

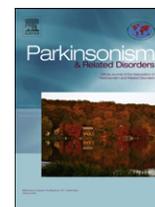
PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/116553>

Please be advised that this information was generated on 2019-03-26 and may be subject to change.



Short communication

Involvement of specific executive functions in mobility in Parkinson's disease

Katrijn Smulders^{a,b}, Marlies van Nimwegen^c, Marten Munneke^{c,d}, Bastiaan R. Bloem^a, Roy P.C. Kessels^{e,f}, Rianne A.J. Esselink^{a,*}^aRadboud University Nijmegen Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, The Netherlands^bHAN University of Applied Sciences, Institute for Studies in Sports and Exercise, Nijmegen, The Netherlands^cRadboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice, Department of Neurology, Nijmegen, The Netherlands^dRadboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice, Scientific Institute for Quality of Healthcare, Nijmegen, The Netherlands^eRadboud University Nijmegen Medical Centre, Departments of Medical Psychology and Geriatric Medicine, Nijmegen, The Netherlands^fRadboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands

ARTICLE INFO

Article history:

Received 14 April 2012

Received in revised form

11 June 2012

Accepted 12 June 2012

Keywords:

Gait

Executive function

Mobility

Working memory

Fluency

ABSTRACT

Postural instability and gait disorders (PIGD) in Parkinson's disease (PD) seem to be associated with executive dysfunction. We investigated which specific executive functions are associated with functional mobility in mildly affected PD patients. Functional mobility (Timed Up&Go Test, TUG), PIGD score, (spatial) working memory, set shifting, response inhibition and response generation were assessed in a large cohort of 232 non-demented PD patients. Both performance on the TUG and PIGD score were weakly associated with working memory and response generation (semantic and phonemic fluency). TUG also correlated with semantic fluency when corrected for disease severity and age. These results indicate that response generation and working memory are associated with (and possibly also causally related to) gait and balance deficits. In order to fully interpret gait and postural stability of PD patients in everyday situations, the role of impairments in working memory and response generation should be taken into account.

© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

Parkinson's disease (PD) is characterized by its motor features including gait difficulty and postural instability. Moreover, already in the early stages of PD some 20% of patients have mild cognitive impairment [1]. Because of the underlying neurodegenerative nature of PD, cognitive impairments are overall related to increased motor severity [2]. For example, the motor subtype with predominantly posture and gait disorders is a strong predictor of severe cognitive decline [3]. However, associations between more specific aspects of cognitive function and motor impairments are less clear [2].

With respect to cognitive domains, the executive functions are particularly affected in PD. Executive deficits can hamper activities in everyday life in PD for various reasons. First, activities of daily living can be affected directly because of an inability to organize, shift, monitor and play. In addition, executive dysfunction can impair daily-life performance more indirectly, via a detrimental effect on motor function. Specifically, there is increasing evidence to suggest that executive functions play an important role in gait

and postural adjustments [4]. For example, even healthy individuals without cognitive deficits reduce their walking speed and take smaller steps when they must perform a secondary cognitive task while walking, suggesting that executive or cognitive control is required for seemingly automatic functions like walking.

The results from such dual-task studies have consistently shown effects on various gait variables, in particular walking speed, stride length and step-to-step variability. However, it has not been clarified which specific aspects of executive function are important in relation to impairments in gait and balance. Here, we aimed to further clarify the association between functional mobility (Timed Up&Go Test), posture instability and gait disorders (PIGD), and four main aspects of executive function [5,6]: updating/working memory, set shifting, response inhibition, and response generation in a large cohort of non-demented PD patients.

2. Methods

2.1. Participants

Our study sample was a subsample of the ParkFit study population [7]. Baseline assessment of cognitive functions and mobility measures are presented here. Inclusion criteria were PD (diagnosed according to the UK Brain Bank criteria), age between 40 and 75 years, a sedentary lifestyle, Hoehn & Yahr (H&Y) ≤ 3 , and Mini-

* Corresponding author. Tel.: +31 (0)24 3668374; fax: +31 (0)24 3541122.
E-mail address: r.esselink@neuro.umcn.nl (R.A.J. Esselink).

Mental State Examination (MMSE) ≥ 24 . The study was approved by the regional medical ethical committee (CMO region Arnhem-Nijmegen) and patients gave their written informed consent.

The present analysis is limited to patients who completed all executive function and mobility tests ($N = 232$, 66% men, 64.4 ± 7.9 years). Mean Unified Parkinson's Disease Rating Scale-III (UPDRS-III) score was 33.4 ± 9.1 and mean MMSE score was 28.1 ± 1.6 . Almost 80% of patients ($n = 183$) was in H&Y stage 2; the other patients had HY stage 1 ($n = 3$; 1%), 1.5 ($n = 6$; 3%), stage 2.5 ($n = 35$; 15%) or stage 3 ($n = 5$; 2%). Most patients (47%) scored category 3 for their level of education (range 1 – no education to 6 – university).

