Comprehensive Trail Making Test: a valuable predictor of driving performance in patients with Parkinson's disease

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Running Head: Comprehensive Trail Making Test and driving in PD

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Abstract

Background: The Trail Making test (TMT) has been identified as predictor of driving ability in patients with Parkinson's disease (PD). However, previous research has not explored the capacity of an alternative version of the TMT, namely of the Comprehensive Trail Making test (CTMT; Reynolds, 2002) to serve as predictor of driving behavior. Main objective of the current work was to evaluate the CTMT on predicting the driving behavior of patients with PD. **Method:** Inclusion criteria were the presence of a valid driver's license, regular car driving, a CDR score ≤ 0.5, and a Hoehn & Yahr score between 1 and 3. Twelve individuals with PD (Age: Mean=63.75, SD=10.50) and 12 cognitively intact individuals (Age: Mean=63.50, SD=10.43) were introduced in the study. Collection of data included a comprehensive neurological/neuropsychological assessment and a driving simulation experiment. **Results:** The strength and number of associations that were observed indicates an advantage of the CTMT as compared to the original TMT on predicting various indexes of driving performance in individuals with PD. Indicatively, CTMT-4 was strongly correlated with average speed (r=-.727, p=.007), speed variation (r=-.762, p=.004), reaction time (r=.686, p=.013), headway variation (r=.734, p=.007), average headway distance (r=.680, p=.015), and wheel variation (r=-.677, p=.016). **Conclusions:** The findings support the usefulness of CTMT on predicting the driving performance of patients with PD. Underlying factors that may explain the effectiveness of the CTMT

could be related to the greater variety of set shifting and inhibition processes that this alternative option integrates as compared to the original TMT.

Keywords: Comprehensive Trail Making Test, Trail Making Test, Parkinson's Disease, driving ability, driving simulator

Introduction

Parkinson's disease (PD) is a slowly progressive, degenerative disease of the basal ganglia, with motor dysfunction as a cardinal feature (Fritsch et al., 2012; Gazewood, Richards,& Clebak, 2013). In addition to motor dysfunction, PD is related to cognitive (memory, visuo-spatial, and executive dysfunction), emot ional (e.g. depression, apathy) and behavioral-neuropsychiatric symptoms (e.g. agitation, hallucinations, delusions) (Dubois & Pillon, 1997; Kupersmith, Shakin, Siegel,& Lieberman, 1982; Starkstein, Preziosi, Bolduc, & Robinson, 1990). Other factors that can also affect the functionality of individuals with PD are related to dosage regulation ("wearing-off syndrome", "on-off phenomenon", "peak dose dyskinesias"), and possible side effects of dopaminergic treatment, such as excessive daytime sleepiness (Knie, Mitra, Logishetty,& Chaudhuri, 2011). An area of functioning that is commonly influenced in a negative way by the multimodal clinical picture of PD, is the driving fitness of individuals belonging to the specific clinical group.

Findings from on-road driving evaluations show increased driving difficulties in drivers with PD as compared to drivers without an underlying neurological condition (Classen et al., 2009; Classen et al., 2011; Grace et al., 2005; Uc et al., 2007; Uc et al., 2009; Wood et al., 2005). Along the same vein, driving simulator experiments indicate an elevated risk for impairments in driving performance in individuals with PD

(Stolwyk et al., 2005; Stolwyk et al., 2006; Ranchet et al., 2011). Also, epidemiologic studies provide some evidence about the presence of an increased crash risk in drivers with PD (Dubinsky et al., 1991; Meindorfner et al., 2005). Indicatively, findings from Germany indicate that 15% of patients with PD holding an active driving license were engaged in car accidents during a period that covered the past five years (Meindorfner et al., 2005).

