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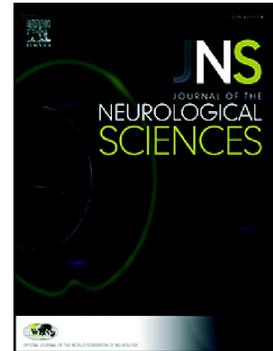
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Extended “Timed Up and Go” Assessment as a Clinical Indicator of Cognitive State in Parkinson’s Disease

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ABSTRACT

Objective: To evaluate a modified extended Timed Up and Go (extended-TUG) assessment against a panel of validated clinical assessments, as an indicator of Parkinson's disease (PD) severity and cognitive impairment.

Methods: Eighty-seven participants with idiopathic PD were sequentially recruited from a Movement Disorders Clinic. An extended-TUG assessment was employed which required participants to stand from a seated position, walk in a straight line for 7 metres, turn 180 degrees and then return to the start, in a seated position. The extended-TUG assessment duration was correlated to a panel of clinical assessments, including the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Quality of Life (PDQ-39), Scales for Outcomes in Parkinson's Disease (SCOPA-Cog), revised Addenbrooke's Cognitive Index (ACE-R) and Barratt's Impulsivity Scale 11 (BIS-11).

Results: Extended-TUG time was significantly correlated to MDS-UPDRS III score and to SCOPA-Cog, ACE-R ($p < 0.001$) and PDQ-39 scores ($p < 0.01$). Generalized linear models determined the extended-TUG to be a sole variable in predicting ACE-R or SCOPA-Cog scores. Patients in the fastest extended-TUG tertile were predicted to perform 8.3 and 13.4 points better in the SCOPA-Cog and ACE-R assessments, respectively, than the slowest group. Patients who exceeded the dementia cut-off scores with these instruments exhibited significantly longer extended-TUG times.

Conclusions: Extended-TUG performance appears to be a useful indicator of cognition as well as motor function and quality of life in PD, and warrants further evaluation as a first line assessment tool to monitor disease severity and response to treatment. Poor extended-TUG performance may identify patients without overt cognitive impairment from whom cognitive assessment is needed.

INTRODUCTION

Parkinson's disease is recognised by an assortment of clinical signs, and may include a resting tremor, bradykinesia, rigidity, reduced postural reflexes, emotional disturbance, sleep disturbance, and cognitive decline. Although traditionally framed as a motor disorder, a plethora of non-motor symptoms has permitted the identification of a broad cognitive decline in some PD patients. Indeed, non-motor items in the Unified Parkinson's Disease Rating Scale are thought to confer accuracy in the determination of quality of life than motor symptoms^{1, 2}. Of these, cognitive impairment is most burdensome to individuals and their carers.

Cluster analyses³, longitudinal and epidemiological work⁴ have illustrated complexity in the distribution, nature, and pattern of cognitive decline in PD. The heterogeneity of the cognitive deficits in PD patients significantly complicates the clinical diagnosis, but usually includes deficits in executive functions⁵, attention⁶, and working memory⁷. Moreover, the postural instability-gait dominant subtype of PD demonstrates a more accelerated cognitive decline than the tremor dominant subtypes^{8, 9} and in idiopathic PD patients, freezing and gait difficulties have been correlated to quality of life and cognitive impairment^{9, 10}.

Motor assessments routinely used in the clinic, such as a 10m Walk, and the Timed "Up and Go" (TUG)¹¹, may potentially be indicators of both motor *and* cognitive aspects of the disease. A recent study found an increasing TUG time correlated with decreasing verbal fluency and quality of life, and could accurately predict a propensity for falling¹². However, the traditional TUG assessment can show variability in correlating to aspects of PD, and is constrained by its inability to differentiate between control subjects, when using test duration

alone¹³. More recently, a modification to the traditional TUG, whereby total distance is increased from 6 to 14 metres, has enabled a more accurate gait assessment in PD¹⁴. Further, the extended-TUG was found to be a valid treatment outcome measure, irrespective of location (home or clinic) or practitioner discipline¹⁵. When coupled with instrumental analysis, subcomponents of the TUG are also more sensitive in identifying patient group differences, particularly in early PD¹⁶. It has previously been hypothesized that the improved sensitivity of this assessment may be due to the longer walking distance, potentially providing greater functional information of relevance to how patients manage with everyday tasks¹⁷. The extended-TUG assessment also correlates closely with patient quality of life¹⁸, a composite outcome measure derived from cognitive, motor and other aspects of the disease.

