, during which at least one-step occurred. Absence of step for >3 s defined the start of a new movement event. For example, for a segment of SAM data output of [0010121001010], where each "bit" represents the number of steps counted in a 3-s period, we would identify 4 movements segments, 3 involving 1 step and 1 involving 4 steps. Movement segments were arrayed by step number in such a way as to show the cumulative percentage of the total number of movement segments (Fig. 1).

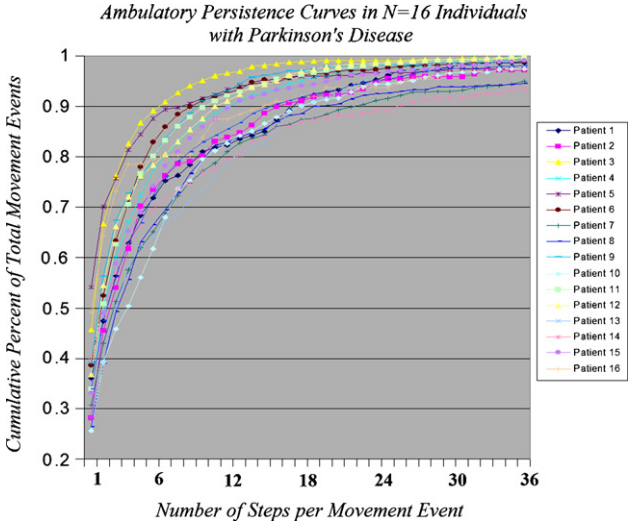

Fig. 1. Ambulatory persistence curves in $N = 16$ individuals with Parkinson's disease.

