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Mild Cognitive Impairment in Parkinson's Disease: Clustering and Switching Analyses in Verbal Fluency Test

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Abstract

Objectives: Mild cognitive impairment is common in non-demented Parkinson disease patients (PD-MCI) and is considered as a risk factor for dementia. Executive dysfunction has been widely described in PD and the Verbal Fluency Tests (VFT) are often used for executive function assessment in this pathology. The Movement Disorder Society (MDS) published guidelines for PD-MCI diagnosis in 2012. However, no investigation has focused on the qualitative analysis of VFT in PD-MCI. The aim of this work was to study the clustering and switching strategies in VFT in PD-MCI patients. Moreover, these variables are considered as predictors for PD-MCI diagnosis. **Methods:** Forty-three PD patients and twenty normal controls were evaluated with a neuropsychological protocol and the MDS criteria for PD-MCI were applied. Clustering and switching analysis were conducted for VFT. **Results:** The percentage of patients diagnosed with PD-MCI was 37.2%. The Mann-Whitney *U* test analysis showed that PD-MCI performed poorly in different cognitive measures (digit span, Wisconsin Card Sorting Test, judgment of line orientation, and comprehension test), compared to PD patients without mild cognitive impairment (PD-nMCI). Phonemic fluency analyses showed that PD-MCI patients produced fewer words and switched significantly less, compared to controls and PD-nMCI. Concerning semantic fluency, the PD-MCI group differed significantly, compared to controls and PD-nMCI, in switches. Discriminant function analyses and logistic regression analyses revealed that switches predicted PD-MCI. **Conclusions:** PD-MCI patients showed poor performance in VFT related to the deficient use of production strategies. The number of switches is a useful predictor for incident PD-MCI. (*JINS*, 2017, *23*, 511–520)

Keywords: Neurodegenerative disease, Movement disorders, Neuropsychological assessment, Cognitive impairment, Executive functions, Diagnosis

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder whose etiology is unknown and which is associated with cognitive impairment and increased risk of developing dementia (PDD) (Aarsland, Zaccai, & Brayne, 2005; Janvin, Larsen, Aarsland, & Hugdahl, 2006). Cognitive impairment in PD patients is heterogeneous and includes deficits in multiple cognitive domains such as attention, executive functions, language, memory, and visuospatial functioning (Barone et al., 2011; Galtier, Nieto, Lorenzo, & Barroso, 2014). Contributions from neuroimaging studies demonstrate that, even in non-demented cases, patients may present hippocampal, frontal, and parietal atrophy related to alterations in different cognitive functions (Beyer et al., 2013; Jokinen et al., 2009; Pereira et al., 2009).

Executive dysfunction, measured by different instruments, has been widely described in PD and includes impairment on form abstract concepts, planning, developing strategies, self-monitoring, self-regulation, inhibition, and flexibility. Numerous studies have reported that PD patients showed an altered performance in different tests associated to executive functions, such as the Wisconsin Cart Sorting Test (WCST) (Liozidou, Potagas, Papageorgiou, & Zalonis, 2012; Paolo, Axelrod, Tröster, Blackwell, & Koller, 1996), Stroop Test (Hsieh, Chen, Wang, & Lai, 2008; Muslimovic, Post, Speelman, & Schmand, 2007), and Trail Making Test part B (TMT-B) (Akamatsu, Fukuyama, & Kawamata, 2008; Camicioli, Wieler, de Frias, & Martin, 2008).

Measures of VFT are also often used to evaluate executive dysfunction; this type of instruments requires a time-restricted generation of multiple response alternatives

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under constricted search conditions, and they are considered measures of cognitive flexibility and search strategy. VFT has been proposed as a frontal impairment measure with more validity and specificity, compared with other instruments such as the WCST (Henry & Crawford, 2004). However, the results obtained in PD with measures of VFT are heterogeneous, both with phonemic and semantic fluency tests; different studies found an altered execution (Bouquet, Bonnaud, & Gil, 2003; Mimura, Oeda, & Kawamura, 2006; Muslimovic et al., 2007), whereas other authors do not find statistical significance (Brand et al., 2004; Schneider, 2007; Troyer, Moscovitch, Winocur, Leach, & Freedman, 1998).

Some authors have proposed a qualitative analysis of VFT as a complementary procedure to measure executive functions; the performance on this type of tasks can be divided into two components: (a) clustering, defined as the production of words within semantic or phonemic subcategories, and (b) switching, considered as the ability to efficiently shift to a new subcategory (Troyer, Moscovitch, & Winocur, 1997). Clustering has been associated to temporal lobe processes such as verbal memory and word storage, whereas switching has been related to frontal lobe processes such as strategic search, cognitive flexibility, and shifting. This affirmation has been supported by posterior publications (Troyer et al., 1997; Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998).