In the present study, we characterized a heterogeneous Australian cohort of idiopathic PD (IPD) patients with the objective of determining readily accessible measures of disease status. We have employed a battery of demographic, motor, and cognitive assessments to elucidate key predictors of cognitive decline, in a diverse idiopathic PD cohort. Of these, an extended-TUG assessment was shown to be an optimal marker of patient function, suggesting it has predictive potential across both motor and cognitive domains.

METHODS

Subjects

Eighty-seven home-based patients with IPD were sequentially recruited from the Movement Disorders Clinics at the Western Australian Neuroscience Research Institute (Perth, Australia) between 2008-2015. All were ambulant and independent with activities of daily

living, none were known to have any other neurological disorder. Patients with dementia were not actively excluded. All patients were examined by a movement disorder neurologist prior to inclusion in the study for verification of the diagnosis in accordance with the UK Brain Bank criteria for IPD¹⁹. The study was approved by the Sir Charles Gairdner Hospital Human Research and Ethics Committee (Approval number 2006/073), and written informed consent was obtained from all participants, in accordance with the National Health and Medical Research Council guidelines.

Clinical assessments

The clinical evaluations included assessments of patient demographics and medications (Table 1), cognition, and other disease-related features. All PD medications were converted to levodopa equivalent daily doses (LEDD)²⁰. Motor symptoms were evaluated in the 'ON' state using the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, and Hoehn and Yahr Scale²¹. The Abnormal Involuntary Movement Scale (AIMS) was used to grade the severity of involuntary movements in the sitting position, both at rest and during a backward counting task²².

Each participant completed a battery of neuropsychological assessments with Clinical Psychologist. Global cognitive function was assessed using the 'Scales for Outcomes in Parkinson's Disease-Cognition' (SCOPA-Cog)²³, and a revised 'Addenbrooke's Cognitive Examination' (ACE-R)²⁴. In addition, the Mini-Mental State Examination (MMSE), 'Barrett Impulsivity Scale 11' (BIS-11), a validated self-report for impulsivity²⁵, and a revised 'Cambridge Behavioural Index' (CBI-R)²⁶ with carer input were administered for each patient. For global quality of life (QoL), the summary index of the Parkinson's Disease

Questionnaire (PDQ-39)²⁷ was used, with scores ranging from 0 (highest QoL) to 100 (lowest QoL). For establishing appropriate dementia cut-off scores, pre-determined cut-off scores for both the SCOPA-Cog (20²⁸) and ACE-R (82.5²⁹) assessments were utilised. s

Extended Timed Up and Go assessment

Participants completed a modified Timed Up and Go (TUG) assessment¹¹, referred to hereafter as an extended-TUG assessment. Participants were assessed within a 3-hour morning window in a self-reported “ON” state as per their regular medication. were asked to sit correctly with their hips to the back of the seat, in a stable and standard chair equipped with armrests. The participants were allowed to use the armrests during the standing movement. Participants were instructed to stand up from their seated position, walk a distance of 7 meters at a comfortable pace, make a 180-degree turn, and then return to the start, in a seated position. The total duration taken to complete this modified and extended TUG was recorded. Participants were allowed gait assistive devices, but assistance by another person was not permitted. All assessments were conducted in the morning to standardize comparisons between the patients. Several studies have used and reported outcomes based on this lengthened walk distance using objective measures^{13, 14, 30}.

