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Research Article

Predicting Behind-the-Wheel Driving Behavior in Parkinson Disease Through Motor and Cognitive Testing in Outpatient Clinics

Nikolaos Andronas[1,2*], Elissaios Karageorgiou[2], Ion N Beratis[1,6], Stella Fragkiadaki[1], Dionysia Kontaxopoulou[1], Dimosthenis Pavlou[3], Eleonora Papadimitriou[4], George Yannis[3], Alexandra Economou[5], Leonidas Stefanis[1], Sokratis Papageorgiou[1]

[1]National and Kapodistrian University of Athens, 1st University Department of Neurology, Eginition Hospital, 72-74 Vasilissis Sofias Ave, 11528 Athens, Greece

[2]Neurological Institute of Athens, 2 Vasileos Alexandrou Ave, 11634, Athens, Greece

[3]National Technical University of Athens, School of Civil Engineering, Department of Transportation Planning and Engineering, 9 Heroon Polytechniou Str, 15780 Zografou, Athens, Greece

[4]Delft University of Technology, Faculty of Technology, Policy and Management, Safety and Security Science Group, Jaffalaan 5, 2628 BX Delft, The Netherlands (*)

[5]National and Kapodistrian University of Athens, School of Philosophy, Department of Psychology, Zografou Campus, 15784 Athens, Greece

[6]Psychology Department, American College of Greece, Deree, 6 Gravias Street, 15342 Athens, Greece

[#](*) At the time that this research started, this author was with the National Technical University of Athens

***Corresponding author:** Nikolaos Andronas, MD, Sleep & Memory Center, Neurological Institute of Athens, Address: 2 Vas. Alexandrou Ave., 11634, Athens, Greece.

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder that affects driving performance, which is attributed in part to motor and cognitive deficits. Studies to date, however, have not consistently associated motor features of PD, as quantified by Hoehn & Yahr and UPDRS-III scales, with driving performance, nor combination of detailed motor and cognitive features. **Objective:** We investigated whether specific motor and cognitive tests performed in clinic can predict behind-the-wheel driving behavior in Parkinson's disease (PD). **Methods:** Twenty-three patients with PD (Age: 63.39 ± 10.29; 1 woman) and twenty-three propensity matched healthy controls (Age: 58.30 ± 10.88; 2 women) were prospectively enrolled through the outpatient clinics of the University of Athens with inclusion criteria of Hoehn &Yahr scale ≤ 3, a valid driver's license, regular car driving, and CDR ≤ 0.5. All participants underwent clinical exams, neuropsychological assessments, and behind-the-wheel driving evaluation in a driving simulator. We quantified motor function through Tandem Walking Test, Tandem Walking with Reverse Number Counting, Rapid Paced Walk, Head Rotation Task, and Foot Tapping Test. Neuropsychological testing assessed global cognition, memory, visuospatial, processing speed, attention, and executive function. Factor analysis for each group of variables (driving, motor, and cognitive) revealed the following ten latent factors: Driving factors: Tactical Driving Praxis, Operational Safety, Car Spatial Road Positioning, Tactical Driving related Accidents, Reaction Time Related Accidents; Motor factors: Motor Speed and Dexterity, Axial Movement; Cognitive factors: Planning and Processing Speed, Visuospatial Attention and Planning, Verbal Learning and Memory. Backward selection linear regression was performed between the above motor-cognitive factors and each driving factor to predict individual driving behaviors, whereas Canonical Correlation Analysis (CCA) revealed the overall relationship between motor-cognitive performance and driving behavior while accounting for their internal dependencies. Finally, simulator accident probability outcomes were predicted from motor-cognitive factors using Linear Discriminant Analysis. **Results:** People with PD drove slower, closer, with variable headway distance, while having worse motor function and cognitive performance in processing speed, set shifting, phonemic fluency, visuospatial perception, spatial executive functioning, and verbal recall ($p<0.05$). Tactical Driving Praxis was predicted through Axial Movement, Speed and Dexterity, and Planning and Processing Speed ($R2= 0.5$; $p=5x10-6$), Car Spatial Road Position through Planning, Processing Speed, Visuospatial Attention, Planning ($R2= 0.2$; $p=0.01$) and Reaction Time Related Accidents through Axial Movement, Learning and Memory, and Visuospatial Attention and Planning ($R2= 0.4$; $p=0.001$). Significant CCA multidimensional associations ($p<0.05$; redundancy index > 0.30) between motor-cognitive and driving factors indicated the combination of all motor-cognitive factors predicted tactical driving and reaction time related accidents driving factors (CCA R1 = 0.85), whereas visuospatial and speed & dexterity factors predicted, in addition, spatial road positioning (CCA R2 = 0.74). Accident Probability was fairly well predicted through UPDRS-III and Hoehn & Yahr scores (Diagnostic Odds Ratio [DOR] 7.99), less so through motor factors (DOR 1.78), but best prediction was achieved through cognitive factors (DOR 15.69). **Conclusions:** Motor and, especially, cognitive phenotypes derived from clinical practice can help predict behind-the-wheel driving behavior in PD, and by extension be incorporated in objective clinical criteria to inform on which patients should pursue behind-the-wheel assessments in determining who may need to stop driving.

Keywords: Parkinson's Disease; Driving; Cognition; Movement Disorders; neuropsychological assessment

Introduction

In modern society driving is essential for independence in daily living, whereas cessation of driving is associated with social isolation, lower quality of life, reduced mobility and level of activity, and depression [1,2]. Driving is a complex mental process that requires great synergy between motor and cognitive systems. Considering that Parkinson's disease (PD) is associated with motor and cognitive impairment, objective and early evaluation of driving ability in people with PD is critical to achieve a balance between independence and public safety [3].

Several studies have shown that drivers with PD have worse performance than healthy matched controls in on-road and simulated driving conditions, exhibiting more driving errors and car accidents [4]. Nonetheless, presence of PD does not always foretell that a motor vehicle accident will occur, [2] and, thus, it would be unjust and arbitrarily imposing on patient autonomy, to establish a blanket rule of preventing people with PD from driving on the basis of a diagnosis alone without assessing actual driving behavior.

Specialty driving schools offer courses for safe driving, but assessments are limited to safe vehicle maneuvering and traffic sign knowledge. There are no standardized protocols to help assess people's driving behavior, especially for elder drivers or drivers with neurological conditions such PD [5]. In these populations, such tools could help identify early the critical period at which driving is becoming unsafe and which can be used by medical professionals and government authorities to protect both the patients and the public [6].

In this study, we aimed to investigate whether specific motor and cognitive tests performed in clinic can predict behind-the-wheel driving behavior in PD, towards developing assessment protocols that predict unsafe driving early, accurately, and cost-effectively.

Methods

Subjects

Out of a total of 106 cohort participants prospectively recruited through the Driver Brain Project of the 2nd Department of Neurology of the National and Kapodistrian University of Athens, Attikon Hospital, 23 patients carried a diagnosis of PD (Age: 63.39 ± 10.29; 1 woman) and 83 were identified as cognitively and motorically unimpaired healthy controls (HC). All participants participated in the study after providing informed written consent as approved by Attikon University Hospital human research ethics committee. All participants underwent clinical examinations, neuropsychological testing, and driving simulation assessments. HC were predominantly friends and family of patients. Inclusion criteria were: valid driving license ($\geq$ 3 years), regular car driving ($\geq$ 2.500 Km/year, $\geq$ 10km/week, and $\geq$ 1 drive/week), and absence of dementia (CDR score $\leq$ 0.5). Patients with PD had mild or moderate PD (Hoehn & Yahr scale $\leq$ 3) of any syndromic phenotype (tremor-predominant or akinetic-rigid predominant). Exclusion criteria were: psychotic symptoms, major depression, severe motor deficits interfering with car control, car sickness, history of alcohol or drug addiction, combined for both eyes visual acuity < 10/20. To minimize demographic confounders due to PD and HC group heterogeneity that could lead to spurious associations, we pursued analyses after propensity matching groups according to age and sex using a logistic regression model, leading to 23 pairs of PD and HC (Table 1). Only data from these 23 pairs of PD-HC were used for the analyses described below.

