

ORIGINAL REPORT

RESPONSIVENESS TO SENSORY CUES USING THE TIMED UP AND GO TEST IN PATIENTS WITH PARKINSON'S DISEASE: A PROSPECTIVE COHORT STUDY

Matteo Cioni, MD^{1,4}, Oriana Amata, MD^{1,2}, Maria Rosaria Seminara, PT³, Pietro Marano, MD³, Filippo Palermo, MSc¹, Viviana Corallo, MD² and Luigia Brugliera, MD²

From the ¹Gait and Posture Analysis Laboratory, ²Physical Medicine and Rehabilitation Residency Program, University of Catania, ³Casa di Cura Carmide-Villa dei Gerani, OU of Neurorehabilitation and ⁴Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy

Objective: To test the effectiveness of the Timed Up and Go (TUG) test to define responsiveness to auditory and visual cues in patients with Parkinson's disease.

Methods: Consecutive patients >50 years old were enrolled if they were classified as stage 1–3 of the Hoehn and Yahr scale; scored ≤45 on part III of the Unified Parkinson's Disease Rating Scale; >23 on the Mini-Mental State Examination; and were able to perform the TUG test without assistance. Within-subject analysis identified positive-responders, negative-responders and non-responders. TUG times with and without sensory cues were studied among all patients, and among responders only using the Friedman Test.

Results: Twenty-two patients (16 men, 6 women), mean age 72.4 years (standard deviation (SD) 8.7 years) were included. Basal mean TUG time was 12.3 (SD 4.0). TUG times after visual cues (11.7 (SD 4.8)) were lower than in basal conditions ($p=0.006$), whereas TUG times after auditory cues were not ($p>0.05$). In the 16 patients who were positive-responders, mean TUG times after visual (11.0 (SD 3.1)) and auditory (11.3 (SD 3.6)) cues were lower than in basal conditions (12.5 (SD 3.8)) ($p=0.0002$).

Conclusion: The TUG test may be used to tailor the rehabilitation programme in patients with Parkinson's disease, identifying those who respond to visual and auditory cueing.

Key words: Parkinson's disease; Timed Up and Go (TUG); sensory cues.

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Correspondence address: Matteo Cioni, Gait and Posture Analysis Laboratory, Department of Biomedical and Biotechnological Sciences, University of Catania, V. le A. Doria 6, 9125 Catania, Italy. E-mail: mcioni@unict.it

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INTRODUCTION

The effects of sensory cues on the gait pattern of patients with Parkinson's disease (PD) were first shown by Martin (1), who reported the usefulness of transverse lines in a contrasting colour to that of the floor. Subsequent studies (2–8) confirmed that, not only visual but also rhythmic, auditory stimuli have a positive influence: the former induced improvements in gait

velocity (4, 6) and stride length (2, 6); the latter in gait velocity, cadence (2, 3, 5), and stride length (3).

In recent years, research has focused on the effects of sensory cues on other functional tasks, such as standing up from a chair, gait initiation, and turning. Bhatt et al. (9) showed that patients with PD improved their postural stability after audio-visual cued training, as evidenced by better control of the centre-of-mass position during the termination phase of the sit-to-stand movement. In the same population, Jiang & Norman (10) reported that kinematics and length of the first 2 steps of gait were significantly improved by high-contrast transverse lines on the floor, but not by auditory cues. Nieuwboer et al. (11) suggested that the enhanced attention triggered by rhythmical auditory, visual and somatosensory cueing increased the speed of turning in freezing and non-freezing patients.

In patients with PD, however, there is considerable inter-individual variability in response to different cueing modalities (6–8). Despite the clinical relevance of the different responses of individual patients to different sensory cues, there is little published information on this topic.