Statistical methods

Data was analysed using IBM-SPSS (v. 23, IBM corporation). A significant nominal *P*-value of ≤ 0.05 was employed. Patients were grouped into tertiles according to extended-TUG times (Slow, Medium, Fast). Clinical assessment and patient variables were used to compare each of the tertile groups. One-way analysis of variance (ANOVA) tests were used to compare the

difference between participant groups, relative to demographic and clinical variables. Pearson correlation coefficients were calculated to determine the relationship between examined variables. The correlation criteria adopted were: $r = .1 - .3$ small, $.3 - .5$ moderate, $.5 - .7$ large and $>.7$ very large.

Generalized linear models (GLM) were created to analyse the relationship between demographic and clinical variables, and cognitive function (determined by SCOPA-Cog and ACE-R assessments). The variables included in the GLMs were gender, disease duration, age of onset, Hoehn and Yahr stage, Schwab and England, and levodopa equivalent daily doses of medications (mg/day). Non-significant factors were removed singularly in order of least significance, until the final models were determined.

RESULTS

Cohort information and clinical data

Mean demographic details and the results of clinical assessments are shown in Table 1. The IPD cohort enrolled in this study were predominantly male, broadly ranging in age, age of onset, and disease duration. The heterogeneous cohort displayed a relatively low mean Hoehn & Yahr [median (interquartile range)] 1 (1-2) score, and an average MDS-UPDRS III motor score of 12.8 (± 14.2). In addition, the PD cohort completed both ACE-R (M=78, SD=14.9) and SCOPA-Cog (M=23.8, SD=8.9) cognitive tools.

Identification of correlates of cognition in the IPD cohort

In an initial screen, Pearson's correlation analysis identified a number of markers associated with cognitive status in the patient cohort. These results revealed a novel role for a modified, extended version of the TUG assessment, which showed a moderate correlation with performance on both the SCOPA-Cog ($r = -.418$, $p < .001$) and ACE-R ($r = -.479$, $p < .001$) assessments. Moreover, the correlation observed between the extended-TUG assessment and both cognitive tools was greater than the weaker correlation values observed with common demographic and quality of life assessments, such as age of onset, MDS-UPDRS I, and PDQ-39 tools (Supplementary Table 1).

Extended-TUG correlates with both cognitive and motor status

To further investigate the extended-TUG assessment, demographic data, patient recorded outcomes, and clinical assessments were examined for potential relationships. Significant correlations (moderate and strong) were observed for the extended-TUG and a number of motor and cognitive variables (Table 2). Predictably, the extended-TUG correlated closely with assessments of overall disease severity, including the Hoehn & Yahr ($r = 0.497$, $p < 0.001$), MDS-UPDRS III ($r = 0.528$, $p < 0.001$), Schwab England ($r = -.702$, $p < 0.001$) and additionally with the PDQ-39 ($r = 0.558$, $p < 0.001$). Notably, moderate correlations were not limited to motor parameters, with an increase in extended-TUG time correlating to poorer performance in SCOPA-Cog ($r = -.421$, $p < 0.001$), MMSE ($r = -.546$, $p < 0.001$) and ACE-R ($r = -.483$, $p < 0.001$). Weaker correlations were observed with the BIS-11 measure of impulsivity and CBI-R (Table 2). Conversely, the extended-TUG assessment did not correlate with levodopa equivalent dosage, age of onset or rest state AIMS score.

Extended-TUG assessment significantly relates to cognitive and motor features of PD

To further illustrate the role of the extended-TUG assessment, subject performance was broken down into tertiles (Slow, Medium, Fast) on the basis of duration (i.e., time taken to complete the test). ANOVA or non-parametric analysis of tertiles revealed significant differences between the slowest tertile and fastest tertile in multiple clinical domains (Figure 1). Patients falling into the slowest group performed significantly worse in SCOPA-Cog ($p < .001$) and ACE-R ($p < .05$) cognitive assessments than those in other groups. Moreover, the slowest group also had significantly lower QoL (PDQ-39; $p < .001$) and patient independence assessments (Schwab-England; $p < .001$). Similarly, clinical measures relating to disease severity, such as the MDS-UPDRS III and Hoehn and Yahr scale, related to the duration of the extended-TUG assessment. While demographic variables such as duration of disease and age at onset showed differences between groups, only the fastest group showed a significantly lower age of onset, when compared to other groups ($p < .05$).