	PD N = 23	**HC** N = 23	*p-value*
Age (years)	63.39 (10.29)	58.30 (10.88)	*p = 0.11*
Sex (F:M)	1:22	2:21	*p = 0.09*
Education (years)	12.82 (3.89)	15.47 (3.43)	*p = 0.005*
Driving Experience (years)	40.94 (10.49)	36.47 (6.14)	*p = 0.09*
Values in parentheses represent standard deviation.			

Table 1: Demographics of people with PD and healthy controls

Due to missing information, education and driving experience were not available for all participants to allow inclusion in propensity modeling. Finally, although not an a priori exclusion criterion, none of the participants in the analyses had provoked a traffic accident in the past based on self-report.

Clinical and neuropsychological evaluations

All participants underwent extensive neurological and neuropsychological evaluations by the same neurologists (NA, SP) and neuropsychologists (SF, DK), and subsequently completed a simulator driving evaluation within two weeks. All participants with PD were evaluated during subjective peak performance during the ON phase for all tasks. Neurological symptoms and signs were quantified according to the predominantly engaged domain into the following scales and scores: (a) Motor: Unified Parkinson's Disease Rating Scale part III-motor examination [UPDRS-III], Hoehn & Yahr [H&Y], Tandem Walking Test [TWT] with or without Reverse Number Counting [TWT-RC]; Rapid Paced Walk Test [RPW]; Head Rotation Task [HRT]; Foot Tapping Test [FTT]) (b) Cognitive-behavioral: Clinical Dementia Rating Scale [CDR]; The Neuropsychiatric Inventory [NPI], Frontal Behavioral Inventory [FBI], (c) Sleep: Athens Insomnia Scale [AIS], Epworth Sleepiness Scale [ESS], and (d) Activities of Daily Living: Informant Questionnaire on Cognitive Decline in the Elderly [IQ-CODE], Instrumental Activities of Daily Living [IADL], Functional Activities Questionnaire [FAQ]. Objective cognitive function was quantified with the following neuropsychological battery and localized in Greek: (a) Global cognition: Mini Mental State Examination [MMSE], Montreal Cognitive Assessment [MoCA], (b) Memory: Hopkins Verbal Learning Test-Revised [HLVT-R], Brief Visuospatial Memory Test-Revised [BVMT], Letter Number Sequencing-WAIS IV [LNS], Spatial Addition-WAIS IV, (c) Visuospatial: Driving Scenes Test-Neuropsychological Assessment Battery [DSC-NAB], Judgement of Lines Orientation [JLO], Useful Field of View [UFOV], Clock Drawing Test [CDT], Witkin's Embedded Figure Test [EFT] (d) Processing speed-Attention: Trail Making Test-A [TMT-A]; Symbol Digit Modalities Test [SDMT]; Psychomotor Vigilance Task [PVT], (e) Executive: Frontal Assessment Battery [FAB]; Trail Making Test-B [TMT-B]; Comprehensive Trail Making Test [CTMT]; Letter Number Sequencing- Wechsler Adult Intelligence Scale IV, Spatial Addition- Wechsler Memory Scale IV. HC completed detailed quantification for all tests, with the exception of UPDRS-III and H&Y, for which they were a priori assigned normal values (zero).

Driving Simulator Evaluation

Driving performance was evaluated through the FOERST Driving Simulator FPF for all participants as described in detail elsewhere [7]. In brief, during the driving simulator task, participants were asked to drive a virtual stick-shift car while seated in a car seat in front of a car dashboard and three LCD wide screens (40'' full HD, angle view 170 degrees), by controlling a steering wheel, three-pedals and a gear-shift. All participants were given the option of driving in automatic vs. gear-shift settings, and all selected gear-shift based on their daily practice. Driving was simulated under two sequential conditions. First, 2.1 km of rural road with 3 m single-carriageway lane width, and, second, 1.7 km of urban road with 3.5 m single-carriageway lane width, both in a sunny environment. Each condition was divided into two traffic loads (low [300 vehicles/hour] vs. high [600 vehicles/hour]). Because many participants mentioned fatigue and/or simulator sickness after the first driving session (rural road), they elected not to complete testing in an urban road environment. Thus, all analyses were based on rural settings. One dangerous situation was simulated during the course (i.e., animal crossing the street). All participants first had a familiarization period under supervision of specialized engineers (DP, EP) with the simulator with no time restriction, during which they felt able to handle the simulator controls (starting, gears, wheel handling etc.), and control the vehicle relative position and speed while driving.

Driving parameters can be organized into two major categories: (i) tactical car control variables (mean vehicle speed and its variation, mean and variation of headway distance, and steering wheel variation) and (ii) operational safety variables (number of sudden brakes, reaction time to unexpected event, number of speed limit violations, number of hits of another vehicle or animal).

Statistical analyses

We investigated (a) individual variable differences between PD and matched HC in motor and cognitive performance, as well as driving behavior, using Student's t-test and Mann-Whitney U test depending on variable violation of normality assumptions. We further examined (b) the predictive association of the clinical bedside motor and cognitive domains to driving features using multivariate regression analyses and canonical correlation analysis (CCA), after performing principal component analysis (PCA) with oblimin rotation ($\delta = 0$) on each of the three categories of features (motor, cognitive, driving). PCA allowed for clustering of information into latent variables (components/factors) that represent abstract domains of motor, cognitive, and driving abilities, thus providing a semantically interpretable representation of these abilities. PCA further allowed dimensionality reduction by selecting only factors (eigenvalues > 1) that carried most of the original data variance. This also allowed more robust and generalizable results through CCA where observations need to be 5-10 times more than variables [8]. We pursued PCA across high and low driving conditions only on rural settings, since fewer participants completed urban driving simulation. The subsequent CCA significance was assessed on the basis of a canonical correlation $R > 0.5$, Wilks' Λ p-value < 0.05, and a redundancy index > 0.3, whereas significant loadings were predefined at > 0.3. Finally, to investigate whether there is (c) a potentially useful threshold of motor and cognitive performance to guide behind-the-wheel driving safety assessments in clinical practice for people with PD, we pursued linear discriminant analysis (LDA) against the combined Accident Probability driving simulator feature across rural-urban and low-high traffic driving conditions. Specifically, we tested models that included the following predictor variables (i) H&Y and UPDRS-III and (ii) latent motor and (iii) latent cognitive factors derived from the aforementioned dimensionality reduction process. This approach was also implemented to test whether a combination of driving, motor, and cognitive factors help distinguish if a person carries a diagnosis of PD. For the above, significance threshold for result interpretation was set at 0.05 post Bonferroni correction, unless otherwise indicated.

Results

In this driving simulator experiment we aimed to study whether and how motor and cognitive features of PD may predict driving behavior. We first sought to examine whether there are any differences in driving behaviors, as well as cognitive and motor performance between PD and HC groups (Tables 2, 3).