The investigations that have been focused in the study of qualitative components of VFT in PD patients are limited and heterogeneous. Regarding the phonemic fluency test, some authors reported that PD patients without dementia (PDND) did not differ when compared to controls in clustering and switching strategies (Koerts et al., 2013; Tröster et al., 1998; Troyer, Moscovitch, Winocur, Leach, et al., 1998), and only PDD presented an altered performance. Some authors only observed an altered execution in PDD in the number of switches (Tröster et al., 1998), while another study reported a deficient performance in cluster size and number of switches (Troyer, Moscovitch, Winocur, Leach, et al., 1998).

However, other authors reported that the poor performance, compared to controls, in clustering and switching strategies were not limited to PDD; PDND also presented an altered performance in cluster size and number of switches (Epker, Lacritz, & Munro Cullum, 1999). The results available were also heterogeneous in the semantic fluency test; different studies reported a normal execution in PDND (Epker et al., 1999; Tröster et al., 1998; Troyer, Moscovitch, Winocur, Leach, et al., 1998) and an altered performance in PDD represented by impairment in only the number of switches (Epker et al., 1999; Troyer, Moscovitch, Winocur, Leach, et al., 1998), or in cluster size and number of switches (Tröster et al., 1998). However, other authors reported that PDND, compared to controls, performed poorly in the number of switches (Koerts et al., 2013). The discrepancies in the qualitative analysis of VFT could be interpreted as a reflection of the heterogeneity classically associated to cognitive impairment in PD.

The construct of mild cognitive impairment in PD (PD-MCI) has recently been developed, as a result of the gradual increase of interest in the heterogeneity of cognitive deficits, and their impact on the quality of life of PD patients. The Movement Disorder Society (MDS) commissioned a task force to develop formal diagnostic criteria for PD-MCI (Litvan et al., 2012). Some studies have reported that between 24% and 35% of newly diagnosed PD patients meet PD-MCI criteria, when a comprehensive assessment was applied (level 2 of the MDS criteria) (Broeders et al., 2013; Stefanova et al., 2015). Pedersen, Larsen, Tysnes, & Alves (2013) examined a sample of PD patients in the early stage of the disease (Hoehn and Yahr stage 1–2); they applied a brief assessment (level 1 of the MDS criteria) and found that 20.3% of patients met PD-MCI criteria. Other studies opted for a comprehensive assessment to examining patients who had a mean PD duration of 8.3 and 14.1 years (level 2 of the MDS criteria); they found that PD-MCI was present in 42.6% to 60.5% of the patients (Domellöf, Ekman, Forsgren, & Elgh, 2015; Galtier, Nieto, Lorenzo, & Barroso, 2016).

Several studies have examined whether cognitive performance in the first stages of the disease could predict the progression of cognitive impairment and dementia development. PD-MCI was predicted by poor performance in language function (semantic task of CAMCOG), visuospatial construction (copying and drawing), and declarative memory (Hobson & Meara, 2015). Moreover, PD-MCI patients who progressed to PDD performed poorly in executive functions measured with VFT (Domellöf et al., 2015; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007; Williams-Gray et al., 2009), and other instruments associated to mental flexibility, inhibition, and form abstract concepts (e.g., TMT-B, WCST, Stroop test) (Domellöf et al., 2015; Lee et al., 2014).

There are no previous studies, to the best of our knowledge, that have focused on studying the clustering and switching strategies in the VFT in PD-MCI patients. Therefore, the aims of this study were (1) to investigate the clustering and switching strategies on phonemic and semantic fluency test in patients with and without PD-MCI and (2) to study these variables as a risk factor for PD-MCI diagnosis. The hypothesis of this study is that the PD-MCI group, compared to the controls and PD patients without mild cognitive impairment (PD-nMCI), will present a less words production in the VFT associated to the deficient use of switching strategies, highly related to frontal lobe processes. The number of switches will be a predictor for incident PD-MCI.