2.2. Materials and procedure

The Timed Up&Go (TUG) test was used as an index of mobility [8]. In this test the patient has to stand up from a chair, walk 3 m at comfortable speed, turn 180° , walk back to the chair and sit down again. The sum score of items 27–30 of the UPDRS-III (arising from chair, posture, gait, postural stability) was used to calculate PIGD score.

Updating/working memory was examined using the Spatial Working Memory (SWM) subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB) [9]. In this computerized task, participants have to search for a hidden token by clicking a number of boxes that are presented in a spatial layout. After finding a token, participants have to search for a new token that is hidden in one of the other boxes. Within-search errors occur if a participant returns to a previously 'opened' box within a search, whereas between-search errors occur if a participant returns to a box that already contained a token in a previous search. Also, a strategy index reflects the efficiency of the search path.

Set shifting was assessed using the Intradimensional/Extradimensional (ID/ED) Set Shift test from CANTAB [9]. Here, participants have to learn a sorting rule by clicking stimuli that differ in different dimensions (shapes and lines) using feedback. After six consecutive correct responses according to the to-be-learned rule, the rule changes and participants have to learn the new sorting rule. Outcome measures were the number of stages completed and the number of errors made (adjusted for the number of stages completed).

Response inhibition was measured using an auditory Stroop paradigm [10], which allowed for precise recording of reaction times per response (in contrast to the widely-used paper-and-pencil Stroop Color-Word Test). In this task, patients hear the words "high" or "low" spoken at a high or low tone, every 2 s. Participants were instructed to respond as fast as possible by repeating the tone of the stimulus. Verbal reaction time and accuracy were combined in a composite score (accuracy/verbal reaction time).

Response generation was measured by the ability to access long-term memory using either a phonological cue (letter fluency; naming as many words as possible starting with the letter "M" in 1 min) or a semantic cue (semantic fluency; naming as many animals in 1 min) [11].

Individual performance on SWM, ID/ED and fluency were compared to age and/or education or IQ corrected available normative data for the CANTAB ($n = 2000$) [12] and the fluency tests ($n = 1856$) [11]. An individual performance was classified as impaired if the individual score was more than 1.65 SD below the normative mean (i.e., below the 5th percentile) [13]. No normative data were available for the Stroop paradigm.

2.3. Data analysis

To test the associations between performance on the TUG and PIGD score and the performance on cognitive tests, univariate regression coefficients were calculated using linear regression. Next, a multivariate linear regression model was constructed to predict TUG and PIGD using the significant variables from the univariate regression together with age, UPDRS-III score and educational level as independent variables. Significant contribution was accepted at $p < 0.05$.

3. Results

PD patients needed on average 9.51 ± 2.85 s to complete the TUG. Mean PIGD score was $2.3 (\pm 1.3)$. Regression coefficients for the association between fluency tests and the TUG were significant, yet weak (beta between -0.198 and -0.340 , Table 1). Similar beta values were observed for the association between Spatial Working Memory and the TUG regarding between-search errors and strategy. Other cognitive outcome measures were not correlated with the TUG. The linear regression analysis with PIGD score as dependent variable produced similar results.

A stepwise multivariate regression model was constructed by entering fluency tests and SWM between errors and strategy scores, together with UPDRS-III score, age and educational level. UPDRS-III (beta = 0.263, $p < 0.001$), age (beta = 0.212, $p = 0.001$), and semantic fluency (beta = -0.197 , $p = 0.002$) contributed significantly to the model, together explaining 24% of the total variance of the TUG. Only UPDRS-III (beta = 0.469, $p < 0.001$) and age (beta = 0.186, $p = 0.002$) survived multivariate regression with PIGD as dependent variable. This model explained 31% of the total variance of PIGD score.

4. Discussion

In this study, we evaluated which of the four domains of executive function is involved in functional mobility in a large cohort of patients with PD. Spatial Working Memory and verbal fluency showed small but significant associations with both the TUG and PIGD scores. Moreover, semantic fluency was significantly associated with mobility, independent of age and severity of motor signs as measured with the UPDRS-III.

The association of response generation and working memory (updating) with the TUG can be explained as an involvement of executive control during this seemingly pure motor task. Ongoing movement requires continuous monitoring and updating in order to adjust to ongoing changes in the environment. Specifically, the

Table 1
Cognitive test performance and univariate regression analysis for prediction of TUG and PIGD.