		Traffic load	PD	HC	PD vs. HC
Driving Metric Category			**Mean (SD) / Median (25th-75th %)**	**Mean (SD) / Median (25th-75th %)**	***p-value***
Tactical car control	**Average Speed (km/h)**	**Low**	**36.66 (10.84) 34.58 (28.21-43.72)**	**47.724 (7.36386) 48.36 (44.27-51.67)**	$P_t = 2.1 \times 10^{-4}$
		High	**34.38 (7.05) 32.87 (29.24-40.22)**	**44.409 (5.910) 46.63 (40.27-48.71)**	$p_t = 8.8 \times 10^{-6}$
	Average Speed – Standard Deviation (km/h)	Low	10.20 (3.97) 9.12 (7.10-11.76)	14.04 (3.84) 48.36 (11.33-16.07)	$p_t = 1.7 \times 10^{-3*}$
		High	9.67 (3.14) 8.40 (6.76-12.25)	12.64 (2.75) 12.90 (9.88-15.12)	$p_t = 1.9 \times 10^{-3*}$
	Headway Average Distance (m)	**Low**	**587.71 (157.63) 581.72 (453.43-706.68)**	**398.9038 (95.21753) 381.61 (344.28-447.22)**	$p_t = 1.9 \times 10^{-5}$
		High	**394.77 (126.89) 248.07 (257.05-463.27)**	**162.32 (96.78) 123.27 (102.27-213.61)**	$P_t = 3 \times 10^{-8}$
	Headway Average Distance – Standard Deviation (m)	**Low**	**263.71 (96.77) 242.28 (187.53-345.77)**	**166.02 (45.98) 152.91 (135.21-212.71)**	$P_t = 1.2 \times 10^{-4}$
		High	**197.68 (58.35) 203.40 (149.39-235.79)**	**92.96 (57.28) 73.08 (51.61-120.19)**	$P_t = 5.5 \times 10^{-7}$
	Lateral Position Average (m)	Low	1.46 (0.14) 1.41 (1.33-1.61)	1.45 (0.11) 1.44 (1.37-1.56)	$p_t = 0.89$
		High	1.545 (0.143) 1.54 (1.47-1.67)	1.58 (0.138) 0.58 (1.47-1.69)	$P_t = 0.42$
	Lateral Position Average – Standard Deviation (m)	Low	0.29 (0.07) 0.27 (0.25-0.32)	1.45 (0.11) 1.44 (1.36-1.56)	$P_t = 0.38$
		High	0.26 (0.06) 0.25 (0.21-0.28)	0.25 (0.06) 0.26 (0.21-0.28)	$P_t = 0.75$
	Average Steering Wheel Position (degrees)	Low	-1.59 (0.72) -1.87 (-2.03/-1.40)	-1.74 (0.66) -1.68 (-1.99/-1.34)	$p_t = 0.48$
		High	-1.95 (0.76) -1.70 (-2.05/-1.52)	-1.74 (0.49) -1.79 (-2.13/-1.44)	$p_t = 0.27$
	Average Steering Wheel Position – Standard Deviation (degrees)	Low	16.55 (2.54) 16.28 (14.99-16.66)	17.35 (1.27) 17.58 (16.37-18.32)	$p_t = 0.18$
		High	15.94 (1.91) 15.76 (14.35-16.73)	17.08 (1.22) 17.37 (16.11-18.12)	$p_t = 0.024*$

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Operational Safety	**Average Reaction Time (ms)**	**Low**	**2164.71 (734.66) 2017 (1455.63-2531.75)**	**1443.52 (342.35) 1383 (1167-1683.5)**	***$p_t = 2.3 \times 10^{-4}$***
		High	2296 (815.90) 2095.5 (1708-2777)	1723.83 (761.61) 1450 (1283-1783.5)	$p_t = 0.024$*
	Accident Probability	Low	0 (0-0)	0 (0-1)	$p_{MW} = 0.32$
		High	0 (0-0)	0 (0-0)	$p_{MW} = 0.52$
	Hit of Side Bars (#)	Low	0 (0-1)	0 (0-0)	$p_{MW} = 0.46$
		High	0 (0-1.75)	0 (0-1)	$p_{MW} = 0.25$
	Outside Road Lines (#)	Low	0 (0-0)	0 (0-0)	$p_{MW} = 1$
		High	0 (0-0)	0 (0-0)	$p_{MW} = 0.35$
	Speed Limit Violation (#)	Low	0 (0-0)	0 (0-0)	$p_{MW} = 0.66$
		High	0 (0-0)	0 (0-0)	$p_{MW} = 0.63$
	Sudden Brakes (#)	Low	1 (1-1)	2 (2-3)	$p_{MW} = 0.0054$*
		High	1.00 (0.25-1.75)	2 (1-3)	$p_{MW} = 0.012$*
Values are mean and SD for parametric test comparisons, and median and quartiles for non-parametric tests. Values in bold represent significant differences after Bonferroni correction. * Significant differences prior to Bonferroni correction, pt: Student's t-test and pMW: Mann-Whitney U test					

Table 2: Driving behavior comparisons between PD and matched healthy controls

		PD	**HC**	**PD vs. HC**
		Mean (SD) Median ($25^{th} – 75^{th}$ %)	**Mean (SD) Median ($25^{th} – 75^{th}$ %)**	***p-value***
Motor	**RPW (secs)**	**6.20 (1.35)**	**4.93 (0.83)**	***$P_t = 8 \times 10^{-4}$***
	FTT time (secs)	5.51 (1.30)	4.88 (0.96)	$P_t = 0.08$
	FTT errors	0 (0 – 0)	0 (0 – 0)	$P_{MW} = 0.07$
	TWT time (secs)	7.06 (1.89)	5.56 (2.07)	$P_t = 0.08$
	TWT errors	0 (0 – 0)	0 (0 – 0)	$P_{MW} = 0.57$
	TWT-RC time (secs)	8.55 (2.49)	6.67 (1.67)	$P_t = 0.0056$**
	TWT-RC errors	0 (0 – 0.5)	0 (0 – 0)	$P_{MW} = 0.161$
	HRT minimum	3 (2 – 3)	3 (3 – 3)	$P_{MW} = 0.151$
	UPDRS-III	**14.78 (10.23)**	**0 (0.00)**	***$Pt = 8.4 \times 10^{-4}$***
	Hoehn & Yahr	**2 (2 – 2)**	**0 (0 – 0)**	***$P_{MW} = 4.2 \times 10^{-5}$***