SUBJECTS AND METHODS

Subjects

The study included 63 participants: 43 patients with idiopathic PD and 20 healthy and neurologically normal controls. Patients were evaluated using the Hoehn & Yahr Scale (Hoehn & Yahr, 1967) and the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987). All the patients met the clinical criteria for the diagnosis of PD (Hughes, Daniel, Kilford, & Lees, 1992). Exclusion criteria

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were as follows: (a) global cognitive deterioration (Mini-Mental State Examination, MMSE; Folstein, Folstein, & McHugh, (1975) < 24) or dementia associated with PD (Emre et al., 2007), (b) major psychiatric disorder, (c) drug or alcohol abuse, (d) visual and/or auditory perception disorders limiting the ability to take the test, and (e) history of stroke and/or head injury with loss of consciousness. Patients and controls were matched in age, education, gender, manual preference, and estimated IQ (Information subtest) (Wechsler, 1997a). The Beck Depression Inventory was administered for the assessment of mood state (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) (Table 1).

Ethics Statement

All participants were informed about the aims of the investigation and participated voluntarily and gave their informed consent. The data were obtained in accordance with the regulations of the local ethics Committee and in compliance with the Helsinki Declaration for Human Research.

Neuropsychological Assessment and PD-MCI Diagnosis

Patients and controls were evaluated with a standardized protocol of cognitive tests. Attention was examined using the Digit span backward (Wechsler, 1997b). Executive functions were assessed with the WCST (Heaton, 1981). Memory was assessed with the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987); the test includes learning over a five-trial presentation of a 16-word list, free and cued delayed recall and recognition. Visuospatial functions were examined using the Judgment of Line Orientation Test (JLOT, 15 items simplified version) (Benton, Hamsher, Varney, & Spreen, 1983). Finally, language was assessed with the Sentences Comprehension Test, based on studies by Grossman, Carvell, Stern, Gollomp, and Hurtig (1992) and Skeel et al. (2001). The said test consists of 30 sentences (auditory stimuli) with different levels of syntactic complexity, each followed by a question to assess their understanding (see Galtier et al., 2016 for detailed description). The PD-MCI criteria proposed by the MDS were applied (Litvan et al., 2012).

Impairment should be present in at least two tests (MDS diagnostic criteria level 1). Impairment in neuropsychological tests may be demonstrated by performance 1.5 standard deviations or more below the mean of the control group. The absence of significant functional decline was confirmed based on a semistructured interview and clinical impression of the subject's general cognitive function.

Clustering and Switching Strategies in the VFT

The VFT (Benton, Hamsher, & Sivan, 1989) consists of asking the participants to rapidly generate words under a constricted search conditions. As regards phonemic fluency, subjects were instructed to generate as many words as possible that begin with the letters "F," "A," and "S," excluding proper names, numbers, and the same words with different suffixes. One minute was allowed for each letter. Subjects were instructed to generate as many different animals as possible in one minute to assess semantic fluency. The proposal of Troyer et al. (1997) was applied for the analysis of clustering and switching strategies. Three scores were calculated for each fluency test: (1) total words generated, (2) mean cluster size, and (3) number of switches.

In phonemic fluency, clusters were defined as groups of successively generated words that began with the same first

Table 1. Demographic data and clinical characteristics

	HC ($n = 20$)	All PD ($n = 43$)	PD-nMCI ($n = 27$)	PD-MCI ($n = 16$)
Variable	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Gender (men/women)	9/11	24/19*	17/10	7/9*
Age (years)	60.85 (12.26)	59.19 (9.64)	58.41 (10.61)	60.50 (7.90)
Education (years)	8.55 (2.72)	7.88 (2.75)	8.44 (2.72)	6.94 (2.59)
MMSE	28.40 (1.50)	27.58 (1.80)	28.04 (1.69)	26.38 (1.36)***
Information (WAIS-III)	14.30 (5.32)	12.50 (5.78)	14.41 (6.16)	9.07 (2.76)***
BDI score	7.88 (4.94)	13.33 (9.37)**	13.26 (9.12)	13.44 (10.07)
HY stage	—	2.28 (0.77)	2.19 (0.74)	2.38 (0.72)
HY stage (range)	—	1–3	1–3	1–3
UPDRS-ME	—	28.46 (13.96)	26.26 (12.80)	31.63 (15.33)
Age at onset	—	50.88 (9.26)	50.63 (9.76)	51.31 (8.65)
Years since diagnosis	—	8.30 (6.33)	7.78 (6.35)	9.19 (6.39)

Note. n = number of the sample in each group; HC = healthy controls; PD = Parkinson's disease; PD-nMCI = PD patients without mild cognitive impairment; PD-MCI = PD patients with mild cognitive impairment; M = mean; SD = standard deviation; MMSE = Mini-Mental State Examination; WAIS-III = Wechsler Adult Intelligence Scale third edition; BDI = Beck Depression Inventory; HY = Hoehn & Yahr scale; UPDRS-ME = Unified Parkinson's Disease Rating Scale – Motor score.