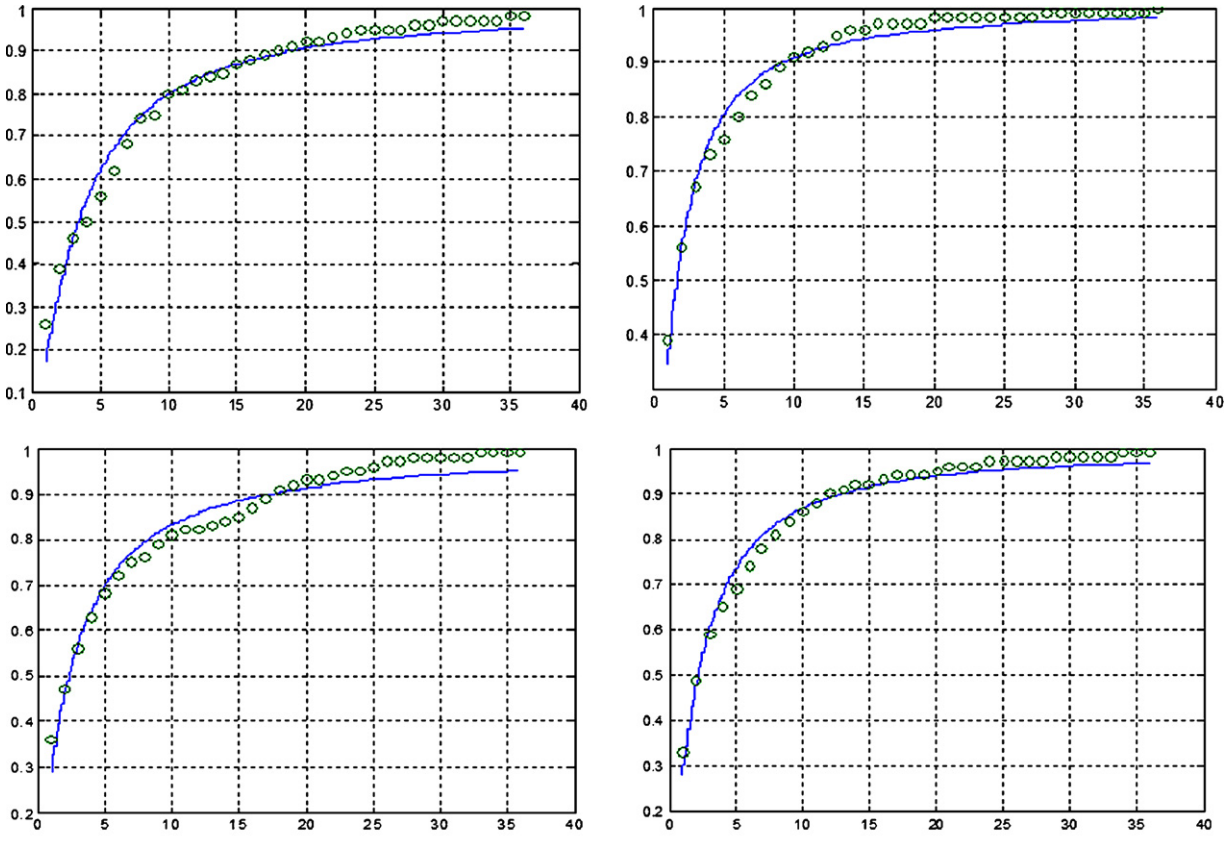

Fig. 2. Curve fitting of sigmoidal curve to the data of 4 representative subjects. A sigmoidal curve with formula $x^n/(k^n + x^n)$ fit the data for all subjects. Green circles represent actual subject behavior, while the blue plotted curve represents the sigmoidal power curve showing the predicted relationship between the percentage of movement events with a particular step number compared to the total number of movement events during the day. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Visual inspection demonstrated that each subject's plot defined an individual curve. We evaluated a number of curves to model the data, however only a sigmoidal curve fit the assumptions of the model, which required the curve to reach a theoretical maximum (in this case at 100% of ambulatory events). Curve fitting for a variety of curves was performed using MatLab, showing that a sigmoidal curve with the formula:

$$y = \frac{x^n}{k^n + x^n}$$

provided the best fit for the data (Root Mean Square Error (RMSE) = 0.02, $R^2 = 0.98$). The influence of the exponent on the curve fitting was minimal, and the simplified formula $y = x/(k + x)$ also fit the data well (RMSE = 0.03, $R^2 = 0.95$). In these curves, the constant "k" defined the point for each subject along the x-axis of the curve where y is at 50% of the maximum value, while the variable "x" represented the number of steps taken prior to pausing, while "y" represents the projected cumulative percentage of ambulatory events with "x" number of steps or less. An example of the fit of the curve for four representative subjects (labeled subject A through D) is presented in Fig. 2, showing actual subject behavior and predicted fitted curve.

The primary outcome variable was the relationship between the executive function of motor planning, as measured by Trail making test A and B, and the constant k. As the constant k represents the point on the curve at which 50% of movement events contained the number of steps or less, the constant k is a measure of the subject's ambulatory persistence. We predicted that performance on the Trail making test as a measure of motor planning would be statistically related to the constant k. We performed a bivariate regression to evaluate if other factors related to disease severity as measured by the UPDRS would contribute to prediction of variability of k. Elements of the UPDRS included in our bivariate model included UPDRS subscale I (patient interview generated mentation and mood subscale), subscale II (patient interview generated activities of daily living subscale), subscale III (clinical neurological exam generated motor subscale), and subscale IV (patient interview derived motor complications of therapy subscale). The Unified PD Rating Scale is a highly validated measure of clinical severity in PD. Significance was set at $p < 0.05$. The Total steps taken per day were also recorded, to evaluate the relationship in this sample between movement process and total number of steps taken. These variables are displayed in Table 2.

The participants' demographics as well as their performance on the UPDRS and Trail making test are listed as noted in Table 1.

Performance on Trail making test part A was associated with constant k ($R = -0.74$, $R^2 = 0.55$, $p = 0.001$, see Fig. 3).

Table 2
Step activity monitoring.