Activities of Daily Living	**IALD**	5 (5 – 5.5)	5 (5 – 8)	$P_{MW} = 0.423$
	NPI	14.235 (11.69)	3 (6.71)	$P_t = 0.018$
	FBI	4.8 (4.65)	1.4 (2.19)	$P_t = 0.136$
	GDS	3.682 (3.03)	2.211 (3.05)	$P_t = 0.064$
	ESS	5.182 (3.92)	7 (4.69)	$P_t = 0.136$
	AIS	3.636 (4.03)	3.312 (2.94)	$P_t = 0.301$
	IQ-CODE	50 (48 – 54)	48 (24 – 49.5)	$P_{MW} = 0.048$*
	FAQ	0 (0 – 0.5)	0 (0 – 0)	$P_{MW} = 0.244$
	CDR-SB	0 (0 – 0.5)	0 (0 – 0)	$P_{MW} = 0.037$*
Cognitive Tests	**MMSE (#)**	29 (27 – 29)	30 (29 – 30)	$P_{MW} = 0.0026$*
	MoCA	24.5 (21.75 – 26)	26 (25.5 – 27)	$P_{MW} = 0.0029$*
	Contrast Sensitivity Test – Left & Rght	1.8 (1.68 – 1.95)	1.95 (1.68 – 2.06)	$P_{MW} = 0.422$
	FAB	**13.19 (2.84)**	**16.43 (1.51)**	**$P_t = 4.4 x 10^{-5}$**
	Fluency Animals	16.043 (5.21)	20.05 (5.19)	$p_t = 0.013$*
	Clock Design Test	7 (6 – 7)	7 (7 – 7)	$P_{MW} = 0.011$
	Fluency Phonemic	**8.74 (3.86)**	**12.90 (3.10)**	**$P_t = 2.6 x 10^{-4}$**
	HVLT 3rd trial	7.91 (1.78)	9.41 (1.68)	$P_t = 0.006$*
	HVLT total	19.26 (4.51)	23.73 (4.48)	$P_t = 0.002$*
	HVLT delayed recall	4.69 (3.052)	7.36 (2.74)	$P_t = 0.004$*
	BVMT 3rd trial	7.44 (2.99)	10.18 (2.34)	$P_t = 0.0014$*
	BVMT total	17 (7.88)	24.14 (7.06)	$P_t = 0.003$*
	BVMT delayed recall	6.35 (3.37)	9.96 (2.39)	$P_t = 0.002$*
	LNS	**7.35 (2.91)**	**10.32 (2.28)**	**$P_t = 4.6 x 10^{-4}$**
	Spatial Addition Test	**7.59 (4.69)**	**13.18 (4.37)**	**$P_t = 0.0002$**
	SDMT written	**29.5 (9.3133)**	**46.36 (10.10)**	**$P_t = 8.9 x 10^{-7}$**
	SDMT oral	**30.96 (11.39)**	**49.86 (10.59)**	**$P_t = 1.1 x 10^{-6}$**
	JLO (score)	14.69 (4.77)	16.77 (3.13)	$P_t = 0.092$
	TMT-A (sec)	**65.17 (33.07)**	**36.67 (11.80)**	**$P_t = 0.00057$**
	TMT-B (sec)	**163.65 (83.26)**	**76.68 (34.40)**	**$P_t = 7.1 x 10^{-5}$**
	Spatial span forward (#)	7.35 (1.80)	7.86 (1.81)	$P_t = 0.342$
	Spatial span backward (#)	**6.04 (1.77)**	**7.96 (1.91)**	**$P_t = 0.0012$**
	CTMT-Part 1 (sec)	**70.68 (28.28)**	**45 (15.01)**	**$P_t = 0.0006$**
	CTMT-Part 2 (sec)	79.23 (40.44)	47.61 (14.35)	$P_t = 0.002$*
	CTMT-Part 3 (sec)	92.32 (51.46)	50.91 (24.09)	$P_t = 0.002$*
	CTMT-Part 4 (sec)	90.27 (46.81)	56.41 (23.93)	$P_t = 0.005$*
	CTMT-Part 5 (sec)	**168.77 (91.13)**	**79.23 (37.39)**	**$P_t = 0.0002$**
	Witkin's Embedded Figure Test (Visual and Spatial Perception)	5.46 (3.78)	9.59 (5.23)	$P_t = 0.0046$*
	Driving scenes test score	38.73 (9.86)	44.86 (6.43)	$P_t = 0.0187$*
	UFOV – central vision and processing speed (msec)	754.78 (1108.33)	346850 (465630)	$P_t = 0.1251$
	UFOV – divided attention (msec)	**2317.18 (1517.72)**	**698.450 (565.182)**	**$P_t = 7.5 x 10^{-5}$**
	UFOV – selective attention (msec)	**3282.41 (1293.98)**	**1777.06 (981.41)**	**$P_t = 1.4 x 10^{-4}$**
	PVT (msec)	379.5 (337.3 – 471.3)	*328.5 (282.5 – 363.5)*	$P_{MW} = 0.014$*

Traffic load: Low [300 vehicles/hour], High [600 vehicles/hour]. Values are mean and SD for parametric test comparisons, and median and quartiles for non-parametric tests. Values in bold represent significant differences after Bonferroni correction. * Significant differences prior to Bonferroni correction

RPW: Rapid Pace Walk, FTT: Foot Tapping Time, TWT: Tandem Walking Test, TWT-RC: Tandem Walking Test – Reverse Counting, HRT: Head Rotation Task, UPDRS-III: Unified Parkinson's Disease Rating Scale part III-motor, IADL: Instrumental Activities of Daily Living, NPI: Neuropsychiatric Inventory, FBI: Frontal Behavioral Inventory, GDS: Geriatric Depression Scale, ESS: Epworth Sleepiness Scale, AIS: Athens Insomnia Scale, IQ-Code: Informant Questionnaire on Cognitive Decline in the Elderly, FAQ: Functional Activities Questionnaire, CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes, MMSE: Mini Mental Status Examination, MoCA: Montreal Cognitive Assessment, FAB: Frontal Assessment Battery, HTLV: Hopkins Verbal Learning Test, BVMT: Brief Visuospatial Memory Test-Revised, LNS: Letter Number Sequencing, SDMT: Symbol Digit Modalities Test, JLO: Judgement of Lines Orientation, TMT-A: Trail Making Test-A, TMT-B: Trail Making Test-B, CTMT: Comprehensive Trail Making Test, UFOV: Useful Field of View, PVT: Psychomotor Vigilance Test

Table 3: Group comparisons between PD and matched HC in features of motor, cognitive, and activities of daily living

Patients with PD performed worse on driving behaviors of tactical car control, revealing lower average speed across traffic loads, worse average reaction times, and maintaining greater headway distance from the vehicle ahead. Additionally, they performed worse on operational safety, especially having fewer sudden brakes when unexpected events occurred. They also performed worse on motor tasks of speed and balance, as well as executive and visuospatial tasks of processing speed, set shifting, working memory, and visuospatial attention.

We then aimed to better understand and more easily interpret cognitive, motor, and driving behaviors across groups by pursuing PCA-based dimensionality reduction for each of the three categories of features. Our analyses identified five driving simulation factors (70.36% of original variance), two motor performance factors (67.46% of original variance), and three cognitive performance factors (66.91% of original variance explained) (Tables 4-6).

We named the factors according to the relative contribution of individual variable loadings to each factor, thus representing major features of driving, cognitive, and motor ability.