*Pearson's chi-squared test was not significant.

**$p < .05$, comparisons between healthy controls and PD group.

***$p < .01$, comparisons between PD-nMCI and PD-MCI.

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two letters, differed only by a vowel sound, rhymed, or were homonyms. In semantic fluency, clusters were defined as groups of successively generated words that belonged to the same semantic subcategory, such as strong-pairs (e.g., cat–dog, turtle–rabbit); farm animals (e.g., cow, ox, goat, lamb, billy-goat, bull, chicken, rooster, dog, horse, donkey, mule, rabbit, duck, goose); forest animals (e.g., wolf, bear, fox); tropical animals, animals of the steppe, animals of the jungle and safari animals (e.g., crocodile, elephant, hippopotamus, giraffe); reptiles (e.g., crocodile, all types of snakes, turtle); birds; fish, including anything living underwater such as mammals (e.g., dolphin, whale) or animals with shells; and insects (Kosmidis, Vlahou, Panagiotaki, & Kiosseoglou, 2004; Troyer et al., 1997).

Cluster size was counted beginning with the second word in each cluster, and the mean cluster size was calculated for each fluency test. Switches were calculated as the number of transitions between clusters, including isolated words. Errors and repetitions were included in calculations of cluster size and switching, according to the proposal of Troyer et al. (1997).

Data Analysis

A nonparametric statistic was used to evaluate differences between groups because the Shapiro-Wilk W test showed that data deviated from the standard normal distribution. The Mann-Whitney and Kruskal-Wallis tests were used to compare the means in pairs of groups and multiple groups, respectively. If the Kruskal-Wallis test result was significant, the two-tailed Mann-Whitney *U* test was used to assess the paired difference between groups (with Bonferroni correction for multiple comparisons applied). Effect size measures were calculated. Correlational analyses were performed using Spearman's correlation coefficient to examine the relation between the total number of words generated and qualitative aspects of verbal fluency (bootstrap methodology with 1000 resamples).

In addition, correlational analyses and analyses of covariance was conducted to explore the effect of demographics variables (variables were transformed into ranks for the tests due to lack of normal distribution). Discriminant function analyses were run to examine the contribution of clustering and switching strategies to PD-MCI diagnosis. Stepwise logistic regression analysis were performed to investigate the VFT as predictor of PD-MCI. Finally, receiver operating characteristic (ROC) curves were graphed and the area under the curves was compared. Optimal cutoffs were defined as the greatest combined sensitivity and specificity, with sensitivity greater than 80%. $p < .05$ was established as level of statistical significance. All the analyses were performed with SPSS-PC software version 15.0 for Windows.

RESULTS

Neuropsychological Assessment and PD-MCI Diagnosis

PD patients and controls did not differ in age, years of education, and estimated IQ. When the MDS Task Force criterion was used, sixteen (37.2%) PD patients met the criteria for PD-MCI. Table 2 summarizes the neuropsychological performances for the PD-MCI, PD-nMCI, and healthy controls. PD-MCI patients performed poorly, compared to healthy controls, in digit span (backward) (r = .52), categories of WCST (r = .69), JLOT (r = .77), and comprehension test (r = .39). PD-MCI patients also performed poorly, compared to PD-nMCI, in digit span (backward)

Table 2. Neuropsychological test scores for PD patients and healthy controls.

	HC ($n = 20$)	PD-nMCI ($n = 27$)	PD-MCI ($n = 16$)			
Variable	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	χ^2	*p*-Value	Post hoc comparisons
Attention-working memory						
-Digit span backward	4.41 (1.37)	4.19 (1.04)	3.00 (0.89)	11.787	.001	PD-MCI < PD-nMCI PD-MCI < Controls
Executive functions						
-WCST (categories)	3.88 (1.97)	2.96 (1.93)	0.81 (0.91)	14.882	<.001	PD-MCI < PD-nMCI PD-MCI < Controls
Learning and memory						
-CVLT-Learning	54.65 (12.65)	47.30 (9.34)	43.80 (13.15)	1.558	.212	
-CVLT-Delay	12.06 (4.07)	10.19 (2.70)	9.47 (4.07)	0.453	.501	
-CVLT-Delay (semantic cued)	13.06 (3.13)	10.74 (2.63)	9.93 (3.45)	0.808	.369	
Visuospatial functions						
-JLOT	13.41 (1.33)	12.93 (1.69)	7.40 (3.09)	21.183	<.001	PD-MCI < PD-nMCI PD-MCI < Controls
Language						
-Comprehension Test	24.53 (2.85)	24.11 (3.07)	20.38 (4.83)	6.728	.009	PD-MCI < PD-nMCI PD-MCI < Controls

Note. *n* = number of the sample in each group; HC = healthy controls; PD = Parkinson's disease; PD-nMCI = PD patients without mild cognitive impairment; PD-MCI = PD patients with mild cognitive impairment; WCST = Wisconsin Card Sorting Test; CVLT = California Verbal Learning Test; JLOT = Judgment of Line Orientation Test.