Category	Value (±S.D.)
Categorical variable	
Sigmoidal constant *k*	2.07 (±0.7)
Overall functional mobility	
Total steps taken per day	4378 (±2057)

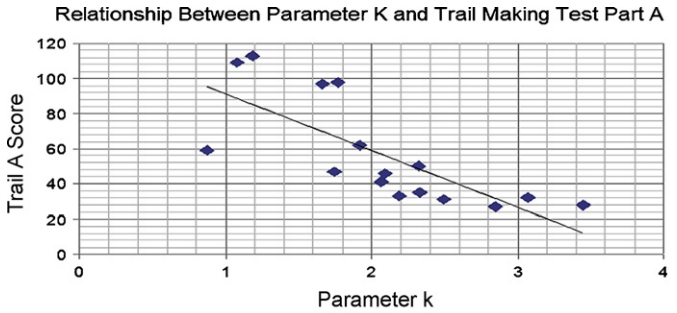

Fig. 3. Relationship between parameter *k* and Trail making test part A. Individuals who performed poorly on the Trail making test (indicating poor motor planning) were apt to have multiple ambulatory events involving fewer numbers of steps (reflected by a lower value for parameter *k*), while individuals with better performance on the Trail making test took on average more steps without pausing (reflected by a higher value for parameter *k*).

Table 3
Model of factors important in determination of ambulatory process in sample.

Variable	*R*	R^2	Significance
Trail making test part A (primary outcome)			
Constant *k*	−0.74	0.55	$p = 0.001$
Model, constant *k*: Trail making test A, UPDRS II	N/A	0.66	$p = 0.0004$

While significant, Trail making test part B was less associated with the constant *k* ($R = -0.62$, $p = 0.01$). Bivariate regression showed two factor model including Trail making test part A and the UPDRS ADL subscale, a historical subscale of disease severity, predicted 66% of the variability of the ambulatory persistence curve in the sample ($R^2 = 0.66$, $p = 0.0007$). The UDPRS motor score did not prove useful in a bivariate model including trail making performance in predicting *k* (Table 3).

The ambulatory persistence curve constant *k* is associated with several elements of the Unified PD Rating Scale (UPDRS). Table 4 shows the interaction of the constant *k* with disease severity in this sample.

Table 4
The interaction of ambulatory persistence constant and disease severity in PD.

Evaluation	Correlation, constant *k*
Age	−0.63
Disease duration	−0.53
Trail making test	
Part A	−0.74
Part B	−0.58
UPDRS	
Total	−0.84
Mentation behavior and mood (I)	−0.54
Activities of daily living (II)	−0.81
Motor examination (III)	−0.68
Complications of therapy (IV)	−0.61
Total ambulation (steps per day)	0.64

The addition of an exponent "*n*" in the ambulatory persistence curve improved the fit of the curve by a small but significant amount. An individual exponent in each subject (range 0.84–1.34) resulted in the best curve fitting. As the size of the exponent approached 1 in most subjects, the effect of the exponent in this model on the predicted values was negligible at lower step numbers, where the preponderance of the stepping behavior in this sample occurred. The exponent "*n*" was not associated with any of the outcome variables.