	Variance explained = 70.36%	**Structure Matrix**					**Pattern Matrix**				
		Tactical Driving Praxis	**Operational Safety**	**Car Spatial Road Positioning**	**Tactical Driving Related Accidents**	**Reaction Time Related Accidents**	**Tactical Driving Praxis**	**Operational Safety**	**Car Spatial Road Positioning**	**Tactical Driving Related Accidents**	**Reaction Time Related Accidents**
Low traffic Load Variables	**Average Speed**	**0.86**	0.40	0.12	**-0.42**	-0.17	**0.77**	0.22	0.078	-0.32	-0.03
	Average Speed-Standard Deviation	**0.81**	0.33	0.17	-0.31	-0.08	**0.74**	0.17	0.12	-0.21	0.04
	Lateral Position Average	-0.07	0.02	**-0.87**	-0.07	-0.269	-0.05	-0.02	**-0.85**	-0.07	-0.021
	Lateral Position Average-Standard Deviation	0.21	**0.77**	0.21	-0.36	-0.05	-0.02	**0.77**	0.25	-0.33	-0.02
	Headway Average Distance	**-0.87**	-0.20	-0.07	**0.45**	0.22	**-0.81**	-0.01	-0.02	0.34	0.08
	Headway Average-Standard Deviation	**-0.85**	-0.26	-0.13	**0.43**	-0.32	**-0.76**	-0.07	-0.09	0.32	0.19
	Wheel Average Position	**-0.04**	-0.20	0.035 (0.159)	**0.678**	-0.05	**0.07**	-0.18	0.03	**0.69**	-0.09
	Wheel Average-Standard Deviation	**0.61**	**0.59**	0.16	-0.01	-0.24	**0.47**	**0.48**	0.16	-0.01	-0.15
	Hit Of Side Bars	0.15	**0.82**	-0.13	-0.17	-0.09	-0.05	**0.82**	-0.01	-0.14	-0.05
	Sudden Brakes	0.262	**0.792**	-0.009	0.023	-0.17	0.08	**0.77**	0.03	0.08	-0.13
	Speed Limit Violation	0.354	**0.547**	0.291	-0.38	0.14	0.21	**0.51**	0.29	-0.33	0.19
	Average Reacion time	**-0.786**	-0.155	-0.264	0.003	**0.48**	**-0.72**	0.01	-0.24	-0.13	0.39
	Accident Probability	0.359	-0.108	0.106	**-0.521**	0.04	0.35	-0.2	0.06	**-0.49**	0.11
High traffic Load Variables	**Average Speed**	**0.94**	0.26	-0.03	0.01	-0.16	**0.95**	0.05	-0.09	0.13	-0.01
	Average Speed-Standard Deviation	**0.79**	0.27	0.16	0.30	0.07	**0.83**	0.12	0.01	0.40	0.18
	Lateral Position Average	0.11	0.22	**-0.90**	-0.005	0	0.16	0.15	**-0.91**	0.02	0.01
	Lateral Position Average-Standard Deviation	0.10	**0.67**	0.07	0.02	-0.06	-0.05	**0.69**	0.11	0.05	00.05
	Headway Average Distance	**-0.89**	-0.18	0.16	0.15	0.10	**-0.92**	0.03	0.23	0.04	-0.06
	Headway Average-Standard Deviation	**-0.89**	-0.05	0.13	0.06	0.05	**-0.97**	0.16	0.21	-0.05	-.010
	Wheel Average Position	-0.10	-0.29	0.17	0.27	**0.70**	0.08	-0.26	0.10	0.24	**0.69**
	Wheel Average-Standard Deviation	**0.62**	**0.5**	0.05	-0.04	**-0.45**	**0.49**	0.39	0.06	0.06	-0.36
	Hit Of Side Bars	-0.06	**0.74**	**-0.49**	0.01	-0.132	-0.20	**0.76**	-0.43	0.02	-0.01
	Sudden Brakes	0.35	**0.62**	-0.19	0	-0.084	0.24	**0.57**	-0.19	0.06	-0.01
	Speed Limit Violation	0.18	**0.52**	0.02	**0.51**	0.29	0.19	**0.52**	0.01	**0.54**	0.32
	Average Reacion time	**-0.65**	-0.04	-0.16	-0.10	**0.52**	**-0.61**	0.11	-0.15	-0.19	0.44
	Accident Probability	-0.13	0.01	0.12	-0.14	**0.69**	**-0.07**	0.05	0.08	-0.18	**0.69**

Table 4: Factors of Driving Simulation Across High and Low Traffic Load in Rural Driving Conditions

Variance explained = 67.46%	Structure Matrix		Pattern Matrix	
Factor of motor performance	**Speed and dexterity**	**Axial movement**	**Speed and dexterity**	**Axial movement**
RPW	**0.81**	-0.26	**0.79**	-0.23
HRT minimum	-0.11	**0.74**	-0.08	**0.73**
FTT time	**0.77**	-0.02	**0.77**	0.01
FTT errors	0.11	**-0.74**	0.09	**-0.74**
TWT time	**0.87**	-0.19	**0.86**	-0.16
TWT errors	**0.71**	0.44	**0.72**	**0.47**
TWT-RC time	**0.83**	-0.387	**0.82**	-0.36
TWT-RC	**0.71**	0.42	**0.72**	**0.44**
RPW: Rapid Pace Walk, FTT: Foot Tapping Time, TWT: Tandem Walking Test, TWT-RC: Tandem Walking Test – Reverse Counting, HRT: Head Rotation Task				

Table 5: Motor performance factors across PD and healthy controls

Variance Explained = 66.91%	Structure Matrix			Pattern Matrix		
Factors of Cognitive Performance	**Planning and Processing Speed**	**Visuospatial Attention and Planning**	**Verbal Learning and Memory**	**Planning and Processing Speed**	**Visuospatial Attention and Planning**	**Verbal Learning and Memory**
FAB	**0.79**	**-0.51**	0.40	**0.7**	-0.11	0.15
Fluency Animals	**0.54**	**-0.58**	0.31	0.34	-0.39	0.06
Clock Design Test	**0.46**	**-0.67**	0.07	0.21	**-0.68**	-0.26
Fluency Phonemic	**0.72**	-0.39	**0.51**	**0.65**	0.07	0.35
MMSE	**0.69**	-0.23	0.13	**0.75**	0.11	-0.04
MoCA	**0.66**	**-0.47**	0.38	**0.55**	-0.14	0.16
HVLT 3rd trial	**0.57**	**-0.49**	**0.86**	0.34	-0.02	**0.75**
HVLT total	**0.61**	**-0.51**	**0.83**	0.39	-0.03	**0.70**
HVLT delayed recall	0.37	-0.36	**0.85**	0.15	0.05	**0.83**
BVMT 3rd trial	**0.86**	-0.43	0.29	**0.84**	-0.01	0.04
BVMT total	**0.84**	**-0.50**	0.30	**0.77**	-0.12	0.03
BVMT delayed recall	**0.85**	**-0.55**	0.38	**0.75**	-0.18	0.01
LNS	**0.77**	**-0.46**	0.16	**0.74**	-0.14	-0.11
Spatial Addition Test	**0.60**	**-0.59**	0.42	0.39	-0.34	0.17
SDMT written	**0.77**	**-0.76**	**0.49**	**0.51**	-0.45	0.15
SDMT oral	**0.75**	**-0.71**	**0.48**	**0.52**	-0.39	0.17
JLO	**0.46**	-0.28	0.35	0.4	0.02	0.24

TMT-A	**-0.54**	**0.90**	**-0.48**	-0.12	**0.80**	-0.12
TMT-B	**-0.69**	**0.86**	-0.31	-0.36	**0.72**	0.09
Spatial span forward	0.17	-0.38	**0.52**	-0.07	-0.24	0.44
Spatial span backward	**0.55**	**-0.60**	0.42	0.32	-0.37	0.17
CTMT-Part 1	**-0.62**	**0.89**	-0.39	-0.26	**0.79**	0.07
CTMT-Part 2	**-0.47**	**0.93**	-0.40	-0.03	**0.90**	-0.02
CTMT-Part 3	-0.39	**0.93**	**-0.46**	0.09	**0.93**	-0.11
CTMT-Part 4	**-0.66**	**0.84**	-0.30	-0.35	**0.70**	0.09
CTMT-Part 5	**-0.78**	**0.73**	-0.33	**-0.56**	**0.46**	0.02
Witkin's Embedded Figure Test (Visual and Spatial Perception)	**0.78**	**-0.48**	0.34	**0.70**	-0.11	0.09
Driving scenes test	**0.68**	**-0.68**	**0.51**	0.43	-0.38	0.23
UFOV - central vision and processing speed	-0.03	**0.65**	**-0.51**	0.41	**0.71**	-0.34
UFOV - divided attention	**-0.56**	**0.85**	-0.34	-0.20	**0.76**	0.03
UFOV - selective attention	**-0.46**	**0.80**	-0.3	-0.1	**0.75**	-0.01
PVT	-0.23	**0.81**	**-0.45**	0.23	**0.85**	-0.18
MMSE: Mini Mental Status Examination, MoCA: Montreal Cognitive Assessment, FAB: Frontal Assessment Battery, HTLV: Hopkins Verbal Learning Test, BVMT: Brief Visuospatial Memory Test-Revised, LNS: Letter Number Sequencing, SDMT: Symbol Digit Modalities Test, JLO: Judgement of Lines Orientation, TMT-A: Trail Making Test-A, TMT-B: Trail Making Test-B, CTMT: Comprehensive Trail Making Test, UFOV: Useful Field of View, PVT: Psychomotor Vigilance Test						

Table 6: Cognitive performance factors across PD and healthy controls

Driving simulation factors were interpreted as latent variables of (a) Tactical Driving Praxis, (b) Operational Safety, (c) Car Spatial Road Positioning, (d) Tactical Driving Related Accidents, and (e) Reaction Time Related Accidents. Motor performance factors were interpreted as (a) Motor Speed and Dexterity, and (b) Axial Movement, and cognitive performance factors were interpreted as (a) Planning and Processing Speed, (b) Visuospatial Attention and Planning, and (c) Verbal Learning and Memory.

