

University of Groningen

Mental slowness in patients with Parkinson's disease

Vlagsma, Thialda T.; Koerts, Janneke; Tucha, Oliver; Dijkstra, Hilde T.; Duits, Annelien A.; Laar, van, Teus; Spikman, Jacoba M.

Published in:
Journal of Clinical and Experimental Neuropsychology

DOI:
[10.1080/13803395.2016.1167840](https://doi.org/10.1080/13803395.2016.1167840)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Vlagsma, T. T., Koerts, J., Tucha, O., Dijkstra, H. T., Duits, A. A., Laar, van, T., & Spikman, J. M. (2016). Mental slowness in patients with Parkinson's disease: Associations with cognitive functions? *Journal of Clinical and Experimental Neuropsychology*, 38(8), 844-852.
<https://doi.org/10.1080/13803395.2016.1167840>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Mental slowness in patients with Parkinson's disease: Associations with cognitive functions?

Thialda T. Vlagsma^a, Janneke Koerts^a, Oliver Tucha^a, Hilde T. Dijkstra^b, Annelien A. Duits^c, Teus van Laar^d and Jacoba M. Spikman^{a,d}

^aDepartment of Clinical & Developmental Neuropsychology, University of Groningen, Groningen, The Netherlands; ^bDepartment of Medical Psychology, Medical Center Nij Smellinghe, Drachten, The Netherlands; ^cDepartment of Psychiatry and Psychology, Maastricht University Medical Center, Maastricht, The Netherlands; ^dDepartment of Neurology, University Medical Center Groningen, Groningen, The Netherlands

ABSTRACT

Introduction: Motor slowness (bradykinesia) is a core feature of Parkinson's disease (PD). It is often assumed that patients show mental slowness (bradyphrenia) as well; however, evidence for this is debated. The aims of this study were to determine whether PD patients show mental slowness apart from motor slowness and, if this is the case, to what extent this affects their performance on neuropsychological tests of attention, memory, and executive functions (EF). *Method:* Fifty-five nondemented PD patients and 65 healthy controls were assessed with a simple information-processing task in which reaction and motor times could be separated. In addition, all patients and a second control group ($N = 138$) were assessed with neuropsychological tests of attention, memory, and EF. *Results:* While PD patients showed significantly longer reaction times than healthy controls, their motor times were not significantly longer. Reaction and motor times were only moderately correlated and were not related to clinical measures of disease severity. PD patients performed significantly worse on tests of attention and EF, and for the majority of neuropsychological tests 11–51% of the patients showed a clinically impaired performance. Reaction times did not, however, predict patients' test performance, while motor times were found to have a significant negative influence on tests of attention. *Conclusions:* PD patients show mental slowness, which can be separated from motor slowness. Neuropsychological test performance is not influenced by mental slowness; however, motor slowness can have a negative impact. When interpreting neuropsychological test performance of PD patients in clinical practice, motor slowness needs to be taken into account.

ARTICLE HISTORY

Received 29 September 2015
Accepted 14 March 2016

KEYWORDS

Parkinson's disease;
Bradyphrenia; Motor
slowness; Cognitive
functions;
Neuropsychological
assessment

The diagnosis of Parkinson's disease (PD) is based on the presence of motor symptoms, with bradykinesia being the single most important diagnostic sign (Wolters, van Laar, & Berendse, 2007). Bradykinesia manifests itself as visible slowness and diminished amplitude of movement (Hughes, Daniel, Kilford, & Lees, 1992). Slowness is, however, assumed to be associated not only with motor behavior in PD, but with mental information processing as well. This mental equivalent of bradykinesia is called bradyphrenia or mental slowness (Revonsuo, Portin, Koivikko, Rinne, & Rinne, 1993; Wolters et al., 2007).

The presence of mental slowness in PD patients is, however, a subject of discussion. Several studies found evidence for the presence of mental slowness (Berry, Nicolson, Foster, Behrmann, & Sagar, 1999; Gauntlett-Gilbert & Brown, 1998; Hsieh, Chen, Wang, & Lai, 2008; Muslimovic, Post, Speelman, & Schmand, 2005; Revonsuo et al., 1993; Sawamoto, Honda, Hanakawa, Fukuyama, & Shibasaki, 2002), whereas other studies could not demonstrate mental slowness in PD (Duncombe, Bradshaw, Iansek, & Phillips, 1994; Hetscher & Pinter, 1993; Phillips et al., 1999). A possible explanation for this lack of consensus is that a broad variety of measures is used

CONTACT Thialda Teakje Vlagsma  t.t.vlagsma@rug.nl  Grote Kruisstraat 2/1, 9712 TS Groningen, The Netherlands.

Research was conducted in the Medical Center Nij Smellinghe, Drachten, the Maastricht University Medical Center, Maastricht, and the University Medical Center Groningen.