Extended-TUG assessment time predicts cognitive status in the IPD cohort

A GLM was generated to discern predictors of patient cognition (SCOPA-Cog and ACE-R). Several potential demographic and clinical variables were inputted, and sequentially removed until all remaining variables showed statistical significance. In both models, disease duration, socio-economic indexation, gender, MDS-UPDRS domain III, DBS status, BIS-11, CBI-R, PDQ-39, smoking history, family history, and daily levodopa equivalence were found not to be significant predictors of SCOPA-Cog or ACE-R performance. The final models derived are reported in Table 3 and Table 4, and indicates that the extended-TUG assessment is the singular important predictor of cognitive performance. Specifically, the extended-TUG assessment was a determinant of total SCOPA score (maximum 60 points): patients in the

fastest tertile were predicted to score 8.3 points higher than those in the slowest tertile ($p < .001$; Table 3); likewise, patients in the fastest tertile were predicted to score 13.4 points higher in total ACE-R score than those in the slowest tertile ($p < .001$; Table 4).

Classification of cognitive state using the extended-TUG assessment

Following the identification of the extended-TUG assessment as a significant predictor of cognitive function, we tested whether the clinical state of cognitive impairment (i.e., cognitively impaired versus non cognitively impaired participants) could be identified from the time taken to complete the extended-TUG assessment. We divided the cohort into CI/non-CI groups using published dementia cut off scores of 19.5 and 82.5 for the SCOPA-Cog and ACE-R assessment tools respectively. Using previously defined cognitive impairment cut-off scores there were 45 and 29 subjects classified as cognitively impaired, for ACE-R and SCOPA-Cog, respectively. Boxplots were generated to visualize performance in the extended-TUG assessment relative to the cognitive state of each group (Figure 2). When using both the SCOPA-Cog ($p < .001$) and ACE-R ($p = .017$) cognitive cut-off points, the CI group performed significantly worse than the non-CI groups.

DISCUSSION

A dichotomy of motor and non-motor symptomatology is well established in the diagnosis, assessment and treatment of PD. Recent work on the profile of cognitive impairment in PD has begun to alter this conceptual paradigm, however there remains a dependency on traditional non-motor assessments for the characterization of cognitive decline. In the current study, several commonplace assessments were related to disease parameters and the current gold standard motor examination (domain III of the MDS-UPDRS). Predictably, motor

examination scores were correlated with age of onset, quality of life and disease duration, however an extended TUG assessment emerged as the strongest correlate for all key parameters of PD, highlighting it as a candidate for further investigation.

Previous studies have identified similar, albeit weaker relationship, between a clinical measure and both motor and cognitive patient outcomes. For example, Campos and colleagues (2015) recently demonstrated that the UPDRS III motor score could also predict cognitive impairment, with each additional point in the UPDRS III increasing the odds of dementia by 22%³¹. However, there is a lack of correlation between the UPDRS III motor score and quality of life³², which is a common indicator of disease severity. In the present study, when broken into tertiles on the basis of duration, the extended-TUG significantly differentiated between a range of clinical markers of PD severity, patient independence, and quality of life. Most striking was the slowest group, which performed significantly worse in all clinical measures, and was characterized by patients with an increased disease duration and an increased disease severity. Such a finding has not previously been reported when using an extended TUG assessment, however utilizing additional instrumental parameters has allowed for disease severity differentiation¹³.