The Timed Up and Go (TUG) test was originally developed by Mathias et al. (12) and was subsequently modified with the inclusion of a timed component by Podsiadlo & Richardson (13). The TUG test displays good short-term test-retest reliability in patients affected by different pathologies (14–18); moreover, good long-term test-retest reliability has also been shown among community-dwelling elders (19). Morris et al. (20) reported high test-retest reliability and high inter-rater agreement in patients with PD (intraclass correlation = 0.87–0.99) in spite of significant inter-individual variability in mobility. The TUG test may be used to evaluate the effects of both pharmacological and rehabilitation interventions in patients with PD. Mirelman et al. (21) reported a decrease of 11% in the time required to perform this test after a 6-week training period with auditory feedback for improving posture and balance; Morris et al. (20) reported a statistically significant decrease in the time required to perform this test after L-3,4-dihydroxyphenylalanine (L-dopa) medication.

These observations suggest that, in patients with PD, the TUG test might be used to quantify functional changes induced by sensory cues, and may be suitable to identify which

patients respond best to certain stimuli and not to others. This would enable clinicians to design a rehabilitation programme with sensory cues tailored to the individual patient, not only on walking but also on other movements, such as sit-to-stand, gait initiation, turning and stand-to-sit.

The goal of this work is to study the effectiveness of the TUG test as a tool to define responsiveness to auditory and visual cues in patients with PD.

MATERIAL AND METHODS

Consecutive patients afferent to a neuro-rehabilitation clinic between January and June 2012, were enrolled if they were older than 50 years of age with a diagnosis of idiopathic PD. Participants were included if they were classified as stage 1–3 of the Hoehn and Yahr (H&Y) scale (22, 23); scored not greater than 45 on part III of the Unified Parkinson's Disease Rating Scale (UPDRS) (24); scored greater than 23 on the Mini-Mental State Examination (MMSE) (25), corrected for age and education (26, 27); were able to walk unassisted for at least 10 m, and to perform the TUG test without assistance or any walking aid. Exclusion criteria were: a diagnosis of parkinsonism; previous rehabilitation treatment with sensory cues; concomitant severe heart disease; severe disturbances of hearing and vision; previous or concomitant severe orthopaedic trauma or disease; and a basal TUG time > 25 s. The latter cut-off was chosen on the basis of the hypothesis that TUG times greater than this value are associated with a degree of functional deterioration, which may not allow practical execution of the test or allow an improvement with sensory cues. Case histories were examined for reference to episodes of freezing. All patients provided informed consent and the research protocol was approved by the ethics review board of the University of Catania.

Design and procedures

This is a prospective cohort study designed to investigate the effects of sensory cues on TUG time compared with no cues. Patients were asked to refrain from taking anti-Parkinson medications on the morning of testing (with the last medication being assumed to be ≥ 12 h previously). All evaluations were performed in the morning and completed during a single laboratory session.

The TUG test was performed under 3 experimental conditions: without sensory cues (basal TUG); with visual cues; and with auditory cues. A practice trial was performed before the basal TUG in all patients.

A statistician who was not involved with the study randomized the sequence of administration of visual or auditory cues to each patient using a random sequence of numbers generated centrally by computer. Allocation was concealed using sealed opaque envelopes. The TUG was performed 10 times for each of the 3 experimental conditions, and patients rested for 5 min at the end of each of the 3 experimental conditions.

TUG testing

A standard TUG test was performed (13, 14): the time to stand up from a standard armchair (seat height 46 cm, arm support height 65 cm), walk a distance of 3 m, turn, walk back to the chair, and sit down, was measured in seconds using a stopwatch. Patients wore their regular footwear and did not use a walking aid. No physical assistance was given. Patients were instructed that on hearing the word "go", they had to get up and walk at a comfortable and safe pace to a line on the floor, turn, return to the chair and sit down. In the visual cues condition to emphasize the visual contrast, parallel white stripes (width 5 cm) were placed perpendicular to a black walkway path at intervals equal to 40% of the patient's height (6). Patients were instructed to look at the white stripes throughout the TUG, even during the sit-to-stand and gait initiation and turning portions of the test, and to match their step length to the interval between the stripes. In the auditory cues condi-

tion, a metronome provided auditory cues at a rate 10% faster than the patient's cadence at a comfortable gait speed (3). The metronome sound was amplified with speakers to allow clear identification of the sound. Patients were instructed to match their strides with the rhythm of the auditory cues. All sessions were recorded using a video camera to allow an offline analysis of TUG performance.

