Effects of Mental Flexibility and Motor Dysfunction on Cognitive Performance in Patients With Parkinson's Disease

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Background: Parkinson's disease (PD) is a neurodegenerative disorder characterized by pervasive motor deficits, often accompanied by specific cognitive impairments, most prominently executive dysfunctions. However, it is often hard to determine whether the impaired performance of patients with PD on executive tests is the result of an executive dysfunction or whether it is due to motor difficulties.
Objectives: The present study aimed to examine the relationship between cognitive inflexibility, an executive dysfunction consistently found in PD, and motor deficiencies in patients with PD using derived scores, from a common executive function test named trail making test (TMT).
Patients and Methods: Fifty patients with PD and 50 demographically matched controls underwent neuropsychological examination which included TMT, part A and part B. Performance on each task was assessed and the following derived scores TMT B/A, TMT B-A/A, and TMT B-A were calculated and compared.
Results: Mann-Whitney tests revealed significant group differences for the mean TMT A (P = 0.006) and TMT B (P = 0.000), which were both higher in the PD group, relative to controls. In addition, significant differences were found for one TMT product score (TMT B-A).
Conclusions: The results presented a significantly lower performance of patients with PD compared to controls, indicating the presence of a mental flexibility impairment which is dissociable and independent from the motor dysfunction.

Keywords: Parkinson's Disease; Trail Making Test; Executive Function

1. Background

Parkinson's disease (PD) is a neurodegenerative disease manifested by loss of dopamine-secreting neurons in the substantia nigra (1), leading to a well-established lack of dopamine in the striatum, disrupting the basal ganglia circuit (2). As a result, a series of functional changes that mediate the cardinal motor features of the disease (3), namely tremor, rigidity, akinesia/bradykinesia and postural deformities may emerge (4, 5). However, PD is not only a complex motor disorder but rather a systemic disease with various nonmotor deficits and neurological symptoms such as autonomic dysfunction (6), sensory (7) and sleep abnormalities (8), hallucinations (9) as well as neurobehavioral and cognitive disorders (10-12). Several comprehensive reviews have reported on impaired cognitive domains, including executive functions, visuospatial ability, speed of mental processing, memory, and learning (10, 11, 13, 14). Among the most common cognitive deficits associated with PD are those related to executive functions (15-17) and impaired mental flexibility appears to be the most prominent one (15, 18-20). Mental flexibility refers to the ability to shift between different thoughts and actions or between different aspects of a stimulus according to changes in a situation, utilize feedback, generate concepts, and devise alternative problem-solving strategies (21, 22). However, given the coexistence, as well as the positive relationship noted between poor cognitive performance and motor deficiencies in PD (23), slowed performance in executive tests could be the result of a variety of factors such as executive dysfunction (17), slowness in any stage in planning, initiating or executing motor responses (24), or perceptual analysis of a stimulus (25).

2. Objectives

The objective of the current study was to investigate whether the impaired performance of PD patients on executive tests is due to motor dysfunction, or due to an executive cognitive impairment such as mental rigidity. For this purpose we used Trail Making Test (TMT) Part A and B (26), which present the same motor and visuoperceptual demands, namely drawing lines to connect randomly arranged circles, while part B additionally measures divided

attention and mental flexibility (21, 27, 28). Since part B differs from part A only in terms of mental flexibility/divided attention, derived scores such as differences, ratios or proportional scores can be used to isolate it. Indeed, previous studies have made use of TMT derived scores, such TMT B-A, B/A and (B-A)/A, in order to isolate mental flexibility or divided attention from performance (29). Among the three derived scores, TMT B-A is shown to be the most robust discriminator between PD patients and controls (30). Based on the above we attempted to test the hypothesis that performance of patients with PD on at least one TMT derived score namely TMT B-A would be significantly lower than expected, indicating that PD slowness is attributable to a mental flexibility deficit rather than a motor dysfunction.

3. Patients and Methods

3.1. Participants

Patients were recruited from the Neurological Clinic of Aeginition Hospital (Athens, Greece). Several inclusion criteria were implemented: (A) diagnosis of idiopathic PD, (B) classification below stage III (mild motor dysfunction) according to the Hoehn and Yahr scale (31) (C) mini mental state examination (MMSE) (32) score above 24, and (D) no psychiatric history. The PD group comprised 50 (14 females) right-handed patients, 32 to 81 years old (mean: 62.52, SD: 11.11), with 4 to 16 years of formal schooling (mean: 11.50, SD: 4.06). The control group consisted of 50 neurologically intact, right-handed adults (17 females), matched for age, gender and educational level. Between-group differences on demographic characteristics were not significant, as revealed by t-tests for age and years of formal schooling as well as chi-square test for gender. Demographic characteristics of the two groups are shown

in Table 1. Informed consent was obtained from each patient. Any human data included in this manuscript was obtained in compliance with regulations of the Aeginition Hospital ethics committee study, which conform to the ethical guidelines of the 1975 Declaration of Helsinki.

3.2. Neuropsychological Examination

TMT was administered to both PD and control groups by well-trained neuropsychologists, who were blind to the purposes of the study. Both parts (A and B) were administered according to the procedure described by Zalonis et al. (33), where the examiner points out errors as they occur, so that the patient can complete the test without errors and scoring is based on time alone (26). TMT is considered to measure scanning and visuomotor tracking, divided attention, and cognitive flexibility (21, 27). Two raw scores (time needed to complete TMT A and TMT B) and three derived scores (TMT B-A, TMT B/A, and TMT (B-A)/A) were calculated for each participant.