To investigate what role the extended-TUG assessment could have in predicting cognitive scores, a generalized linear model incorporating a large bank of potential variables, including MDS-UPDRS III was utilized. The results established the extended-TUG as the single best predictor of PD cognition in both SCOPA-Cog and ACE-R assessments. The results demonstrated that an extended-TUG time greater than 15.3 seconds (i.e., membership of the slowest group in our study), predicts cognitive scores of 19 in the SCOPA-Cog and 70 in the ACE-R. Importantly, both models predict patient cognitive function to be below previously

defined cut-off scores used to indicate dementia²⁸. This observation is pertinent given the poor correlation of cognitive scores with numerous validated outcomes, including age of onset and disease duration in previous studies^{33, 34}. Moreover, in the present study, the validated MDS-UPDRS III measure was not found to be a significant predictor of cognitive performance in each model.

That the extended-TUG assessment, ostensibly a motor test, can predict cognitive status indicates the inherent complexity in PD pathophysiology, and the need to routinely assess non-motor symptoms. While the standard TUG has widely been documented as an effective first line motor examination, more recent studies have illustrated the applicability of this tool in determining aspects of patient cognition³⁵. In PD pathophysiology, the dual syndrome hypothesis describes concurrent frontostriatal neurotransmitter depletion and sub-cortical atrophy³⁶. The assertion that motor and cognitive symptoms are shared in PD, anchored by subcortical pathology, is further supported by the gait literature. For example, impairment of executive function, attention and verbal fluency have been reported to associate with slowed gait speed, falls risk, and impaired balance⁸⁻¹⁰.

In light of the present findings, we propose the extended-TUG as a first-line holistic assessment of PD severity; integrating aspects of cognition, motor function and quality of life. There are logistical advantages of such a multipurpose preliminary assessment, most notably the short time required and lack of need for specialist interpretation. Moreover, an extended-TUG duration beyond 15 seconds could flag patients with presumptive cognitive impairment for further assessment. However, a patient's extended-TUG assessment must be interpreted in an individual's context, as reported confounders of walking speed include

medication, existing injuries, or other causes of gait disturbance (such as a previous cerebrovascular event)^{37, 38}.

LIMITATIONS

To overcome possible selection bias, home-based PD patients were recruited sequentially from numerous clinics across the Perth metropolitan region. A single researcher was involved in the timing of each patient; a considerable limitation was the single duration measure of time, rather than timed segments (sit to stand, time at turn and so forth). A second limitation was the allowance of walking assistance tools, which were not excluded due to the increased risk of patient falls imposed by doing so. Statistical limitations should also be considered. Patient selection was made on the basis of independence and mobility in that those unable to walk unassisted were excluded, as demonstrated by a comparatively low mean cohort Hoehn and Yahr score. Patient medication was optimized, but LEDD, not specific medication type, was considered as a variable in GLMs. Use of a medication subclass, dopamine agonists, was recorded as a binary variable at the time of visit and incorporated as a variable in the GLM, but was non-significant. This is the first publication incorporating an extended TUG and multiple cognitive assessments, and as such, external validation in larger patient populations is required. Of those who completed the test, eTUG duration must be interpreted cautiously in the context of each individual.

CONCLUSIONS

This is the first study correlating an extended-TUG assessment with multiple validated cognitive tools. We have demonstrated that the extended-TUG has emerged as arguably the

most clinically useful predictor of disease status, by motor and non-motor scores. Furthermore, the simplicity of this assessment allows for an initial screening and presumptive classification prior to the completion of gold standard tools, such as the MDS-UPDRS. Therefore, if an extended-TUG is consolidated as a robust indicator of cognitive status in larger cohorts, its applications are both immediate and deserving of further development. In the absence of obvious causes, poor extended-TUG performance could demarcate patients for whom in-depth cognitive assessment is indicated but not self-evident. We propose the extended-TUG as an accessible monitoring tool for disease progression and treatment response in PD.