In the field of research that focuses on the driving capacity of individuals with PD, considerable effort has been directed toward the identification of neuropsychological measures that can serve as predictors of driving fitness. An indicative neuropsychological test that has been identified in several studies as predictor of driving skills in patients with PD is the Trail Making Test (TMT), especially part B of the specific test (Amick et al., 2007; Classen et al., 2009; Grace et al., 2005; Stolwyk et al., 2006; Uc et al., 2006). Abilities, such as visual search, motor speed, and spatial skills are examined in both parts of the test (Crowe, 1995; Gaudino et al., 1998). In addition, part B assesses aspects of executive control, such as mental flexibility and task shifting (Beratis et al., 2013; Kortte et al., 2002; Olivera-Souza et al., 2000). In the study of Amick et al. (2007) a significant association was found between a greater number of driving errors and a poorer performance on the parts A and B of the TMT in drivers with PD that underwent an on-road driving evaluation. Similarly, drivers with PD that were characterized as unsafe according to their on-road driving performance had important difficulties on the part B of the TMT (Grace et al., 2005). Along the same vein, the study of Classen et al. (2009) found in patients with PD that the part B of the TMT was significantly associated with the overall driving performance and the number of driving errors during an on-road assessment. Furthermore, during on-road driving that required the visual identification of targets, the TMT was identified as the strongest

predictor for at-fault safety errors in drivers with PD (Uc et al., 2006). Also, the part B of the TMT correlated with the majority of the driving measures that were obtained during a driving simulator assessment, such as traffic signal approach speed, traffic signal deceleration point, mean curve speed, and curve direction effect on mean lateral position (Stolwyk et al., 2006).

An alternative version of the TMT is the Comprehensive Trail Making Test (CTMT) that was developed by Reynolds (2002) with the aim to improve the capacity of the original instrument to identify executive dysfunction (Strauss, Sherman, & Spreen, 2006). An advantage of the CTMT as compared to the TMT is that it engages a greater spectrum, in terms of variety and difficulty, of set-shifting and inhibition processes (Reynolds, 2002; Strauss et al., 2006). Therefore, the CTMT appears to have enhanced sensitivity in terms of detecting executive impairments in various clinical populations (Strauss et al., 2006). Nonetheless according to our knowledge, previous studies have not applied the CTMT in patients with PD who are commonly characterized by the development of executive dysfunction (Ding, Ding, Li, Han, & Mu, 2015; Zgaljardic, Borod, Foldi, & Mattis, 2003).

In light of the above considerations the goals of the present study were the following. Firstly, by using as reference point previous findings that identify the original TMT as a useful predictor of driving performance in patients with PD, to assess the effectiveness of the CTMT in predicting the driving behavior of individuals belonging to the specific clinical group. An additional objective was the comparison of the CTMT with the original TMT regarding their capacity to predict the driving performance of patients with PD. Our expectation was that the CTMT could prove to be a more effective predictor of driving performance as compared to the TMT because of its nature that integrates a broader range of set-shifting and inhibition abilities.

Finally, the third goal of the current work was to explore the capacity of the CTMT to differentiate between cognitively intact individuals and patients with PD by detecting aspects of executive dysfunction that this clinical group commonly develops.

Methodology

Participants

The sample of the present study was comprised of 12 male individuals with PD (Age: Mean=63.75, SD=10.50) and 12 male cognitively intact individuals (Age: Mean=63.50, SD=10.43) that visited the Cognitive Disorders / Dementia Unit of the 2nd Department of Neurology at the University General Hospital "ATTIKON" in Athens.The demographic characteristics of the two groups as well as their driving experience and history of road accidents are presented in Table 1. According to Table 1, participants with PD and controls were similar in terms of age, education and overall driving experience. In line with our methodology, no history of accidents was reported for any member of the two groups during the period of the last two years.

Table 1. Demographic and driving characteristics of the patients with PD and the control group

	Control group	PD group	P-values
Age, y, mean±SD	63.5±10.4	63.7±10.5	0.954
Gender, n, M/F	12/0	12/0	
Education, y, mean±SD	15.6±3.7	13.2±3.9	0.125
Driving experience, y, mean±SD	38.4±7.0	42.2±10.5	0.346
Reported accidents (2 years) - median (range)	0 (0-0)	0 (0-0)	
Disease Duration, y, mean±SD	-	8.3±5.4	