© 2016 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

to assess speed of information processing as an indication of mental slowness. Some measures also include the measurement of higher order cognitive functions such as memory or executive functions (EF; Albinet, Boucard, Bouquet, & Audiffren, 2012). Furthermore, previously many studies aimed to assess speed of information processing as an indication of mental slowness, but used measures that also included a manual motor response. However, in terms of neural networks, a global distinction can be made between the central processes of planning, preparing, and initiating a motor response and the physical execution of that manual motor response (i.e., peripheral nervous system). The central processes primarily involve activity in the prefrontal cortex, the supplementary, premotor cortex and the primary motor cortex, whereas the actual motor response involves primarily muscle activity in the arm and hand (Wolters et al., 2007). Since peripheral motor dysfunction is common in certain patient populations (e.g., patients with dystonia, Huntington's disease, and PD), it is crucial to distinguish between the assessment of speed of mental information processing and motor speed (Salthouse, 1994, 1996) when determining actual mental slowness. For this purpose, information-processing tasks that allow differentiation between reaction time (i.e., measure of information-processing speed as an indication of mental slowness) and motor time are preferred to more standard neuropsychological tests that include manual or verbal motor activity (e.g., Trail Making Test or Stroop), which do not allow disentanglement of both components. To our knowledge, such tasks have not yet been applied to study the concepts of mental and motor slowness in patients with PD. Therefore, our main objective was to examine whether mental and motor slowness could be measured separately and consequently whether these can be differentiated from each other in PD patients using such a paradigm. Based on the assumption that bradykinesia and bradyphrenia are characteristic clinical signs of PD, we expect this to be demonstrated by longer motor as well as longer reaction times of PD patients than of healthy controls. On the other hand, since we assume bradykinesia and bradyphrenia to be distinguishable concepts, it is hypothesized that motor and reaction times can be correlated, but do not show a one-to-one relationship.

Furthermore, if PD patients exhibit mental slowness, the second aim is to determine to what extent this mental slowness influences the performance on

neuropsychological tests. Neuropsychological tests are frequently used for the assessment of cognition in PD patients and have demonstrated that cognitive impairments, especially within the domains of attention, memory, and EF, are common in this group (Elgh et al., 2009; Muslimovic et al., 2005). However, the majority of tests contain either a direct (outcome is measured as time of completion, e.g., Trail Making Test) or an indirect (presentation of stimuli at a fixed pace, e.g., Rey Auditory Verbal Learning Test) speed component. It seems therefore likely that impaired performances of PD patients on such tests can, at least partially, be explained by their mental slowness. So far, only a small number of studies investigated the influence of mental slowness on cognitive test performance. Both Albinet et al. (2012) and Salthouse (1992) showed that mental slowness (partially) accounted for healthy participants' age-related differences in cognitive test performance. Moreover, differences on tests for focused and divided attention between patients with traumatic brain injury and healthy controls disappeared when scores were controlled for mental slowness (Spikman, van Zomeren, & Deelman, 1996). Only one study investigated the role of mental slowness in PD patients and concluded that mental slowness was not related to executive functioning (Liozidou, Potagas, Papageorgiou, & Zalonis, 2012). Knowledge about the influence of slowness on neuropsychological tests performance is crucial in clinical practice, since it has to be determined whether impaired test performance can be interpreted as deficits of memory, attention, and EF, or has to be attributed to slowness of information processing. Since most neuropsychological tests require also manual or verbal motor activity, the effect of motor slowness on neuropsychological test performance is examined as a subquestion. Finally, it is determined to what extent motor slowness, as measured with an information-processing task, and motor symptoms and disease severity, as measured with more clinical measures (Unified Parkinson's Disease Rating Scale motor section, UPDRS-III, and the Hoehn and Yahr scale, H&Y) are associated.

Method

Participants

Fifty-five patients with idiopathic PD who were diagnosed according to the UK Parkinson's

Disease Brain Bank Criteria were included. Exclusion criteria were dementia (i.e., Scales for Outcomes in Parkinson's Disease–Cognition Scale, SCOPA–COG, score ≤ 17 ; Verbaan et al., 2011) and other severe neurological and psychiatric comorbid conditions. Patients were recruited at the Department of Neurology of three medical centers in The Netherlands. Neuropsychological assessment was conducted while patients were on their regular dopaminergic medication and in the on phase. Four patients were not on dopaminergic therapy, and two patients did not report their current medication use. Furthermore, five patients underwent deep brain stimulation (targets: subthalamic nucleus, $N = 3$; globus pallidus, $N = 1$; thalamus, $N = 1$), which was performed more than one year prior to study inclusion. A levodopa equivalent daily dose (LEDD) was calculated for all patients who were on dopaminergic medication (Esselink et al., 2004). The UPDRS–III and the H&Y scale were used to assess disease severity. Patients in H&Y Stages 4 and 5 were not included in this study. The study was approved by the medical ethical committee and was conducted in accordance with the declaration of Helsinki. All patients gave written informed consent.