4. Results

To test the normality of distributions, the one-sample Kolmogorov-Smirnov test was performed for each group, while skewness was also calculated. Since assumptions for normality were violated, nonparametric statistics were applied in subsequent analyses. Mann-Whitney tests showed significant group differences for both raw scores (patients with PD were slower). Regarding the derived scores, the two groups differed significantly only on TMT B-A. Performance of the PD group was lower for all the three derived scores compared to controls, but only the TMT B-A difference was significant. However, differences in the remaining two derived scores almost reached significance (P = 0.054) (Table 2).

Table 1. Demographic Data of the Patients With Parkinson's Disease and the Control Group (n = 50)

Variable	Parkinson's Disease		Control		P Value
	Mean ± SD	Range	Mean ± SD	Range	
Age, y	62.52 ± 11.11	[32-81]	62.42 ± 11.17	[32-80]	> 0.05
Education, y	11.50 ± 4.06	[4-16]	11.70 ± 3.56	[6-16]	> 0.05
Gender, No.					> 0.05
Male	36		33		
Female	14		17		

Table 2. Performance of the Two Groups on Trail Making Test (n = 50) [a]

Variable	PD Group		Control Group		P Value
	Mean ± SD	Range	Mean ± SD	Range	
TMT A, s	71.62 ± 31.19	29-176	60.18 ± 29.48	[19-148]	< 0.05
TMT B, s	192.56 ± 108.83	42-512	131.10 ± 62.61	[45-276]	< 0.01
Product score TMT B/A	2.70 ± 1.12	1.28-6.53	2.28 ± 0.84	[1.11-5.19]	0.054
Product score TMT B-A	120.94 ± 92.73	13-412	70.92 ± 45.70	[8-185]	< 0.01
Product score TMT (B-A)/A	1.70 ± 1.12	0.28-5.53	1.28 ± 0.84	[0.11-4.19]	0.054

[a] Abbreviations: PD, Parkinson's disease; TMT, trail making test.

5. Discussion

We expected that performance of patients with PD on TMT parts A and B would be significantly lower compared to controls. Indeed, patients with PD were slower than the matched controls in both parts of TMT, indicating reduced psychomotor speed and mental flexibility as well as divided attention. Previous studies have also demonstrated lower than expected performance of patients with PD on both TMT parts (10, 30, 34).

However, raw TMT scores cannot differentiate between the effects of motor dysfunction and the mental rigidity observed in patients with PD, since, as previously mentioned, executive dysfunction can be coupled with and exacerbated by motor slowing (35, 36). Derived TMT scores have been used by various PD studies to subtract the effects of motor and psychomotor slowness from performance and as a more-sensitive discriminator between patients with PD and controls (30, 37, 38). It is proposed that TMT B-A derived score is the most robust cognitive discriminator between patients and controls with a performance continuum through controls, patients with PD, and demented patients with PD (30). In our study, TMT B-A scores were significantly different between the two groups, thus indicating dissociation between motor dysfunction and mental rigidity of the patients with PD, regardless of the motor dysfunction.

TMT B/A also appears to be a sensitive indicator of cognitive decline in some cases (29, 38). Felmingham et al. (39) also recommended the use of a ratio score (TMT B/TMT A), because slower performance on TMT-A appeared to underlie deficits in TMT-B. Slowing of information processing speed appears to be responsible for difficulties in more complex cognitive tasks. Our results did not show such differences in TMT B/A, although significance was almost reached (P = 0.054). It could be speculated that a greater sample could allow t-test analyses and reveal the expected differences in TMT B/A between patients with PD and controls.

In the present study, we stated the hypothesis that performance of patients with PD on at least one TMT-derived score namely TMT B-A would be significantly lower than expected, indicating that PD slowness is attributable to a mental flexibility deficit rather than a motor dysfunction. This was confirmed by the results. Overall, our findings suggest that lower performance on TMT B is not caused solely by a slowed motor performance, but is rather the result of a decreased ability to shift between sets; a process that is considered as a critical composite of mental flexibility (21, 40).

Even though our results support the existence of a mental inflexibility in the PD group, they do not exclude a possible motor and/or cognitive slowing co-existence. Indeed, since raw TMT-A scores show an impaired performance of patients with PD compared to controls, the overall lower performance of the PD group on TMT could be partly due to motor response difficulties or central processing speed deficits in the sense of a general cognitive slowing, besides mental flexibility deficiencies.

Our findings also suggest that motor slowness and cognitive dysfunction in terms of mental inflexibility can be dissociated based on TMT performance. These two different components have been suggested to involve different pathological and neural mechanisms. Therefore, subthalamic nucleus deep brain stimulation seems to improve motor function, but is often correlated with cognitive decline in domains such as executive function (41). Additionally, unilateral pallidotomy has been shown to increase contralateral upper limb mobility, but has had no effect on executive function performance, as measured by Stroop and TMT A and B (42). Furthermore, evidence from dopaminergic therapy has indicated that although dopamine replacement improves motor symptoms, some cognitive functions are improved, while others are unaltered or even hindered (43). The above findings indicate possible clinical significance of the use of TMT and its derived scores for assessing the effects of treatment on motor and cognitive function.

In conclusion, the performance of patients with PD on both parts of the TMT indicates that motor dysfunction and mental inflexibility are two distinct PD deficits which may coexist. However, the use of TMT test as well as the derived scores can help differentiate between their effects, providing a chance to evaluate the course of the disease while assessing the effects of treatment on motor and cognitive function. Future studies including a wide variety of cognitive measures could provide a better evaluation of a possible cognitive slowing, which may interfere with motor dysfunction and mental flexibility.

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