UPDRS-III, mean±SD	-	14.7±7.5	
H&Y, mean±SD	-	2.0±0.4	
CDR, mean±SD	-	0.1±0.2	
IADL	5.0±0.0	5.7±1.6	0.152

Note. UPDRS-III: Unified Parkinson's Disease Rating Scale Part III, H&Y: Hoehn and Yahr scale, CDR: Clinical Dementia Rating, IADL: Instrumental Activity of Daily Living

Diagnosis of PD was made by a specialized neurologist in the field of movement disorders according to the following established criteria (UK Parkinson's Disease Society Brain Bank, Hughes et al., 2012).For participating in the study, patients with PD should have a score equal to or less than 0.5 on the CDR (Morris, 1993) and a score between 1 and 3 on the H&Y scale (Hoehn & Yahr, 1967). The assessment of the patients with PD, for all components of the data collection process, took place while they were in the on-phase of their medication cycle. Disease duration, the UPDRS score, the H&Y score, and the CDR of the patients with PD are presented in Table 1.

Also, all participants should fulfill the following criteria regarding their driving profile: (a) a valid driving license, (b) driving for more than 3 years, (c) driving more than 2500km during the last year, (d) driving at least once a week during the last year, (e) driving at least 10km/week during the last year, (f) no history of major accidents, (g) absence of any important kinetic or eye disorder, (h) absence of dizziness or nausea while driving, (i) absence of alcohol or any other drug addiction, and (j) no history of a major depressive episode.

Procedure

The participants underwent: (a) a clinical medical and neurological assessment, (b) an extensive neuropsychological assessment that included the administration of the TMT and the CTMT in two different sessions taking place in different days(≈2 month interval), and (c) a driving simulation experiment. The experiment took place at the Department of Transportation Planning and Engineering of the National Technical University of Athens.The driving simulator consisted of a motion based quarter-cab manufactured by the FOERST Company along with 3 LCD wide screens 40'' (full HD: 1920x1080pixels). The overall dimensions were 230x180cm, while the base width is 78cm and the total field of view is 170 degrees.

The structure of the driving simulator experiment was the following. Initially, there was a practice drive (5-10 minutes) in order to achieve familiarization with the simulation environment and subsequently the actual driving evaluation was performed in a rural area, with a moderate traffic volume and without the presence of an exogenous distractor.

The study was approved by the Ethics Committee of the University General Hospital "ATTIKON".Informed consent was obtained from all individuals studied; it was explained to them that participation was on a voluntary basis and that they had the right to withdraw any time they wished to. Participants were informed on the nature of the study, the duration of their engagement and the type of information that they would be asked to give during the data collection process. Also, participants were ensured of the anonymity and confidentiality of the procedure.

Measures

Trail Making Test (TMT)

The TMT is comprised of two subtasks, Part A (TMT-A) and Part B (TMT-B) (Reitan, 1979). Each subtask is shown on a white paper (A4 dimensions) and the participants are asked to connect randomly located circles, as fast as possible. Part A includes circles with numbers only (1-25) that have to be connected in numerical order, while Part B includes circles with both numbers (1-13) and letters (A-M) that have to be connected alternately. Abilities, such as visual search, motor speed, and spatial skills are examined in both parts of the test. In addition, part B is considered to assess aspects of executive control, such as mental flexibility and task shifting (Strauss et al., 2006).

Comprehensive Trail Making Test (CTMT)

The CTMT consists of five trails that assess psychomotor speed, visual scanning, sequencing, task switching/cognitive flexibility, attention, inhibition, and distractibility (Reynolds, 2002). Trail1 of the CTMT, like Part A of the original TMT, instructs participants to draw a line connecting numbered circles in ascending order as quickly as possible. However, Trail 1 of the CTMT has a more complex spatial structure than TMT-A because of the placement of the stimuli in ways that require from the participant to shift direction on several occasions (Strauss et al., 2006). For Trail 2, participants connect numbered circles in ascending order from 1 to 25, while ignoring 29 empty distractor circles that are included to assess inhibition and distractibility. Trail 3 includes 13 empty distractor circles and19 distractor circles with line drawings inside, providing a further measure of visual scanning, attention, and distractibility. On Trail4, participants connect numbers from 1 to 20, 11 of which are Arabic numerals (e.g., 1), whereas the other nine are written words (e.g., two). Trail 5 is similar to Part B of the TMT in which the participant not only alternates between numbers and letters in sequence, but it also includes five empty distractor circles. Trails 4 and 5 were included

to assess different types of task-switching abilities, thus increasing the sensitivity of the CTMT to brain dysfunction. As with the original TMT, performance is evaluated by recording the number of seconds taken to complete each trail.