In addition, data of two healthy control groups were used that came from several sources. Exclusion criteria were major neurological diseases and/or psychiatric disorders. One control group (HC1; $N = 65$) was assessed with the simple information-processing task (see below for a detailed description of this task); data were provided by Schuhfried GmbH test company, Vienna, Austria. PD patients' performances on neuropsychological tests were compared to data of a second group of healthy controls (HC2), who were assessed with all neuropsychological tests that were used in the present study, except for the simple

information-processing task. HC2 was composed out of healthy controls that were included in our previous studies. For tests of attention, memory, and EF the number of controls with available data ranged from $N = 77$ (Stroop) to $N = 136$ (Zoo Map). For the Rey Auditory Verbal Learning Test (RAVLT), data of 32 controls were available. Table 1 shows descriptive variables and disease characteristics of PD patients and both healthy control groups. Level of education of all participants was classified on a 5-point scale ranging from (1) uncompleted or special education: < 9 years of education, to (5) completed university (of applied sciences).

Neuropsychological assessment

Speed of information processing

The simple information-processing task (S1 condition) of the Vienna Test System (Prieler, 2008) was used to measure reaction time and motor time separately. During the task, the participants' dominant index finger rested on a key (rest key). A black circle was constantly present in the middle of the lower half of the screen, and as soon as this circle turned yellow, participants were instructed to lift their index finger and to press the response key as fast as possible. The distance between the rest key and the response key was 5.5 cm. The interstimulus interval ranged between 1.5 to 6.5 s, and the duration of the presentation of the yellow circle was 1 second. The task consisted of five practice trials and 28 test trials. For each participant, two scores were calculated: (a) mean reaction time (RT)—that is, the mean time between the appearance of the target stimulus and lifting the dominant index finger over all correctly completed trials—and (b) mean motor time (MT)—the mean time

Table 1. Descriptive and disease characteristics of PD patients and healthy control groups.

Participant characteristics	PD		HC1		HC2	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age in years	61.0 (9.5)	42–79	63.1 (5.1)	55–80	59.0 (7.6)	38–87
Education in years (Med; IQR)	4.0 (1.0)	2–5	3.0 (1.0)	2–5	3.0 (1.0)	2–5
Sex						
Male n (%)	36 (65.5)		41 (63.1)		72 (52.2)	
Female n (%)	19 (34.5)		24 (36.9)		6 (47.8)	
UPDRS–III	21.2 (8.2)	8–46	—		—	
H&Y (Med; IQR)	2.5 (0.5)	1–3	—		—	
LEDD	731.3 (457.8)	0–2080.0	—		—	
SCOPA–COG	28.8 (4.4)	19–37	—		—	

Note. Educational level was classified on a 5-point scale; 1 = unfinished or special education, < 9 years of education, 5 = Bachelor or Master's degree. PD = Parkinson's disease; HC = healthy controls; Med = median; IQR = interquartile range; UPDRS–III = Unified Parkinson's Disease Rating Scale Part III, motor section, range = 0–108 maximum; H&Y = Hoehn and Yahr scale, range = 0–5 maximum; LEDD = levodopa equivalent daily dose; SCOPA–COG = Scales for Outcomes in Parkinson's Disease–Cognition, range = 0–43 max.

between lifting the dominant index finger and pressing the response key over all correctly completed trials. Both reaction time and motor time were measured in milliseconds.

Neuropsychological tests of attention, memory, and executive functions

The Trail Making Test Part A (TMT; in seconds; Reitan, 1958) and the Stroop Word Card (in seconds; Stroop, 1935) were used to assess attention. Short-term verbal memory was measured with the Digit Span Forward (total score; Wechsler, 1987). The Rey Auditory Verbal Learning Test (Dutch version; RAVLT; Deelman, Brouwer, van Zomeren, & Saan, 1980) is a verbal memory test that was used to measure immediate recall (IR; max. score = 75) and delayed recall (DR; max. score = 15) of unrelated verbal information. EF were assessed with the TMT B/A ratio (Reitan, 1958) and Visual Elevator (Test of Everyday Attention; TEA; max. score= 10; Robertson, Ward, Ridgeway, & Nimmo-Smith,1994), Stroop Color-Word/Color card ratio (Stroop, 1935), and the subtest Zoo Map (total score) of the Behavioural Assessment of the Dysexecutive Syndrome (BADS; Wilson, Alderman, Burgess, Emslie, & Evans, 1996).