We subsequently examined whether we could predict performance in the five driving behavior domains from the derived cognitive and motor domains across groups using multivariate regression with backward selection (Table 7), an approach that could help assess whether routine clinical assessments can guide driving recommendations.

	Adjusted R^2	**F**	**P**
Tactical Driving Praxis	**0.55**	**14.416**	**5.3×10^{-6}**
Final Model	Coefficients (SE)		
Constant	0.013 (0.112)		0.905
Planning and Processing Speed	0.369 (0.128)		0.007
Speed and Dexterity	-0.336 (0.121)		0.009
Axial Movement	0.328 (0.121)		0.011
Car Spatial Road Position	**0.205**	**5.261**	**0.011**
Final Model	Coefficients (SE)		
Constant	-0.203 (0.165)		0.228
Planning and Processing Speed	-0.581 (0.193)		0.005
Visuospatial Attention and Planning	-0.747 (0.279)		0.012
Reaction Time Related Accidents	**0.382**	**7.791**	**0.001**
Final Model	Coefficients (SE)		
Constant	-0.178 (0.142)		0.22
Visuospatial Attention and Planning	-0.591 (0.225)		0.014
Learning and Memory	-0.48 (0.146)		0.003
Axial Movement	-0.534 (0.151)		0.001

Table 7: Prediction of Tactical Driving Praxis, Car Spatial Road Position, and Reaction Time Related Accidents by motor and cognitive factors

Performance in three of the five driving behavior domains (Tactical Driving Praxis, Car Spatial Road Position, and Reaction Time Related Accidents) could be predicted by motor and cognitive domain performance. Instead, our regression models of motor and cognitive factors could not predict Operational Safety or Tactical Related Accidents.

In order to examine the combined relationship between the five derived factors of driving behavior on one hand and the five derived clinical motor and cognitive factors on the other, while accounting for their inter-relations, we subsequently pursued CCA between these two groups of factors (Figure 1).

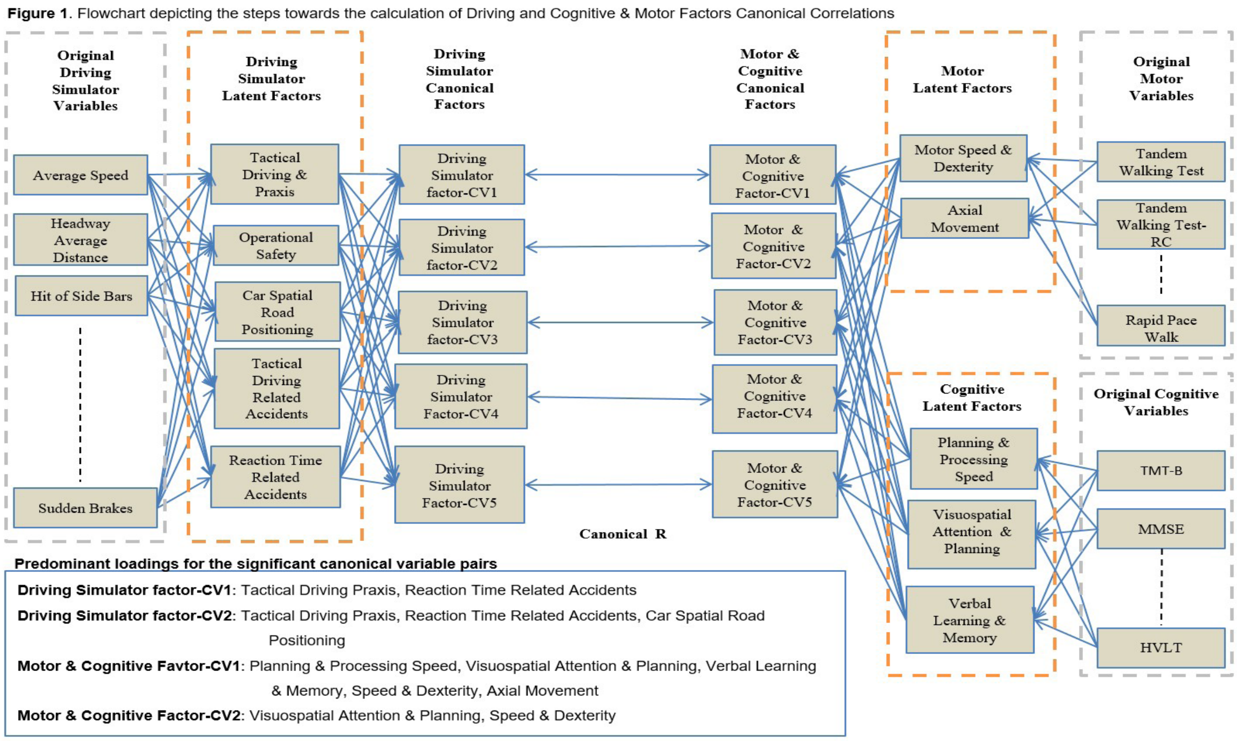

Figure 1: Flowchart depicting the steps towards the calculation of driving and cognitive & motor factors canonical correlations

We obtained five orthogonal canonical correlations (CC) that explained these combined relationships (Table 8).

Canonical Variate Pair	1	2	3	4	5
Canonical Correlation *R*	**0.848**	**0.741**	0.462	0.210	0.105
Wilks' Λ (*p*)	**0.095 (< 10^{-4})**	**0.337 (0.018)**	0.747 (0.532)	0.949 (0.839)	0.989 (0.579)
Redundancy Index – Driving Simulation Set	**0.404**	**0.304**	0.207	0.089	0.048
Redundancy Index – Motor & Cognitive Set	**0.544**	**0.311**	0.163	0.090	0.031
Factor Contributions (*L*)					
Driving - Tactical driving praxis	**-0.854**	**-0.354**	-0.301	-0.144	0.182
Driving - Operational Safety	-0.148	0.223	0.089	-0.948	0.147
Driving - Car spatial road positioning	0.159	**-0.605**	0.617	0.035	0.476
Driving - Tactical driving related accidents	-0.128	-0.094	0.50	-0.048	-0.85
Driving - Reaction time related accidents	**0.583**	**-0.541**	-0.524	-0.237	-0.191
Cognitive - Planning and processing speed	**-0.721**	-0.014	-0.685	0.106	0.011
Cognitive - Visuospatial attention and planning	**0.584**	**0.746**	0.209	0.119	0.212
Cognitive - Verbal learning and memory	**-0.581**	0.14	0.242	0.665	-0.376
Motor - Speed and dexterity	**0.538**	**0.552**	-0.177	-0.365	-0.491
Motor - Axial movement	**-0.753**	0.044	0.141	-0.637	-0.081

Table 8: Canonical Correlation of Driving and Cognitive & Motor factors

The first two CC satisfied the predetermined criteria of significance, with the first CC associating predominantly tactical driving (L2 = 73%) and reaction time related accidents (L2 = 34%) to all motor and cognitive factors (L2 = 29 – 57%), whereas the second, associating car spatial road positioning (L2 = 37%) and reaction time related accidents (L2 = 29%) to visuospatial attention and planning (L2 = 56%) and motor speed and dexterity (L2 = 30%).