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FIGURE LEGENDS

Figure 1. Assessment of the effects of extended-TUG tertiles (Fast, Medium, Slow) on (A) SCOPA-Cog, (B) ACE-R, (C) PDQ-39, and (D) Schwab-England clinical tools.

Figure 2. Boxplot representation of cognitive state relative to extended-TUG assessment time (A) Classification of cognitive impairment (dementia cutoff <19), as determined by the SCOPA-Cog assessment. (B) Classification of cognitive impairment (dementia cutoff <74.5), as determined by the ACE-R assessment.

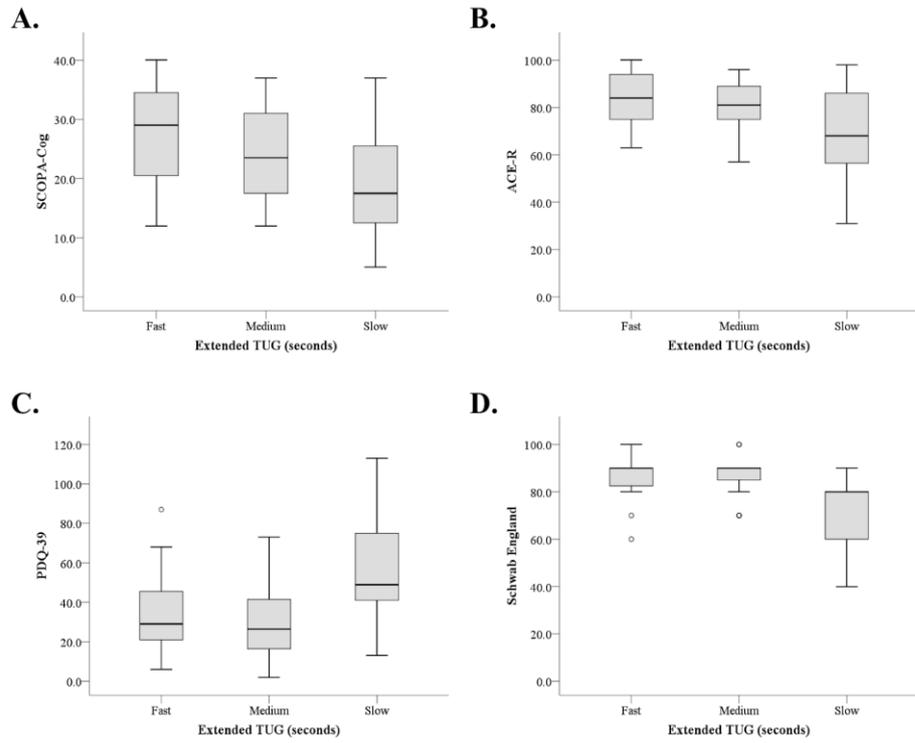


Figure 1

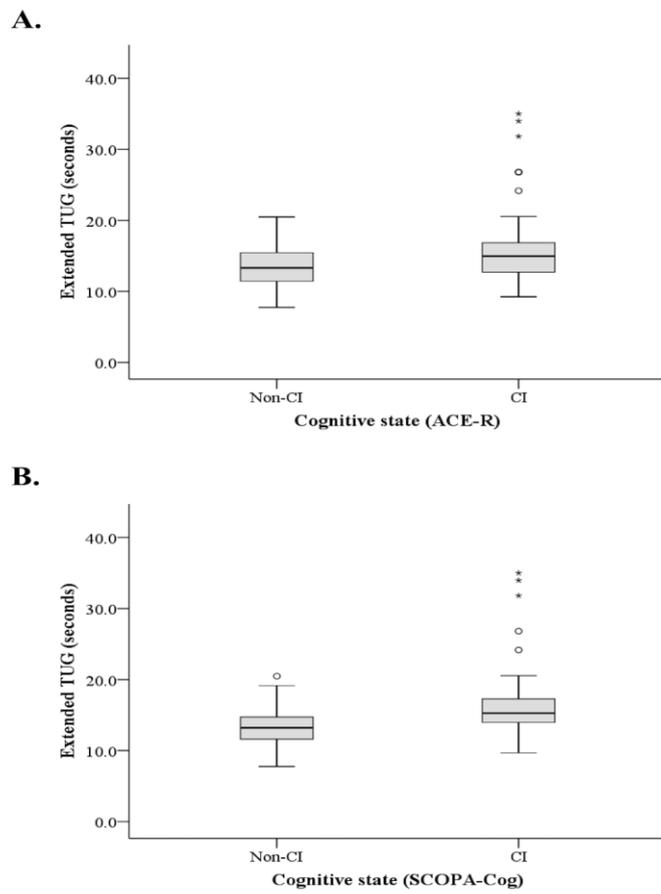


Figure 2

Table 1. Baseline Clinical Characteristics of the IPD cohort ($n=87$) used in this study.

Clinical Characteristic/Assessment		Mean (SD) or n
Gender (n)	Male	54
	Female	33
Age (Years)		68.9 (31.8)
Age of onset (Years)		53.3 (10.2)
Disease duration (Years)		10.4 (6.8)
Treatment Duration (Years)		8.4 (6.8)
Daily LD equivalents (mg/day)		671 (389)
Schwab-England (0-100)		81.6 (13.9)
Hoehn Yahr (Stage 0-4)		1.6 (1.0)
UPDRS Score	I	7.6 (4.4)
	II	17.8 (9.7)
	III	12.8 (14.2)
	IV	4.4 (6.5)
Extended-TUG (Seconds)		14.8 (5.6)

LD: Levodopa; UPDRS: Unified Parkinson's Disease Rating Scale

Table 2. Pearson Correlates of the extended-TUG assessment

Disease Variables		Pearson Correlation (r)	Significance (p)
Disease Duration	Years	.287	.008
Age at Onset	Years	.201	.069
Daily LD equivalent		.115	.305
Hoehn & Yahr Scale		.497	<.001
Schwab England		-.701	<.001
UPDRS	III	.528	<.001
Abnormal Involuntary Movement Scale	Rest	.028	.800