Statistical analyses

IBM Statistical Package for the Social Sciences Version 22 was used for data analysis. Analyses of covariance (ANCOVAs) with age, gender, and level of education included as covariates were used to compare the performances of PD patients and healthy controls on the simple information-processing task and neuropsychological tests (Tables 2 and 3). For statistical analysis an alpha of .05 was applied. In case of multiple comparisons (Table 3) a Bonferroni-corrected alpha was used per cognitive domain. Furthermore, effect sizes for group differences were calculated (Cohen’s *d*). Correlations were calculated to determine the associations between the RT, MT, UPDRS, neuropsychological tests (Pearson’s *r*), and H&Y (Spearman’s *r_s*). Performances of PD patients and controls on the simple information-processing task and other neuropsychological tests were also analyzed from a clinical perspective—that is, performances on tests were compared to representative normative data as provided by the test developers. Performances that fell within the lowest 10% of the normative samples were considered as being impaired (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Finally, hierarchical linear regression analyses (method: enter) were used to study the influence of speed of information processing

Table 2. Performances of PD patients and healthy controls on the simple information-processing task of the Vienna Test System.

	PD		HC1	ANCOVA	Covariates			ES
	Mean (SD)	Mean (SD)	Mean (SD)	<i>F</i> (<i>p</i>)	Age	Sex	Edu	<i>d</i>
Simple information-processing task								
Motor time	232.73 (78.64)	218.35 (72.19)	218.35 (72.19)	1.97 (.163)	<i>ns</i>	<i>ns</i>	<i>ns</i>	0.19
Reaction time	363.53 (84.67)	316.34 (75.93)	316.34 (75.93)	10.10 (.002)*	<i>ns</i>	<i>ns</i>	<i>ns</i>	0.60

Note. PD = Parkinson’s disease; HC = healthy controls; ANCOVA = analysis of covariance; ES = effect size; Edu = education. Times in ms. **p* < .01.

Table 3. Performances of PD patients and healthy controls on tests of cognition.

Domain	Cognitive measure	PD		HC2	ANCOVA	Covariates			ES
		% ≤ 10th pc (<i>N</i>)	Mean (SD)	Mean (SD)	<i>F</i> (<i>p</i>)	Age	Sex	Edu	<i>d</i>
Attention	TMT A	25.5 (14)	43.18 (13.19)	33.34 (9.40)	24.38 (<.001)*	*	<i>ns</i>	<i>ns</i>	0.90
	Stroop Word Card	50.9 (28)	50.96 (9.66)	47.16 (7.68)	5.02 (.027)*	*	<i>ns</i>	<i>ns</i>	0.44
Memory	Digit span forward	3.6 (2)	8.73 (1.65)	8.82 (1.69)	0.06 (.815)	*	<i>ns</i>	<i>ns</i>	0.05
	RAVLT IR	35.2 (19)	38.35 (11.25)	38.84 (10.36)	0.53 (.470)	*	*	*	0.04
	RAVLT DR	11.1 (6)	7.85 (3.14)	7.38 (3.38)	0.40 (.528)	<i>ns</i>	*	*	0.15
EF	TMT ratio	20.0 (11)	2.48 (0.93)	2.17 (0.53)	4.64 (.033)	*	<i>ns</i>	<i>ns</i>	0.44
	Stroop ratio	3.6 (2)	1.64 (0.28)	1.54 (0.18)	4.73 (.032)	*	<i>ns</i>	*	0.41
	Visual Elevator total score	18.2(10)	7.83 (2.28)	8.44 (1.65)	2.42 (.122)	*	<i>ns</i>	<i>ns</i>	0.32
	Zoo Map total score	27.3 (22)	8.29 (5.68)	10.84 (4.71)	10.49 (.001)*	*	<i>ns</i>	*	0.51

Note. PD = Parkinson’s disease; HC = healthy controls; ANCOVA = analysis of covariance; ES = effect size; Edu = education; EF = executive functions; TMT = Trail Making Test; RAVLT = Rey Auditory Verbal Learning Test; IR = immediate recall; DR = delayed recall; TMT ratio = TMT B/ TMT A; Stroop ratio = Color-Word/Color card. ANCOVA was conducted for the RAVLT IR and DR with level of education included as a covariate. *Significant *p* < Bonferroni-corrected alpha.

on patients' performances on each neuropsychological test separately. The assumptions for regression analyses were met. MT (Block 1) and RT (Block 2) were respectively included as independent variables into each model. Scores on tests of attention (TMT A and Stroop Word Card), memory (Digit Span Forward and RAVLT), and EF (TMT B/A, Stroop ratio, Visual Elevator and Zoo Map) were dependent variables.