Statistical analysis

Three analyses were conducted. On the basis of the hypothesis that individual patients respond differently to different sensory cues, repeated measure analysis of variance was performed using, as independent variables, auditory and visual cues, and, as dependent variable, basal TUG time obtained in the 10 trials for each patient at baseline and after stimulation test (data normally distributed). This allowed us to identify positive-responders (in whom there was a significant positive effect on performance), negative-responders (in whom there was a significant negative effect), and non-responders (in whom there was no effect). *Post-hoc* testing of the effectiveness of different sensory cues was conducted using the Newman-Keuls stepwise multiple comparisons test. Performance in TUG time among all patients, and among responders only was studied using the non-parametric Friedman Test, since data were not normally distributed (Kolmogorov-Smirnov normality test).

The possibility that results were influenced by a learning effect was studied using regression analysis.

TUG times are expressed in s, data are presented as mean and standard deviation (SD), and the significance level for differences was set at $\alpha \leq 0.05$. Data were analysed using SPSS software (SPSS Inc., Chicago, Ill. Version 16).

RESULTS

Fifty-six patients with a diagnosis of PD were treated during the study period. Of these, 22 consecutive patients (39%, 95% confidence interval (CI) ± 12.8) met the inclusion criteria. Mean age was 72.4 years (SD 8.7 years) and 16 were men. The patients' demographics and clinical data are shown in Tables I and II. Seven patients were classed as stage 2.0 of the H&Y

Table I. Patients' demographics

Patients	Age, years	Sex (M/F)	Height, cm	Weight, kg
1	70	M	173	98
2	68	M	164	63
3	76	M	172	106
4	84	M	165	60
5	79	F	153	65
6	70	M	174	86
7	79	M	174	80
8	66	M	168	70
9	63	F	155	60
10	54	F	160	61
11	80	M	165	75
12	56	M	165	70
13	83	M	160	60
14	71	F	158	50
15	78	M	152	60
16	82	M	162	70
17	79	M	170	90
18	62	M	170	85
19	79	M	170	59
20	69	F	155	50
21	66	F	160	60
22	78	M	160	70

M: male; F: female.

Table II. Clinical data

Patients	H&Y stage	UPDRS Part III score	Time from onset (years)	MMSE score	History freezing	L-dopa (mg)	Main AP drug	Status
2	2.5	28	2	26.2	Yes	275	–	NR
8	2	30	2	30	Yes	–	Pramipexole	NR
6	2.5	40	6	27	Yes	375	–	R
7	2.5	34	5	24	No	–	Rotigotine	R
10	2	28	6	30	No	–	Pramipexole	R
11	2.5	30	1	30	No	–	Rotigotine	R
16	2	36	6	24	No	–	Rotigotine	R
18	2.5	30	2	30	No	–	Selegiline	R
20	2.5	37	18	30	Yes	375	Pramipexole	R
22	2	25	1	30	No	–	Rotigotine	R
4	2	27	1	23.1	Yes	–	Rotigotine	R
9	2	30	2	30	No	250	Rasagiline	R
17	2.5	29	6	28	No	–	Ropinirole	R-A
1	2.5	37	7	28.9	No	600	–	R-V
3	3	42	19	25	Yes	850	Rotigotine	R-V
5	3	42	10	25	No	–	Rotigotine	R-V
14	2.5	40	5	27.3	Yes	525	Ropinirole	R-V
21	2.5	32	4	30	No	–	–	R-V
12	3	40	9	26.9	No	125	–	WR
13	3	37	1	27.1	Yes	375	Rotigotine	WR
15	2.5	37	5	23.7	No	375	Pramipexole	WR-A
19	2	32	5	28.9	No	887.5	–	WR-A