Driving Simulator Measures

The following indexes of driving performance were estimated from the driving simulator task: average speed (average actual speed in km/h), speed variability (the standard deviation of speed), driver reaction time at unexpected incidents (time between obstacle's appearance on the road and the braking time in msec), mean headway distance (average distance from the ahead driving vehicle in meters), headway variability (the standard deviation of headway distance), wheel variability (the standard deviation of steering wheel position in degrees), number of crashes, number of speed limit violations, and number of sudden brakes.

Statistical Analysis

For comparing the group of individuals with PD and the control group on the various variables included in the analysis, independent-samples t-test analysis was applied. The associations of the TMT and CTMT subtests with the various indexes of driving performance were assessed with the Pearson correlation coefficient separately for the group of individuals with PD and the control group.

Statistical significance was set at the .05 level. The Statistical Package for the Social Sciences (SPSS), version 21 (Chicago, ILL) was used to analyze the data.

Results

According to Table 2, the two groups did not differ in measures assessing general cognitive status. On the contrary, significant differences in favor of the control

group were observed in neuropsychological measures assessing executive functioning, verbal fluency, and free recall of episodic verbal memory(Table 2).

Table 2. Comparison of patients with PD and of a control group on various neuropsychological measures with the use of the independent samples t- test

	Control group		PD group		t-test
	Mean	SD	Mean	SD	p-values
MMSE, mean±SD	29.3	0.8	28.5	1.6	.185
FAB	16.5	1.3	12.3	2.8	<.001**
CDT	6.9	0.3	6.1	1.5	.083
Verbal Fluency	13.1	3.1	8.2	2.9	.001**
HVLT-Total	22.5	4.7	18.8	3.3	.038*
HVLT-Delayed Recall	6.9	2.1	5.2	2.8	.095

Note. MMSE: Mini Mental State Examination, FAB: Frontal Assessment Battery, CDT: Clock Drawing Test, HVLT-Total: Hopkins Verbal Learning Test – Total score of Immediate recall, HVLT-Delayed Recall: Hopkins Verbal Learning Test – Delayed recall

*$p \leq 0.05$, **$p \leq 0.01$*

Performance of the individuals with PD and of the control group on the TMT and CTMT subtests as well as on the indexes of driving performance are presented in Table 3. Significant differences between the PD group and the control group were observed on all TMT and CTMT subtests, in favor of the control group. In reference to driving indexes, significant differences between the two groups were observed on the average headway distance and on the headway variability (Table 3). The individuals with PD had significantly greater average headway distance as well as headway variability (Table 3).In addition, a strong trend for statistical significance was observed in the case of average speed and reaction time as indicated by the medium to large effect

sizes that were observed in the two cases (Table 3).According to the aforementioned trend, patients with PD tended to have reduced average speed and increased reaction time in the appearance of unexpected incidents.

Table 3. Comparison of the patients with Parkinson disease (PD) and of the control group on the trail tests and the driving indexes with the application of the independent-samples t-test