Results

Demographic data

No differences were found between HC1 and PD patients with regard to age ($t = -1.46$, $p = .149$), gender ($\chi^2 = 0.07$, $p = .787$), and level of education (Mann-Whitney $U = 1617.50$, $p = .342$). Overall, there were also no differences between PD patients and HC2 in age ($t = 1.39$, $p = .167$), gender ($\chi^2 = 2.81$, $p = .093$), and level of education (Mann-Whitney $U = 3232.00$, $p = .086$). The RAVLT subgroup of HC2 ($N = 32$) did not differ from PD patients with regard to age ($t = -0.15$, $p = .878$) and gender ($\chi^2 = 2.01$, $p = .156$). However, level of education was significantly different between this subgroup and PD patients (Mann-Whitney $U = 585.50$, $p = .006$). Because the results show some trend-level differences between patients and controls, and since it is known that age, gender, and level of education can be of influence on cognitive test performance, these demographic variables were included as covariates in further analyses. Demographic data are presented in Table 1.

Simple information-processing task and neuropsychological test performance

In comparison to healthy controls, PD patients showed a significantly slower RT (medium effect size, see Table 2). No differences were found between groups with regard to MT. From a clinical perspective, the simple information-processing task revealed clinically impaired mental slowness in 11% of PD patients and clinically impaired motor slowness in 7% of PD patients (performance \leq lowest 10% of normative sample). In the healthy control group, 5% of controls showed clinically impaired mental slowness and 6% impaired motor slowness. The percentage of impairments did not significantly differ between groups for

both mental and motor slowness (RT: $\chi^2 = 1.70$, $p = .192$; MT: $\chi^2 = 0.38$, $p = .536$).

A significant but moderate correlation was found between the RT and MT of the simple information-processing task (PD patients: $r = .40$, $p = .003$; controls: $r = .41$, $p = .001$). In addition, no significant associations were found between the scores on the UPDRS-III and H&Y and the RT and MT (RT and H&Y: $r_s = .11$, $p = .465$; RT and UPDRS: $r = .17$, $p = .227$; MT and H&Y: $r_s = .09$, $p = .553$; MT and UPDRS: $r = .23$, $p = .108$).

Table 3 presents the average performance of PD patients and healthy controls on tests of attention, memory, and EF. PD patients performed significantly worse than healthy controls on tests of attention and on the Zoo Map. Groups did not differ with regard to the performances on other tests of EF and memory. However, for six out of nine tests, 11 to 51% of PD patients' test scores were considered as clinically impaired.

In Table 4 the univariate associations between MT, RT, and neuropsychological test performance of PD patients are presented. A significant correlation was found between MT and the TMT A and Stroop ratio. RT also showed a significant correlation with the Stroop ratio. Consequently, hierarchical regression analyses were conducted to study whether neuropsychological test scores of PD patients can be predicted from MT and RT. MT and RT were separately included (i.e., MT = Block 1, RT = Block 2) in the regression models to determine their individual contribution to the model. Table 5 shows that MT alone appeared to be a significant predictor of performance on the TMT A [$R^2 = .09$, $F(1, 54) = 5.53$, $p = .022$]. However, when RT was included the model was

Table 4. Univariate Pearson's correlations between MT, RT, and neuropsychological tests in PD patients.

Domain	Cognitive measure	MT	RT
Attention	TMT A	.31*	.16
	Stroop Word Card	.25	.26
Memory	Digit Span Forward	-.20	-.02
	RAVLT IR	-.25	-.18
	RAVLT DR	-.13	-.10
EF	TMT ratio	.16	.07
	Stroop ratio	.41*	.36**
	Visual Elevator total score	-.10	-.21
	Zoo Map total score	-.17	-.05

Note. PD = Parkinson's disease; TMT = Trail Making Test; RAVLT = Rey Auditory Verbal Learning Test; IR = immediate recall; DR = delayed recall; TMT ratio = TMT B/TMT A; Stroop ratio = Color-Word/Color card; MT = motor time; RT = reaction time; EF = executive functions.

* $p < .05$. ** $p < .01$.

Table 5. Predictors of PD patients' performance on tests of attention and EF based on hierarchical linear regression analysis.

Domain	Cognitive measure	Variable	R^2	R^2 change	B	β	t	p
Attention	TMT A	Constant			31.187		5.80	<.001**
		Motor time	.09		0.052	0.31	2.35	.022*
EF	Stroop ratio	Constant			1.093		6.88	<.001**
		Motor time	.17		0.001	0.32	2.38	.021*
		Reaction time	.22	.05	0.001	0.23	1.74	.089

Note. PD = Parkinson's disease; EF = executive functions; TMT = Trail Making Test. Regression analysis, method: enter.