In this report, we have shown a relationship between a measure of ambulatory persistence and performance on the Trail making test in a sample of 16 individuals with PD. We specifically demonstrate that in this sample the constant *k* defined by the curve, a measure related to the mean number of steps taken per ambulatory event, is highly associated with performance on Trail making A. Notably, a clinician rated UPDRS motor subscale did not improve our capacity to predict *k*. Our result suggests that elements of motor performance or planning measured by Trail making test part A are more highly associated with motor persistence than disease severity as measured by the clinician-rated Unified PD Motor subscale. Several factors could account for this finding. First, Trail making test part A has been described by some authors as a test of motor planning [11]. This planning includes disengaging attention from the current location of their pen, searching the paper for future target locations, and planning actions that will move the pen to the subsequent targets. In this context, Trail making test part A more specifically tests motor planning than Trail making test part B, which also has elements of working memory, and tests capacity for set shifting (e.g. 1 to A to 2 to B to 3 to C, etc.) [9,11,19]. Trail making test part A is also thought to measure mental processing speed. Therefore, the increased "pausing" and shorter duration movement trains (lower "*k*") measured in our sample in individuals with poorer performance on Trail making test part A might be also reflective of bradyphrenia. Finally, motor speed influences the speed that individuals can move the pen from target to target. While all three factors influence performance on the task, the fact that the clinician rating of disease severity did not contribute to the model suggests that factors other than simple motor speed contribute to the increased frequency of pausing in individuals with higher Trail making test scores. Our results therefore suggest that some features of defining a "trail" on the Trail making test parallel processes necessary for defining an overground trail during ambulation. Conversely, higher order executive functions evaluated by Trail making test part B appear to be less important in determining this variable.

The performance of activities of daily living is one of the most important goal oriented behaviors performed by people and thus the finding that there was a significant relationship between gait persistence and UPDRS Activities of Daily Living scale (generated by interview of patient history) comes as no surprise. In a recent study, disease stage as defined by UPDRS and Hoehn and Yahr stage and medication accounted for only 17.3% of the variability of quality of life scores in individuals with PD, while mood and cognitive dysfunction are highly correlated with quality of life [5].

Although our sample included only individuals with PD and variable executive and motor functions, the excellent fit of the curve to ambulatory persistence, as well as the highly significant relationship between ambulatory persistence and the historically generated UPDRS Activities of Daily Living Scale, suggests the possibility that other disorders may display a similar relationship between ambulatory persistence and self-perceived or caregiver perceived function. In our sample, we excluded individuals with significant cardiac, pulmonary, or orthopedic disease, and we excluded patients with prior history of stroke. We therefore showed

that cognition and particularly the executive functions measured by the Trail making test correlates with activity patterns. However, it is likely that other medical conditions that do not necessarily impact cognition may also influence ambulatory persistence. In future clinical practice features extracted from gait data, as this proposed in the present paper, might turn out to be very useful for the accurate quantification of the planning ability in neurodegenerative diseases. Finally, based on the characteristics of the sensor, we were limited to evaluating stepping behavior in 3 s increments. Selection of different pause lengths as the "significant pause length" may alter the characteristics of the power curve. Larger studies, disease specific studies, and evaluations in control populations are needed to further evaluate the general relevance of our findings in this patient sample.