H&Y: Hoehn & Yahr; UPDRS: Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination; M: male; F: female; L-dopa: L-3,4-dihydroxyphenylalanine/carbidopa or benserazide; AP: dopaminergic anti-parkinsonian drugs; R: positive-responder to auditory and visual cues; R-V: positive-responder to visual cues only; R-A: positive-responder to auditory cues only; WR: negative-responder to auditory and visual cues; WR-A: negative-responder to auditory cues only; NR: non-responder.

scale, 11 stage 2.5, and 4 stage 3.0. All but 1 received pharmacological treatment with L-dopa and/or dopaminergic agents at home. On the day of testing, however, the entire population had been off medications for at least 12 h.

The mean basal TUG time for the entire population was 12.3 s (SD 4.0). TUG times after visual cues (11.7 s (SD 4.8)) were significantly lower than those recorded in basal conditions ($p=0.006$); whereas there was no statistical difference between TUG times after auditory cues and basal condition ($p>0.05$).

Regression analysis of the results of the 10 trials conducted in the 3 different experimental conditions (basal, visual, auditory) did not show a significant learning effect with each trial performed (basal: $r^2 0.002$, $Y=-0.06*X+12.60$, $p=0.51$; visual: $r^2 0.0001$, $Y=-0.02 * X+11.80$, $p=0.86$; auditory: $r^2 0.0001$, $Y=-0.01*X+12.30$, $p=0.91$).

Table III shows the results of the TUG test in the 16 patients (72.7%) who were classified as positive-responders: 10 responded to visual and auditory cues, and 6 to 1 of these only (5 to

Table III. Values in the Timed Up and Go test for patients who are positive responders to both cues or auditory/visual only

Patients	Status	Basal TUG, s Mean (SD)	Visually cued TUG, s Mean (SD)	Auditory cued TUG, s Mean (SD)
4	R	9.4 (0.9)	8.7 (0.7)*	7.3 (0.3)***
6	R	14.6 (2.6)	11.7 (1.1)**	11.8 (1.15)**
7	R	9.6 (0.4)	8.8 (0.7)**	8.4 (0.52)***
9	R	9.6 (0.5)	8.4 (0.6)***	8.9 (0.2)**
10	R	10.2 (0.6)	9.0 (0.6)***	9.2 (0.8)**
11	R	11.7 (0.6)	11.0 (0.40)**	10.6 (0.49)***
16	R	14.1 (1.2)	11.3 (0.7)***	10.3 (1.1)***
18	R	9.4 (0.4)	8.3 (0.4)***	8.5 (0.2)***
20	R	12.0 (1.3)	11.1 (0.9)**	11.4 (0.6)*
22	R	11.1 (1.4)	9.4 (0.4)***	9.0 (0.4)***
1	R-V	12.5 (1.4)	11.3 (0.5)**	12.9 (0.4)
3	R-V	24.8 (3.6)	20.6 (1.8)**	22.5 (2.1)
5	R-V	10.6 (0.8)	9.6 (0.3)*	10.1 (1.3)
14	R-V	11.3 (1.2)	10.2 (0.8)*	11.5 (0.6)
21	R-V	14.5 (0.6)	12.0 (0.5)***	14.1 (1.2)
17	R-A	15.0 (0.7)	15.0 (1.1)	13.8 (0.8)**

* $p<0.05$; ** $p<0.01$; *** $p<0.001$ (Newman-Keuls Multiple Comparison Test). TUG: Timed Up and Go test; R: positive-responder to auditory and visual cues; R-V: positive-responder to visual cues only; R-A: positive-responder to auditory cues only; SD: standard deviation.