* $p < .05$. ** $p < .001$.

no longer significant [$R^2 = .10$, $F(2, 54) = 2.77$, $p = .072$]. Furthermore, a different pattern was found for the complete model of the Stroop Color-Word/Color card ratio. The complete model (including MT and RT) explained a significant percentage of variance in the Stroop Color-Word/Color card ratio [$R^2 = .22$, $F(2, 54) = 7.10$, $p = .002$]; however, only MT was found to contribute significantly to the model (see Table 5). For the other neuropsychological tests, neither the combination of MT and RT nor MT or RT separately were significant predictors of PD patients' performances; the results of complete models were as follows: attention [Stroop Word Card: $R^2 = .09$, $F(2, 54) = 2.67$, $p = .079$], memory [Digit Span Forward: $R^2 = .05$, $F(2, 54) = 1.24$, $p = .298$; RAVLT IR: $R^2 = .07$, $F(2, 54) = 2.00$, $p = .146$; RAVLT DR: $R^2 = .02$, $F(2, 54) = 0.52$, $p = .597$], and EF [TMT B/A ratio: $R^2 = .02$, $F(2, 54) = 0.64$, $p = .532$; Visual Elevator: $R^2 = .04$, $F(2, 51) = 1.12$, $p = .335$; Zoo Map total score: $R^2 = .03$, $F(2, 54) = 0.82$, $p = .444$].

Discussion

To our knowledge, this is the first study that measures RT and MT separately in order to determine whether mental slowness can be differentiated from motor slowness in patients with Parkinson's disease. PD patients showed on average a significantly longer RT on a simple information-processing task than healthy controls. Surprisingly, PD patients' MTs were not significantly slower than healthy controls. This is remarkable since bradykinesia is a core feature of PD. These findings indicate that mental slowness can be present in PD patients in the absence of motor slowness and strengthen findings of previous studies that demonstrated mental slowness in PD even though these studies did not use tasks that allowed the differentiation of mental and motor slowness (Berry et al., 1999; Gauntlett-Gilbert & Brown,

1998; Hsieh et al., 2008; Muslimovic et al., 2005; Revonsuo et al., 1993; Sawamoto et al., 2002).

The finding that mental and motor slowness are distinctive constructs was also substantiated by the moderate correlations between RT and MT in both patients and controls, which indicates that RT and MT only share a relatively small amount of variance (i.e., 16%). Interestingly, clinical ratings of motor symptoms and disease severity (i.e., scores on UPDRS-III and H&Y scale) were related neither to RT nor to MT. A possible explanation for this finding is that standard clinical measures of motor symptoms in PD assess motor slowness (i.e., bradykinesia) in a different way from reaction time paradigms. The unexpected finding that patients did not show significantly slower MTs than healthy controls strengthens this interpretation. The UPDRS, for example, assesses motor slowness with several items that do not only ask the observer to evaluate the speed of a specific motor action, but also ask them to evaluate the amplitude, hesitations, and halts of the action per side of the body. Even though the bradykinesia subscale of the UPDRS is a valid measure of motor slowness (Buck, Wilson, Seeberger, Conner, & Castelli-Haley, 2011), to our knowledge the relation with reaction time paradigms has not been studied so far and may represent an interesting subject for future research.

The second aim of the current study was to determine the influence of mental slowness on neuropsychological test performance of PD patients. This is relevant, because the majority of neuropsychological tests include a speed component (i.e., in the outcome measure or paced presentation of stimuli). Hence, PD patients' performances on these tests may be negatively influenced by disease-related mental slowness, which may have consequences for the interpretation of test results in clinical practice. The group of PD patients that was included in the present study showed a profile of cognitive impairments that was

consistent with previous studies (Koerts, Tucha, Lange, & Tucha, 2013; Muslimovic et al., 2005; Watson & Leverenz, 2010), indicating that a representative group of PD patients was included. Results of regression analyses showed that RT as an indication of mental slowness did not predict PD patients' performances on any of the neuropsychological tests of attention, memory, and EF, which is in line with the findings of Liozidou et al. (2012). MT, on the other hand, was found to be a significant predictor of PD patients' performance on TMT A and the Stroop Color-Word/Color card ratio. With regard to the TMT A this is not surprising, since this paper-and-pencil test involves manual motor activity because it requires patients to search and connect succeeding numbers as fast as possible by drawing a line. Regarding the Stroop Color-Word/Color card ratio it seems that even though we used the ratio score that implies to control for the speed component (measured with the Color card), this measure still reflects motor behavior—that is, reading words out loud as fast as possible.