	Active	.280	.010
ACE-R		-.483	<.001
MMSE		-.546	<.001
SCOPA-Cog		-.421	<.001
CBI		.371	.001
BIS-11		-.232	.036
PDQ-39		.558	<.001

LD: Levodopa; UPDRS: Unified Parkinson's Disease Rating Scale. ACE-R: Addenbrooke's Cognitive Examination-Revised; MMSE: Mini-Mental State Examination; SCOPA-Cog: Scales for Outcomes in Parkinson's Disease-Cognition; CBI-R: Cambridge Behavioural Index- revised.

Table 3. Final Model Parameter Estimates: Predictors of SCOPA-Cog score.

Variable		β coefficient	Std. Error	Significance
(Intercept)		18.964	1.5467	.000
Extended-TUG	Fast	8.332	2.2075	.000
	Medium	5.607	2.1873	.010
	Slowest	0 ^a	.	
(Scale)		66.981 ^b	10.3975	

*Comparison category set to zero

Table 4. Final Model Parameter Estimates: Predictors of ACE-R score.

Variable		β coefficient	Std. Error	Significance
(Intercept)		70.214	2.6345	.000
Extended-TUG	Fast	13.440	3.7967	.000
	Medium	10.363	3.7967	.006
	Slowest	0 ^a	.	
(Scale)		194.337 ^b	30.7273	

*Comparison category set to zero

Extended “Timed Up and Go” Assessment as a Clinical Indicator of Cognitive State in Parkinson’s Disease

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Highlights

- Time to complete the extended Timed Up and Go correlated closely with validated motor and non-motor assessments
- extended-TUG duration was the sole significant predictor of cognition as assessed by SCOPA-Cog and ACE-R score in respective generalised linear models
- Larger cohorts and extended-TUG subcomponent analysis, are needed to consolidate the Extended-TUG as a holistic indicator of disease status