Variable	PD		Control Group		t-test		
	Mean	SD	Mean	SD	t	p	d
Neuropsychological measures							
TMT-A	74.67	42.28	36.42	9.43	3.059	.010*	1.25
TMT-B	180.75	97.91	84.58	36.24	3.191	.007**	1.30
CTMT-1	80.08	31.86	46.92	9.22	3.464	.004**	1.41
CTMT-2	95.58	45.97	50.25	12.13	3.303	.006**	1.34
CTMT-3	107.92	62.47	52.58	17.03	2.961	.007**	1.20
CTMT-4	110.08	53.67	56.33	17.43	3.300	.006**	1.34
CTMT-5	192.42	93.15	93.33	37.92	3.413	.004**	1.36
Driving measures							
Average Speed	37.13	13.93	46.77	8.25	2.063	.051	-0.84
Speed Variation	11.49	4.84	13.73	4.60	1.163	.257	-0.47
Reaction Time	1744.91	536.14	1438.42	311.24	1.695	.105	0.69
Headway Variation	265.44	121.96	181.07	53.57	2.194	.044*	0.89
Headway Average	600.35	189.94	402.35	109.52	3.128	.005**	1.27
Sudden Brakes	2.08	2.75	2.42	.79	.404	.690	-0.16
Speed Limit Viol.	.50	1.17	.58	1.51	.152	.881	-0.05
Wheel Variation	16.41	3.97	17.87	1.69	1.173	.259	-0.47

Note: TMT-A=Trail Making Test-Part A; TMT-B=Trail Making Test-Part B; CTMT-1= Trails 1 of the Comprehensive Trail Making Test; CTMT-2= Trails 2 of the Comprehensive Trail Making Test; CTMT-3= Trails 3 of the Comprehensive Trail Making Test; CTMT-4= Trails 4 of the Comprehensive Trail Making Test; CTMT-5= Trails 5 of the Comprehensive Trail Making Test

*$p \leq 0.05$, **$p \leq 0.01$

The correlation analysis that explored the associations of TMT and CTMT subtests with indexes of driving performance showed a large number of significant correlations in the group of individuals with PD, especially with average speed, speed variation, reaction time, average headway distance and headway variability (Figure 1).

Figure 1 to be inserted here

In reference to the comparison of the TMT with the CTMT, the results indicate an advantage of the CTMT. Firstly, the CTMT had always the strongest correlation with the driving indexes used in the analysis (Figure 1). Secondly, the CTMT correlated in a significant way with a greater number of driving indexes than the TMT (Figure 1). A subtest of the CTMT that showed very strong correlations with average speed, speed variation, reaction time, average headway distance and headway distance variation is the CTMT-4.

On the contrary, the analysis showed a minimal number of significant associations between TMT or CTMT subtests and indexes of driving performance in the control group of individuals (Figure 1). Actually, the only significant correlation in the control group was between CTMT-1 and headway variability.

Discussion

Main goal of the present study were the exploration of the capacity of the CTMT to predict the driving behavior of individuals with PD in comparison to the original TMT. An additional objective was to evaluate the effectiveness of the CTMT to detext executive dysfunction in patients with PD. In line with our prediction, the current results support the view tha the CTMT is a valuable predictor of driving performance in

patients with PD, even at a greater extent than the original TMT. As concerns the second objective of this work, the patients with PD had significantly lower performance in all subtests of the CTMT with effect sizes that were similar or even greater than those observed in the case of the TMT. Hence, this pattern of findings indicates that the CTMT may be considered as an effective alternative option that can successfully replace the classical TMT for detecting aspects of executive dysfunction in the specific clinical population.

Regarding the association with driving behavior, the present findings show that TMT and CTMT subtests are associated with a broad variety of driving indexes in individuals with PD that include longitudinal driving control measures, namely average speed, speed variability, average headway distance and headway variability as well as lateral driving control measures, such as wheel position variability. Moreover, significant associations were also observed with driving safety measures, such as reaction time, sudden breaks and number of speed limit violations. On the other hand, the analysis showed a minimal number of significant associations between TMT or CTMT subtests and driving performance in a group of cognitively intact individuals of the same age and gender. Hence, this pattern of findings appears to apply specifically in the group of drivers with PD and does not generalize in the general driving population. In agreement with this outcome are also previous studies that have observed a similar profile of findings in the case of the original TMT (Uc et al., 2006; Stolwyk et al., 2006).