The current study has a few limitations that need to be mentioned. First, the heterogeneity of the patient group with regard to treatment (dopaminergic treatment $N = 44$; nondopaminergic treatment/treatment unknown $N = 6$; deep brain stimulation, DBS, $N = 5$) is a limitation, since dopaminergic treatment and DBS can have positive as well as negative effects on cognition (Cools, 2006; Cools, Barker, Sahakian, & Robbins, 2001, 2003). When comparing, however, the results on descriptive measures and the RT and MT between patients on dopaminergic treatment and patients who received DBS or of whom the treatment strategies were unknown, no differences were found (data not shown). Furthermore, when analyzing the MTs, we did not control for possible minor on-off fluctuations. Since there were no significant differences between patients and controls regarding the MTs of the simple information-processing task, we assume that the minor on-off fluctuations did not negatively influence test performance. Another limitation is the use of the UPDRS-III total score instead of a sum score of the individual bradykinesia items. Since the total score also includes the evaluations of rigidity and tremor, it is possible that the association between the UPDRS-III and RT and MT would have been different when these items

were excluded. Also, the use of normative data, without adjustments for age, gender, and education, when determining the percentage of impaired RTs and MTs in PD patients and healthy controls can be considered a limitation. However, when, for example, an age-related norm group was used, the size of the normative sample would have been substantially smaller. Therefore the use of a general norm group was preferred. Since the percentage of impaired performances on the simple information-processing task did not significantly differ between patients and controls, the sensitivity of the paradigm appears to be insufficient and must be considered a limitation. A final limitation is that for PD patients the exact disease duration was not reported in this study. The possible influence of disease duration on test performance could therefore not be analyzed.

In conclusion, PD patients show mental slowness that can be separated from slowness of movement. However, this mental slowness did not have an influence on the performances of PD patients on various neuropsychological tests for attention, memory, and EF. Interestingly, patients showed no motor slowness on the simple information-processing task. Also, their MTs were not related to clinical measures of disease severity (including bradykinesia), indicating that both measures assess motor slowness in a different way. MTs did, however, determine patients' performance on two test measures of which the outcome was measured in terms of speed. We tentatively conclude that these findings indicate that mental slowness is not a substantial factor that needs to be taken into account when interpreting results of PD patients on these neuropsychological tests. PD patients' motor speed, on the other hand, can be of influence on test performances and needs to be taken into consideration in clinical practice.

Acknowledgements

We are grateful to Schuhfried GmbH, in particular M. Vetter and R. Debelak, for the friendly cooperation and providing normative data for our analyses.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Dutch Organization for Scientific Research (NWO), the National Initiative Brain and Cognition (NIHC) [grant number 056-11-012]. This quick-result project is embedded in the pillar “The Healthy Brain, Program Cognitive Rehabilitation.”