Table IV. Timed Up and Go test times in negative-responders to visual and auditory cues

Patients	Status	Basal TUG (s)	Visually cued	Auditory cued
		Mean (SD)	TUG (s) Mean (SD)	TUG (s) Mean (SD)
12	WR	8.7 (0.5)	10.4 (0.5)***	9.9 (0.5)***
13	WR	16.6 (1.5)	26.9 (3.2)***	27.6 (3.2)***
15	WR-A	19.2 (1.2)	20.1 (1.2)	23.4 (1.0)***
19	WR-A	8.4 (0.5)	8.2 (0.5)	10.4 (0.2)***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Newman-Keuls Multiple Comparison Test). WR: negative-responder to auditory and visual cues; WR-A: negative responder to auditory cues only; SD: standard deviation; TUG: Timed Up and Go test.

visual and 1 to auditory cues). The majority of positive responders were stage 2.0 or 2.5 on the H&Y scale, and 2 were stage 3 (Table II). In positive responders, mean TUG times after both visual (11.0 (SD 3.1)) and auditory (11.3 (SD 3.6)) cues were significantly lower than those in basal condition (12.5 (SD 3.8)) ($p = 0.0002$). Tables IV and V show the results for the 4 negative responders and the 2 non-responders, respectively. The former were classed as stage 2–3 of H&Y, and the latter stage 2.0–2.5.

DISCUSSION

The results of this study suggest that there is a wide spectrum of responsiveness to sensory cues in patients with PD, and that the TUG test may be used to identify those who might respond to visual or auditory cues, or both, or none. Overall, 6 patients (27%, 95% CI 9–46%) were non-responders or negative responders: 18% (95% CI 9–35%) non-responders and 9% (95% CI 0–21%) negative responders. Among the 16 responders, 63% (95% CI 39–87%) were responders to both auditory and visual stimuli, 31% (95% CI 8–57%) to visual stimuli only, and 6% (95% CI –6–18%) to auditory stimuli only. When responders were studied, auditory and visual stimuli were both effective in improving the TUG time.

In previous studies the responsiveness to sensory cues in patients with PD has been evaluated during tests such as walking in a gait laboratory (3, 4, 7, 8), dual-motor task (28), seat to stand task (9), gait initiation (10), or functional turning (11). We chose to investigate responsiveness to sensory cues with the TUG test, because it requires a sequence of complex movements that are functionally related to activities performed in daily life. Moreover, the test appears to have good reliability, validity and responsiveness to change (14–21).

Table V. Timed Up and Go (TUG) test times in non-responders

Patients	Status	Basal TUG (s)	Visually cued	Auditory cued
		Mean (SD)	TUG (s) Mean (SD)	TUG (s) Mean (SD)
2	NR	8.5 (0.5)	8.0 (0.6)	8.2 (0.5)
8	NR	7.5 (0.8)	7.5 (0.8)	8.0 (0.5)

* $p < 0.05$; ** $p < 0.01$ (Newman-Keuls Multiple Comparison Test). NR: non-responder; SD: standard deviation.

The inter-individual variability in response to different cueing in patients with PD is documented in the literature. In one study, 7 patients with PD (54%, 95% CI 27–81%) showed strong responses to visual cues, with significant changes in spatial-temporal parameters (stride length, velocity, and duration of swing phase) and kinematics (hip flexion and knee extension), but the remaining 6 patients (46%, 95% CI 19–73%) did not (7). Azulay et al. (8) showed that 50% (95% CI 26–75%) of patients with PD displayed an increase in velocity greater than 10% when exposed to strip lines and normal light. In addition, Richards et al. (6) demonstrated that the activation pattern of the tibialis anterior muscle in the first portion (0–16%) of the gait cycle was markedly modified by sensory cues in only 7 patients with PD (46%, 95% CI 21–71%), and that some of them were responsive only to one modality of sensory stimulation (auditory or visual), whereas others were responsive to both (6).