Finally, we examined whether the derived driving factors on one hand and clinical motor and cognitive factors on the other can help predict if a person has PD by applying LDA. Of the different models, best cross-validation results for predicting PD were achieved through Driving Behavior factors alone, as well as the combination of motor and cognitive factors, whereas their combination led to mildly worse sensitivity (Table 9).

		HC	PD	Total	Se	Sp	LR+	LR-	DOR
Driving, Motor & Cognitive factors	HC	13 (72.2)	5 (27.8)	18	0.56	0.72	2.02	0.61	3.33
	PD	7 (43.8)	9 (56.3)	16					
Driving factors	HC	18 (78.3)	5 (21.7)	23	0.79	0.78	3	0.27	11.15
	PD	4 (78.3)	15 (21.7)	19					
Cognitive & Motor factors	HC	14 (77.8)	4 (22.2)	18	0.74	0.78	3.3	0.34	9.73
	PD	5(26.3)	14 (73.7)	19					
HC: Healthy Controls, PD: Parkinson's Disease, Se: Sensibility, Sp: Specificity, LR+: Positive Likelihood ratio, LR-: Negative Likelihood ratio, DOR: Diagnostic Odds Ratio									

Table 9: Cross-validation results in predicting PD by combining motor, cognitive, and driving factors

In the same vein, we examined whether motor and cognitive factors can predict accidents during simulated driving in patients with PD. Combined accident probability across low and high traffic conditions and across rural settings was best predicted though cognitive factors, and less so through H&Y and UPDRS-III motor scales. Motor factors, alone or in combination with cognitive factors, led to weaker predictions (Table 10).

		No Accident	Accident	Total	Se	Sp	LR+	LR-	DOR
H&Y & UPDRS-III	No accident	18 (85.7)	3 (14.3)	21	0.57	0.86	3.99	0.50	7.99
	Accident	3 (42.9)	4 (57.1)	7					
Motor Factors	No accident	8 (72,7)	3 (27.3)	11	0.40	0.72	1.47	0.83	1.78
	Accident	6 (60)	4 (40)	10					
Cognitive Factors	No accident	9 (81.8)	2 (18.2)	11	0.78	0.82	4.27	0.27	15.69
	Accident	2 (22.2)	7 (77.8)	9					
Motor & Cognitive Factors	No accident	8 (80)	2 (20)	10	0.56	0.80	2.78	0.56	4.99
	Accident	4 (44.4)	5 (55.6)	9					
HC: Healthy Controls, PD: Parkinson's Disease, Se: Sensibility, Sp: Specificity, LR+: Positive Likelihood ratio, LR-: Negative Likelihood ratio, DOR: Diagnostic Odds Ratio									

Table 10: Cross-validation results in predicting accident probability in PD by motor and cognitive factors

Discussion

In this study we aimed to investigate whether specific motor and cognitive tests performed in clinic can predict behind-the-wheel driving behavior in Parkinson's disease, through a multidisciplinary driving simulator experiment.

First, our individual feature group comparisons between PD and HC groups indicated that drivers with PD performed worse in both metrics of tactical car control and operational safety, which are also in keeping with prior literature [9-14]. Our results add to our knowledge that people with PD maintain lower average speed and greater headway distance from the vehicles ahead. These behaviors may burden urban networks through traffic jams, further complicating the use of roads by drivers and pedestrians. Reduced speed may also lead to dangerous overtaking by following vehicles, increasing the rate of accidents [15]. Additionally, the increased reaction time observed in people with PD is a critical operational safety metric that has been associated with increased risk of accidents [11,16]. The worse performance observed in executive and visuospatial abilities in PD is in line with previous studies [17-20] and is likely to interfere negatively with dynamic driving demands, both tactical and operational. This can be expressed as difficulties in adjusting driving behaviors according to changing traffic burden, when approaching intersections or traffic lights, changing lanes, or car maneuvering [9,12,21-23].

A novelty in our work involves the detailed inclusion of in-clinic motor tasks (RPW, FTT, TWT, TWT-RC, and HRT), in addition to the UPDRS-III and H&Y, for predicting driving behavior in PD. In contrast to UPDRS-III and H&Y, these tasks can be performed by non-experts. As anticipated, participants with PD performed worse than HC on RPW and TWT-RC, but not on the other metrics (Table 3). This can be explained by RPW being affected by cardinal motor features of PD, namely rigidity and bradykinesia, whereas TWT-RC represents both motor and cognitive features of speed, balance, and executive functioning. The lack of significant differences between groups for the other metrics, despite a trend in most, is more likely explained by mild to moderate overall motor symptom severity in our participants (median H&Y = 2), and less so by not capturing relevant clinical signs, which are more pronounced later in the disease course. Motor scales, especially RPW, TWT-RC proved reliable to lesser extent before Bonferroni correction.

Dimensionally reducing our original dataset (Tables 4-6) allowed for interpretation of driving, motor, and cognitive performance into latent conceptual domains. These latent variables provide a degree of abstraction that permits us to describe relations among a class of events or variables that share something in common, rather than making highly concrete statements restricted to the relation between more specific, seemingly idiosyncratic variables. In other words, latent variables permit us to generalize relationships [41]. Some caution is required when interpreting loading contributions to latent factors depending on their sign. Specifically, positive or negative loading signs in Tables 4, 5, and 6 guide interpretation of a factor's scores as to whether a high factor score indicates better or worse performance. For example, a high score in factor Speed and Dexterity indicates worse performance (Table 5), since its loadings stem from large values in tests regarding speed (i.e., slow performance). Our latent driving simulator factors showed similar loading contributions in high and low traffic loads except for accidents related to tactical driving and reaction time (Table 4). The differential loading of driving simulation metrics observed between low (i.e., wheel positioning, headway distance, average speed) and high (i.e., speed limit violation) traffic loads to tactical driving related accidents can be explained through driving adaptation to dynamic road conditions that have different driving demands. For example, in low traffic loads there is more time-to-closure (τ), defined as the ratio of the current distance-to-target over the current speed towards the target, [42] by maintaining longer headway distances, whereas in high traffic loads, where headway distance has little variability, speed limit violation contributes more to accident outcomes. Similarly, although reaction time contributes similarly to both high and low traffic loads, its contribution in high traffic loads is co-mediated by wheel position manipulation, possibly indicative of more spatial restrictions in high traffic load environments.

In western societies maintaining driving independence is considered an instrumental activity of daily living that enables individuals to engage in activities that are identified as crucial to maintain their quality of life [24]. In order to do so, studies indicate that drivers with PD have developed both strategic and operational compensatory driving behaviors. On a strategic level, interview-based feedback with patients revealed that their awareness of PD-related symptoms (rigidity, fatigue, reduced concentration) interfering negatively with their driving performance made them avoid driving long distances, plan a priori optimal routes, and plan rest stops [25]. Additionally, they avoid driving in the dark, snow or heavy rain, or crowded urban environments [42, 43]. Behind the wheel studies also indicate that driving behavior outcomes are defined by tactical parameters, which include all voluntary actions made by the driver to maintain safety and avoid potentially dangerous driving situations [18, 26].