References

- Albinet, C. T., Boucard, G., Bouquet, C. A., & Audiffren, M. (2012). Processing speed and executive functions in cognitive aging: How to disentangle their mutual relationship? *Brain and Cognition*, 79(1), 1–11. doi:10.1016/j.bandc.2012.02.001
- Berry, E. L., Nicolson, R. I., Foster, J. K., Behrmann, M., & Sagar, H. J. (1999). Slowing of reaction time in Parkinson's disease: The involvement of the frontal lobes. *Neuropsychologia*, 37(7), 787–795.
- Buck, P. O., Wilson, R. E., Seeberger, L. C., Conner, J. B., & Castelli-Haley, J. (2011). Examination of the UPDRS bradykinesia subscale: Equivalence, reliability and validity. *Journal of Parkinson's Disease*, 1(3), 253–258. doi:10.3233/JPD-2011-11035
- Cools, R. (2006). Dopaminergic modulation of cognitive function—Implications for L-DOPA treatment in Parkinson's disease. *Neuroscience and Biobehavioral Reviews*, 30(1), 1–23.
- Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral Cortex*, 11(12), 1136–1143.
- Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). L-dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*, 41(11), 1431–1441.
- Deelman, B. G., Brouwer, W. H., van Zomeren, A. H., & Saan, R. J. (1980). Cognitive impairment after trauma capitis. In A. Jennekens-Schinkel, J. J. Diamant, H. F. A. Diesfelt, & R. Haaxma (Eds.), *Neuropsychologie in Nederland* (pp. 253–282). Deventer: Van Loghnum Slaterus.
- Duncombe, M. E., Bradshaw, J. L., Iansek, R., & Phillips, J. G. (1994). Parkinsonian patients without dementia or depression do not suffer from bradyphrenia as indexed by performance in mental rotation tasks with and without advance information. *Neuropsychologia*, 32(11), 1383–1396.
- Elgh, E., Domellof, M., Linder, J., Edstrom, M., Stenlund, H., & Forsgren, L. (2009). Cognitive function in early Parkinson's disease: A population-based study. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies*, 16(12), 1278–1284. doi:10.1111/j.1468-1331.2009.02707.x
- Esselink, R. A., de Bie, R. M., de Haan, R. J., Lenders, M. W., Nijssen, P. C., Staal, M. J.,... Speelman, J. D. (2004). Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: A randomized trial. *Neurology*, 62(2), 201–207.
- Gauntlett-Gilbert, J., & Brown, V. J. (1998). Reaction time deficits and Parkinson's disease. *Neuroscience and Biobehavioral Reviews*, 22(6), 865–881.
- Helscher, R. J., & Pinter, M. M. (1993). Speed and power of higher cerebral functions in parkinsonian patients. *Journal of Neural Transmission. Parkinson's Disease and Dementia Section*, 5(1), 35–44.
- Hsieh, Y. H., Chen, K. J., Wang, C. C., & Lai, C. L. (2008). Cognitive and motor components of response speed in the Stroop test in Parkinson's disease patients. *The Kaohsiung Journal of Medical Sciences*, 24(4), 197–203. doi:10.1016/S1607-551X(08)70117-7
- Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery, and Psychiatry*, 55(3), 181–184.
- Koerts, J., Tucha, L., Lange, K. W., & Tucha, O. (2013). The influence of cognitive reserve on cognition in Parkinson's disease. *Journal of Neural Transmission*, 120(4), 593–596. doi:10.1007/s00702-012-0916-6
- Lezak, M. D., Howieson, D. B., Loring, D. W., Hannay, H. J., & Fischer, J. S. (2004). *Neuropsychological assessment*. New York, NY: Oxford University Press.
- Liozidou, A., Potagas, C., Papageorgiou, S. G., & Zalonis, I. (2012). The role of working memory and information processing speed on Wisconsin Card Sorting Test performance in Parkinson disease without dementia. *Journal of Geriatric Psychiatry and Neurology*, 25(4), 215–221. doi:10.1177/0891988712466456
- Muslimovic, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*, 65(8), 1239–1245. doi:10.1212/01.wnl.0000180516.69442.95
- Phillips, J. G., Schiffter, T., Nicholls, M. E., Bradshaw, J. L., Iansek, R., & Saling, L. L. (1999). Does old age or Parkinson's disease cause bradyphrenia? *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 54(8), M404–M409.
- Prieler, J. (2008). *Reaction test*. Mödling: Schuhfried GmbH.
- Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. *Perceptual and Motor Skills*, 8, 271–276. doi:10.2466/PMS.8.7.271-276
- Revonsuo, A., Portin, R., Koivikko, L., Rinne, J. O., & Rinne, U. K. (1993). Slowing of information processing in Parkinson's disease. *Brain and Cognition*, 21(1), 87–110.
- Robertson, I. H., Ward, T., Ridgeway, V., & Nimmo-Smith, I. (1994). *Manual: The Test of Everyday Attention*. Bury St. Edmunds: Thames Valley Test Company.
- Salthouse, T. A. (1992). Influence of processing speed on adult age differences in working memory. *Acta Psychologica*, 79(2), 155–170.
- Salthouse, T. A. (1994). The nature of the influence of speed on adult differences in cognition. *Developmental Psychology*, 30(2), 240–259.
- Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, 103(3), 403–428.

- Sawamoto, N., Honda, M., Hanakawa, T., Fukuyama, H., & Shibasaki, H. (2002). Cognitive slowing in Parkinson's disease: A behavioral evaluation independent of motor slowing. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 22(12), 5198–5203.
- Spikman, J. M., van Zomeren, A. H., & Deelman, B. G. (1996). Deficits of attention after closed-head injury: Slowness only? *Journal of Clinical and Experimental Neuropsychology*, 18(5), 755–767. doi:10.1080/01688639608408298
- Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, 18, 643–662.
- Verbaan, D., Jeukens-Visser, M., Van Laar, T., van Rooden, S. M., Van Zwet, E. W., Marinus, J., & van Hilten, J. J. (2011). SCOPA-cognition cutoff value for detection of Parkinson's disease dementia. *Movement Disorders: Official Journal of the Movement Disorder Society*, 26(10), 1881–1886. doi:10.1002/mds.23750
- Watson, G. S., & Leverenz, J. B. (2010). Profile of cognitive impairment in Parkinson's disease. *Brain Pathology*, 20(3), 640–645. doi:10.1111/j.1750-3639.2010.00373.x
- Wechsler, D. (1987). *Wechsler Memory Scale-Revised*. San Antonio, TX: The Psychological Corporation.
- Wilson, B. A., Alderman, N., Burgess, P. W., Emslie, H., & Evans, J. J. (1996). *Behavioural Assessment of the Dysexecutive Syndrome*. Bury St. Edmunds: Thames Valley Test Company.
- Wolters, E. C., van Laar, T., & Berendse, H. W. (Eds.). (2007). *Parkinsonism and related disorders* (1st ed.). Amsterdam: VU University Press.