Regarding the original TMT, the associations that were detected with a variety of driving indexes are in line with previous research that has identified the specific neuropsychological test as a useful predictor of driving performance in patients with PD (Amick et al., 2007; Classen et al., 2009; Crizzle et al., 2012; Grace et al., 2005;

Ranchet et al., 2012; Stolwyk et al., 2006; Uc et al., 2006). As indicated by these accumulating findings, the cognitive functions engaged by the specific test, such as visual search, motor speed, spatial skills, mental flexibility and task shifting, appear to be interwoven with the driving performance of individuals belonging to the specific clinical population.

As concerns the effectiveness of the CTMT, this alternative option appears to be advantageous as compared to the original TMT, by taking under consideration the strength and number of significant associations that were observed with a variety of driving indexes. It could be argued that the broader range of set shifting and inhibitory processes that are assessed by the CTMT (Reynolds, 2002; Strauss et al., 2006) appears to increase the capacity of this instrument to predict various indexes of driving performance, such as average speed, speed variation, reaction time, and headway distance. One of the subtests of CTMT that showed the best results was CTMT-4 that requires from the participants to connect numbers in ascending order that are either Arabic numerals or written words. It is likely that the more simple nature of CTMT-4 as compared to TMT-B reduces the possibility for floor effects and, thus, provides complementary information about the mental-flexibility resources of the patients with PD.

In the present study we detected some differences on the average values of various driving indexes between the individuals with PD and the control group, but of a smaller extent as compared to previous studies (Classen et al., 2011; Stolwyk et al., 2006; Uc et al., 2007; Uc et al., 2009). Possible reasons that could explain the current pattern of findings are the strict inclusion criteria utilized for the selection of the participants who were required to be active drivers with a significant amount of kilometers driven in a given period of time as well as the absence of any car accidents

in the past 2 years. Moreover, the exclusion of individuals with advanced stages of PD, the small sample size that allows the detection only of large effect sizes, and the considerable heterogeneity that appears to exist on the driving performance of the specific clinical population (Uc et al., 2009) could also explain the specific findings. Nonetheless, the link that was exclusively observed in the clinical group between measures engaging executive resources and various driving indexes could be useful for detecting those individuals with questionable or problematic driving competence among the general PD driving population.

A limitation that should be noted is the small sample size of the study. However, this constraint does not influence in a critical way the findings regarding the TMT and CTMT because of the large effect sizes that were observed. Also, by comparing patients with PD and cognitively intact individuals that were practically matched in terms of age, gender and driving experience the present study achieved sufficient control on potential confounding factors that could blur the main outcomes of this work. Another, parameter that needs to be recognized is that the driving measures were obtained from a simulation environment and not from an on-road driving evaluation. However, the driving simulator is considered as a valid method for examining driving behavior and provides the opportunity to evaluate participants under the exact same conditions as well as to measure critical driving indexes that is not feasible to be assessed under an on-road driving conditions (Fisher, Rizzo, Caird & Lee, 2011; Lew et al., 2005; Yannis, Papantoniou & Nikas, 2015). Nonetheless, future studies could increase our insight and strengthen the current findings by investigating the capacity of CTMT to predict driving performance with the use of larger sample sizes under on-road driving conditions. Also, a reasonable target for further research is the exploration of the capacity of CTMT to predict the driving performance in patients with other neurological disorders in which

the original TMT has also yielded positive results, such as in Alzheimer Disease (AD) or stroke patients.

In conclusion, the findings of this study indicate a strong association between CTMT subtests and various measures of driving performance that were obtained with the application of a driving simulator evaluation. Moreover, the overall pattern of results, according to the strength and number of associations that were observed, indicates an advantage of the CTMT as compared to the original TMT on predicting the driving performance of individuals with PD. This is a novel finding that renders originality to the present work and paves the way for the application of the CTMT in future studies that will also explore the driving capacity of individuals with PD or of drivers with other types of cognitive disorders. These observations may have considerable practical importance because they improve our insight about the link that exists between cognitive dysfunction due to PD and driving performance in the specific clinical population. In summary, the CTMT task, by combining various executive processes with psychomotor speed demands and visual search skills, appears to be an effective choice for the prediction of driving performance in individuals with PD and has the potential to support the development of efficient driving recommendations for the specific clinical population.

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