Despite that both non-motor and motor symptoms affect driving behavior, it is not a sine qua non that people with PD should be automatically precluded from driving, especially when symptoms are mild [10, 11, 27]. For this reason, we focused on identifying early features and their combinations that interfere significantly with driving behavior, and we thus recruited our cohort of active drivers with PD with mild motor and cognitive signs. Even more, although not part of our exclusion criteria, none of the participants had a history of traffic accidents provoked by them. To that extent, we pursued multivariate regression with backward selection and identified which latent cognitive and motor factors best predicted individual driving behavior domains (Table 7). Of the five driving domains, the performance in three (i.e., Tactical Driving Praxis, Car Spatial Road Position, Reaction Time Related Accidents) could be significantly explained by cognitive and motor symptoms. Tactical driving praxis, a critical parameter of driving behavior, [16] was best predicted by cognitive-motor domains (planning and processing speed, speed and dexterity, and axial movement) whose performance is mediated by frontal subcortical systems [28]. Instead, spatial elements of driving behavior, as represented in Car Spatial Road Position, were mediated predominantly by spatial cognitive abilities that typically involve parieto-frontal dorsal executive networks, as represented in visuospatial attention and planning, and less so by frontal and frontal-subcortical executive function networks of planning and processing speed. Additionally, executive-predominant features contributed to reaction time related accidents, but were co-mediated by learning and memory features that involve temporo-parietal networks as well. Overall, the above suggest that tactical driving praxis and car spatial positioning are voluntary agencies associated with planning and linked to frontal cortical and subcortical networks. Instead, reaction time related accidents, an operational safety feature further mediated by immediate "reflex" re-action, further require an ability to learn and retain information, possibly learning how to avoid environments providing little time to react, and perhaps "remembering" how to react in accident-prone environments.

Since multivariate regression approaches do not account for the combined relationship between the five derived factors of driving behavior on one hand and the five derived clinical motor and cognitive factors on the other while accounting for their inter-relations, we pursued CCA. Our CCA on objective data on simulated driving behavior add to our understanding of the aforementioned observations and prior studies by revealing the main dimensions that associate a set of driving behavior features to a set of cognitive and motor performance features (Table 8). Specifically, the predominant association was between driving canonical variate of tactical driving praxis and reaction time related accidents to multidomain cognitive features, especially executive functions of planning and processing speed (~52% of explained variance), as well as axial motor function (~57% of explained variance), which typically localize to frontal and frontal-subcortical networks and are well known to be affected in PD [28]. Nonetheless, significant contributions were also observed in visual attention and planning (~34% of explained variance), likely reflective of parieto-frontal dorsal executive network deficits in PD, verbal memory (~34% of explained variance), which may indicate temporo-parietal network deficits through frequent co-morbid Alzheimer's disease pathology, and motor speed and dexterity (~29% of explained variance), another characteristic motor feature of PD localizing in frontal and frontal-subcortical networks[28]. The above confirm hypotheses raised by previous studies that both motor and non-motor symptoms of PD influence tactical and accident related driving behavior [2, 12, 13, 20, 29-33]. Our CCA (Table 8) also revealed that spatial elements of driving (i.e., Car Spatial Road Positioning) together with reaction time accidents were associated to cognitive domains of visuospatial attention and planning and motor domain of speed and dexterity. This finding suggests that there is a less prominent, but still significant, contribution by the dorsal executive parieto-frontal network on unique aspects of driving performance whose hubs are also in posterior brain areas [28].

The data obtained, combining the specific driving simulator, motor, and neuropsychological variables into factors, also provide the opportunity to examine whether any of their combinations can help diagnose Parkinson's disease, while using expert diagnosis following clinical criteria as the gold standard. Specifically, using LDA, and after cross-validation, best results were achieved through driving simulator factors, and similar accuracy was observed when combining motor and cognitive factors, where approximately three out of four people were correctly classified (Table 9). Instead, weaker prediction was observed when combining all factors, probably a result of overfitting as the number of variables in the model increases disproportionally to the number of observations. These results can prove useful for planning public health and safety policies. First, at face value, older people who participate in simulator driving assessments, such as in re-certification driving examinations, could be given a likelihood of having PD and whether they would benefit from being evaluated by an expert. Similarly, in well-visits that include motor and cognitive performance, non-expert health professionals can pursue motor and cognitive tasks that specifically target the aforementioned domains towards identifying people at risk for having PD. Even more, as the next frontier, driving-related technological advancements, such as built-in car sensors, on-road traffic cameras, and GPS systems, can provide information on strategic and tactical driving parameters, which in turn could serve in identifying people who are at risk for PD and guide them for formal assessments.

Inversely, if a person has PD, it is useful to identify who is at higher risk of being in an accident using objective motor or cognitive metrics obtained in clinical settings [27, 34]. Our LDA analyses of combining motor and cognitive factors (Table 10), revealed that the commonly used UPDRS and H&Y PD motor scales provided fair, but not as useful, predictive accuracy, especially when compared to cognitive testing. This is in keeping with previous studies on the utility of motor scales such as UPDRS [35-38] and cognitive testing [12, 14, 18, 22, 39-41]. Otherwise, the faster-to-extract motor factors from our analyses yielded mildly worse specificity levels to the UPDRS and H&Y scales, pointing to a potentially more time-efficient motor task combination that can be used in non-expert settings, although its utility is to be established given its comparatively low sensitivity. Finally, the combination of motor and cognitive factors led to weaker predictive accuracy, possibly relating to overfitting when the number of variables is disproportionate to the number of participants, as well as motor factors alone not adding significantly useful information to cognitive metrics.

Combining the above information, our findings indicate that quantification of cognitive abilities, especially those mediated by frontal, frontal-subcortical, and parieto-frontal executive networks, as well as driving simulator metrics, especially of tactical driving praxis and car spatial road positioning, can be useful in early diagnosis of PD as well as in predicting accidents in people with PD. Additionally, motor factors of speed and dexterity, as well as axial movement, can also prove useful on their own, especially in predicting tactical driving parameters and, indirectly, accident probability. With the advent of self-administered cognitive tests, the cost of performing these assessments in quantifying a person's cognitive performance can be further decreased, and all the above assessments can be performed in non-expert settings at a large scale.

Such an infrastructure can also help in planning future studies in lager samples sizes that can help validate their utility in real-world settings and policy planning. Our current study is, thus, limited by its relatively smaller sample size, despite the deep phenotyping of our participants. Nonetheless, our driving and clinical inclusion criteria were very strict, in order to resemble participants who are current drivers and at the early stages of their disease. The above indicate that driving behaviors in our cohort were mostly affected by non-motor symptoms of the disease, which do not show large variations, depending on the sample size, compared to the variations that would be present with motor symptoms. Another, parameter that needs to be recognized is that the driving measures were obtained from a simulator in rural road and not in urban or in highway setting. Although a simulator permits very accurate and reproducible data, examination is performed in a virtual environment and not in real conditions as an on-road driving evaluation. However, driving in a simulator setting is still considered 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 indices, which is not feasible under on-road driving conditions [42, 43]. Nonetheless, future studies could increase our insight and strengthen our findings using larger sample sizes under on-road driving conditions or analyzing real word data from the safety systems that nowadays modern vehicles have. This approach could also be applied to other degenerative diseases that have motor and cognitive symptoms such as Alzheimer's Disease, Multiple Sclerosis, and Stroke.

In conclusion, the findings of this study indicate that driving ability in PD is related to an interrelation between cognition, especially executive and visuospatial abilities, and motor performance. Driving simulator factors alone or in combination with factors of cognition and motor performance can be used for distinguishing PD form healthy individuals. From our results it is evident that cognitive testing alone, or in combination with easy to administer motor tasks, can be used by physicians as an objective tool for predicting driving behavior, including accident probability, in order to suggest who may need to stop driving in this specific population.

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