| Test ($N = 232$) | Outcome measure | Test performance | | Univariate regression with TUG ^c | | Univariate regression with PIGD ^d | |
|--------------------------------|-------------------------|-------------------|-------------------------|---|-------|--|-------|
| | | Mean \pm SD | % impaired ^e | Beta | SE | Beta | SE |
| <i>Updating/working memory</i> | | | | | | | |
| SWM ^a | Within-search errors | 2.91 \pm 4.36 | 4 | 0.032 | 0.043 | 0.196* | 0.019 |
| | Between-search errors | 43.37 \pm 20.97 | 4 | 0.274* | 0.009 | 0.271* | 0.004 |
| | Strategy | 35.63 \pm 5.41 | 4 | 0.206* | 0.034 | 0.137* | 0.015 |
| <i>Set shifting</i> | | | | | | | |
| ID/ED ^b | Stages completed | 7.52 \pm 2.00 | 17 | -0.041 | 0.094 | -0.098 | 0.041 |
| | Total errors (adjusted) | 54.87 \pm 46.14 | 18 | 0.051 | 0.004 | 0.106 | 0.002 |
| <i>Inhibition</i> | | | | | | | |
| Auditory Stroop | Composite score | 1.48 \pm 1.72 | NA | 0.049 | 0.109 | 0.009 | 0.048 |
| <i>Response generation</i> | | | | | | | |
| Fluency | Phonemic | 11.51 \pm 4.66 | 6 | -0.198* | 0.040 | -0.142* | 0.018 |
| | Semantic | 18.00 \pm 5.71 | 26 | -0.340* | 0.031 | -0.224* | 0.014 |

*Significant regression coefficients ($p < 0.05$).

^a Spatial Working Memory.

^b Intradimensional/Extradimensional Set Shift.

^c Timed Up&Go Test.

^d Postural Instability and Gait Disorders.

^e Impaired performance was defined as more than 1.65 SD deviation below the normative mean. For the auditory Stroop test, no normative values were available.

turning and transfer components of the TUG might demand executive processing. Alternatively, one could argue that processing speed underlies both executive functions and the TUG [14]. However, the Stroop task is presumably the most time-critical cognitive task in our design, but was not associated with performance on the TUG.

It is important to note that the patients in our sample were relatively mildly affected. The H&Y stages and UPDRS-III scores were low. This indicates that our research sample of PD patients probably had only minor gait difficulties and postural instability. With regard to the extent of executive dysfunction, impairments were present in set shifting (17–18%) and semantic fluency (26%), but not in working memory and phonemic fluency. However, even small decrements in executive function may affect motor function in more complex daily-life environments, which require more planning and switching than the TUG test which was performed under well-controlled circumstances in our study. Also, since PD progressively affects both cognitive and motor functions, the interaction between both domains might place PD patients in vulnerable everyday situations in more advanced disease stages.

The results from this study revealed that in non-demented PD patients with minor gait deficits, response generation and working memory are the executive functions that are weakly associated with functional mobility. With regard to clinical practice, we recommend that in order to fully interpret gait and postural stability of PD patients in everyday situations, the role of impairments in working memory and response generation, even when mild, should be taken into account.

Competing interests

All authors declare they have no competing interests for publication.

Funding

This work was supported by the Stichting Internationaal Parkinson Fonds (RAJE and BB), ZonMw, The Netherlands Organization for Health Research and Development (MM and BB, 75020012), the

Michael J Fox Foundation for Parkinson's research (MM and BB), and The Netherlands Organisation for Scientific Research (RCPK, VIDI 452-08-005).

References

- [1] Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. *Neurology* 2009;72(13):1121–6.
- [2] Green J, McDonald WM, Vitek JL, Evatt M, Freeman A, Haber M, et al. Cognitive impairments in advanced PD without dementia. *Neurology* 2002;59(9):1320–4.
- [3] Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, McKeith IG. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatr* 2006;77(5):585–9.
- [4] Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord* 2008;23(3):329–42.
- [5] Fisk JE, Sharp CA. Age-related impairment in executive functioning: updating, inhibition, shifting, and access. *J Clin Exp Neuropsychol* 2004;26(7):874–90.
- [6] Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cognit Psychol* 2000;41(1):49–100.
- [7] Van Nimwegen M, Speelman AD, Smulders K, Overeem S, Borm GF, Backx FJ, et al. Design and baseline characteristics of the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multifaceted behavioral program to increase physical activity in Parkinson patients. *BMC Neurol* 2010;10:70.
- [8] Podsiadlo D, Richardson S. The timed "up & go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39(2):142–8.
- [9] Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge neuropsychological test automated battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. *Dementia* 1994;5(5):266–81.
- [10] Cohen G, Martin M. Hemisphere differences in an auditory stroop test. *Percept Psychophys* 1975;17(1):79–83.
- [11] Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. Normative data for the animal, profession and letter M naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *J Int Neuropsychol Soc* 2006;12(1):80–9.
- [12] Robbins TW, James M, Owen AM, Sahakian BJ, Lawrence AD, McInnes L, et al. A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. *J Int Neuropsychol Soc* 1998;4(5):474–90.
- [13] Lezak MD, Howieson DB, Bigler ED, Tranel D. *Neuropsychological assessment*. 5th ed. New York: Oxford University Press; 2012.
- [14] McDowd J, Hoffman L, Rozek E, Lyons KE, Pahwa R, Burns J, et al. Understanding verbal fluency in healthy aging, Alzheimer's disease, and Parkinson's disease. *Neuropsychology* 2011;25(2):210–25.