Whether sensory cueing tests should be performed with or without specific pharmacological treatment for PD is a matter of debate. On the basis of the observation that sensory cues are a powerful means of circumventing dopamine deficits in PD (29), we chose to evaluate patients who were off medications for at least 12 h to test the effect of sensory cues on dopaminergic and non-dopaminergic cerebral pathways without or with a lower interference of dopaminergic medications. We also choose the cut-off of 12 h because a longer period of discontinuation was clinically impractical. In his classic paper Martin (1), showed a qualitative improvement in walking with visual cueing without pharmacological treatment. Forsberg et al. (30) were the first to perform gait analyses and to quantitate walking improvement with “visual guidance” in patients who were off L-dopa. Richards et al. (6) have shown that the effects of visual and auditory cues on stride length, velocity and stance in patients with PD were only evident when off L-dopa. In the same line of evidence, Azulay et al. (7) showed that, when on L-dopa, the visual cues did not significantly modify spatio-temporal or kinematic parameters in their group of 13 patients with PD or in 7 patients who were responders to visual cues. On the other hand, Lewis et al. (4) showed that, when on L-dopa, visual cues were significantly effective in reducing gait velocity and stride length of 24% and 23%, respectively. Moreover, Rochester et al. (31) have shown that auditory cues were significantly effective, both when off or on L-dopa, on stride time, walking speed, double-limb support duration and stride fluctuations. Interestingly, these authors (31) suggest that external cues could have a selective role in targeting non-dopaminergic gait dysfunction with the potential to increase mobility and reduce gait instability.

The inference that may be drawn from our work is strengthened by several characteristics: (i) this is a prospective cohort study of consecutive patients with PD at stage 2–3 on the H&Y scale, who were off medication for 12 h before the test. This allowed us to reduce the effect of medications on the possible dopaminergic and non-dopaminergic pathways triggered by sensory or auditory stimuli; (ii) the TUG test was repeated 10 times for each of the 3 experimental conditions to reduce random error and to explore the possible influence of a learning

effect on overall results; (iii) we demonstrated that a learning effect did not influence the results through repetition of the test in each of the 3 experimental conditions; (iv) we have designed the study and analysed the results (within-subject analysis) to investigate the responsiveness to sensory cues of individual patients, which allowed us to identify responders, non-responders and negative responders; (v) the sequence of sensory cues (auditory or visual) administered to patients was randomized to reduce selection bias concerning evaluators, and attention bias pertaining to patients; (vi) there is convergence of evidence with data reported in the literature.

Limitations of this work include the fact that it is not a randomized control trial; the sample size is relatively small, and patients are derived from a tertiary referral centre. Results therefore cannot be generalized to the entire population of patients with PD, but they support the hypothesis that the administration of stimuli in a rehabilitation programme for patients with PD may need to be tailored to the specific individual rather than designed in a standard fashion.

Our observations may have strong clinical implications from a rehabilitation standpoint. The TUG test might be used to select those patients who benefit from a rehabilitation programme, which includes visual or auditory stimuli, and to exclude non-responders or negative-responders, in whom the intervention may be useless or even potentially harmful. Moreover, our results provide suggestions for future research, not only to confirm them, but also to test other hypotheses, as follows: (i) responders to sensory cues who are already under treatment with long-acting dopaminergic agents might best be treated with a training strategy with sensory cues with the aim of stimulating non-dopaminergic pathways and optimizing the stimulation of dopaminergic one; (ii) responders, who are off L-dopa might be treated with a training strategy with sensory cues before placing them on pharmacological treatment with L-dopa. According to previous observation this approach might reduce gait instability (30) by preferentially activating non-dopaminergic pathways; (iii) negative responders, who are off L-dopa, might be re-tested with TUG when on L-dopa and, if they become responders, trained with sensory cues while on pharmacological treatment to reduce the risk of falls.

In conclusion, this study suggests that the TUG test may be used to tailor the rehabilitation programme in patients with PD, identifying those who may respond to visual and auditory cueing. Moreover, further studies are necessary to define how to use the results of the TUG test in patients who are on or off medication, to optimize the stimulation of dopaminergic and non-dopaminergic pathways in these patients.

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