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References

[1] T.A. Buckley, C. Pitsikoulis, C.J. Hass, Dynamic postural stability during sit-to-walk transitions in Parkinson disease patients, Mov. Disord. 23 (9) (2008) 1274–1280.
[2] M.E. Busse, C.M. Wiles, R.M.W. van Deursen, Community walking activity in neurological disorders with leg weakness, J. Neurol. Neurosurg. Psychiatry 77 (2006) 359–362.
[3] K.L. Coleman, D.G. Smith, D.A. Boone, A.W. Joseph, M.A. Del Aguila, Step Activity Monitor: long-term continuous recording of ambulatory function, J. Rehabil. Res. Dev. 36 (1999) 8–18.
[4] L. Crevits, A. Vandierendonck, E. Stuyven, S. Verschaete, J. Wildenbeest, Effect of initiation and visual fixation disengagement on prosaccades in Parkinson's disease patients, Neuropsychologia 42 (2004) 624–632.
[5] Global Parkinson's Disease Survey Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov. Disord. 17 (2002) 60–67.
[6] E. Haeuber, M. Shaughnessy, L.W. Forrester, K.L. Coleman, R.F. Macko, Accelerometer monitoring of home- and community-based ambulatory activity after stroke, Arch. Phys. Med. Rehabil. 85 (2004) 1997–2001.
[7] A.J. Hughes, S.E. Daniel, L. Kilford, A.J. Lees, Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J. Neurol. Neurosurg. Psychiatry 55 (1992) 181–184.
[8] M. Kliegel, L.H. Philips, U. Lemke, U.A. Kopp, Planning and realisation of complex intentions in patients with Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 76 (2005) 1501–1505.
[9] K.B. Kortte, M.D. Horner, W.K. Windham, The trail making test. Part B. Cognitive flexibility or ability to maintain set? Appl. Neuropsychol. 9 (2002) 106–109.
[10] E. Labyt, D. Devos, J.-L. Bourriez, F. Cassim, A. Destée, J.-D. Guieu, L. Defebvre, P. Derambure, Motor preparation is more impaired in Parkinson's disease when sensorimotor integration is involved, Clin. Neurophysiol. 114 (12) (2003) 2423–2433.
[11] M.D. Lezak, D.B. Howieson, D.W. Loring, Neuropsychological Assessment, fourth ed., Oxford University Press, New York, 2004.
[13] C.D. Marsden, Which motor disorder in Parkinson's disease indicates the true motor function of the basal ganglia? Ciba Found Symp. 107 (1984) 225–241.
[14] M.F. Macko, E. Haeuber, M. Shaughnessy, K.L. Coleman, D.A. Boone, G.V. Smith, K.H. Silver, Microprocessor-based ambulatory activity monitoring in stroke patients, Med. Sci. Sports Exerc. 34 (2002) 394–399.
[15] C.M. McDonald, L.M. Widman, D.D. Walsh, S.A. Walsh, R.T. Abresch, Use of step activity monitoring for continuous physical activity assessment in boys with Duchenne Muscular Dystrophy, Arch. Phys. Med. Rehabil. 86 (2005) 802–808.
[16] O.R. Pearson, M.E. Busse, R.W.M. Van Deursen, C.M. Wiles, Quantification of walking mobility in neurological disorders, Q. J. Med. 97 (2004) 463–475.
[17] M. Plotnik, N. Giladi, J.M. Hausdorff, Bilateral coordination of walking and freezing of gait in Parkinson's disease, Eur. J. Neurosci. 27 (8) (2008 Apr) 1999–2006.
[18] M. Plotnik, F. Tamar, I. Rivka, S. Edna, D. Amos, Korczyn Motor switching abilities in Parkinson's disease and old age: temporal aspects, J. Neurol. Neurosurg. Psychiatry 65 (1998) 328–337.
[19] J.M. Schear, S.D. Sato, Effects of visual acuity and visual motor speed and dexterity on cognitive test performance, Arch. Clin. Neuropsychol. 4 (1989) 25–32.
[20] M. Shaughnessy, K.M. Michael, J.D. Sorkin, R.F. Macko, Steps after stroke: capturing ambulatory recovery, Stroke 36 (2005) 1305–1307.
[21] O. Sofuwa, A. Nieuwboer, K. Desloovere, A.M. Willems, F. Chavret, I. Jonkers, Quantitative gait analysis in Parkinson's disease: comparison with a healthy control group, Arch. Phys. Med. Rehabil. 86 (May (5)) (2005) 1007–1013.
[22] G. Vingerhoets, E. Vermeule, P. Santens, Impaired intentional content but spared incidental retention of contextual information in non-demented patients with Parkinson's disease, Neuropsychologia 43 (2005) 675–681.
[23] D. Weintraub, C.L. Comella, S. Horn, Parkinson's disease. Part 2. Treatment of motor symptoms, Am. J. Manag. Care. 14 (March (2 Suppl.)) (2008) S49–S58, Review.
[24] D. Weintraub, C.L. Comella, S. Horn, Parkinson's disease. Part 1. Pathophysiology, symptoms, burden, diagnosis, and assessment, Am. J. Manag. Care 14 (March (2 Suppl.)) (2008) S40–S48, Review.
[25] Z.K. Konstantine, R. Mraz, S.J. Grahamb, An fMRI study of the trail making test, Neuropsychologia 43 (2005) 1878–1886.