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Table 3. Clustering and switching strategies for PD patients and healthy controls

	HC ($n = 20$)	PD-nMCI ($n = 27$)	PD-MCI ($n = 16$)			
Variables	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	χ^2	*p*-Value	Post hoc comparisons
Letters fluency						
Total words	25.47 (9.55)	26.30 (9.18)	16.31 (6.47)	13.272	.001	PD-MCI < PD-nMCI PD-MCI < Controls
Mean cluster size	1.82 (0.74)	1.78 (0.88)	1.81 (0.74)	1.711	.425	
Number of switches	14.28 (6.52)	16.00 (7.30)	8.12 (4.01)	13.265	.001	PD-MCI < PD-nMCI PD-MCI < Controls
Animals fluency						
Total words	17.00 (5.24)	16.04 (4.06)	15.19 (2.71)	2.414	.299	
Mean cluster size	2.78 (1.05)	2.78 (0.90)	5.09 (3.75)	5.239	.073	
Number of switches	4.89 (2.25)	4.82 (2.13)	2.81 (1.80)	10.444	.005	PD-MCI < PD-nMCI PD-MCI < Controls

Note. n = number of the sample in each group; HC = healthy controls; PD = Parkinson's disease; PD-nMCI = PD patients without mild cognitive impairment; PD-MCI = PD patients with mild cognitive impairment.

(r = .52), categories of WCST (r = .59), JLOT (r = .70), and comprehension test (r = .40). The visuospatial functions were the cognitive domain with the highest percentage of impaired patients (41.9%).

Clustering and Switching Strategies

The two-tailed Mann-Whitney *U* test for the phonemic fluency test revealed that the controls generate a significantly greater number of words (r = .48) and switches (r = .43) than the PD-MCI group. PD-MCI patients also performed poorly, compared to the PD-nMCI group, in total words generated (r = .51) and the number of switches (r = .53). No differences were found between groups in mean cluster size. Concerning semantic fluency, the results showed that the PD-MCI group differed significantly, compared to controls (r = .44) and PD-nMCI (r = .44), in the number of switches, whereas no differences were found in total words and in mean cluster size. The PD-MCI group, compared to PD-nMCI patients and controls, generate a larger cluster size, although the differences did not reach statistical signification (Table 3).

Correlation analyses were carried out for PD patients between the qualitative variables (clustering and switching strategies) and total number of words generated in VFT. Total words generated was significantly correlated with switches but not with the mean cluster size. Similar results were obtained for the control group and the PD-nMCI group. Regarding PD-MCI, total words only correlated significantly with switches in phonemic fluency (Table 4). Correlation analyses were conducted to explore the association of the performance in the VFT with education, Information subtest, BDI score, and WCST (Table 5 and Table 6). Regarding PD patients, the number of categories in WCST was associated significantly with phonemic fluency (total words and number of switches) and semantic fluency (mean cluster size and number of switches).

In addition, the Information subtest correlated significantly with total words generated and switches in phonemic and semantic fluency. No significant correlations were found between VFT and education or BDI score. In regards to the control group, the number of categories in WCST was associated significantly only with phonemic fluency (total words). No significant correlations were found between VFT

Table 4. Correlation (Spearman's non-parametric rank) between the qualitative variables and total number of words generated in Verbal Fluency Test

	HC ($n = 20$)			All PD ($n = 43$)			PD-nMCI ($n = 27$)			PD-MCI ($n = 16$)		
Variables	Rho	*SE*	CI	Rho	*SE*	CI	Rho	*SE*	CI	Rho	*SE*	CI
Letters fluency												
Mean cluster size	−.11	.29	−.65/.49	−.01	.17	−.34/.30	.14	.20	−.29/.51	.21	.31	−.47/.77
Number of switches	.77*	.16	.30/.95	.88*	.05	.74/.94	.86*	.08	.66/.95	.74*	.17	.32/.96
Animals fluency												
Mean cluster size	.31	.28	−.32/.76	.01	.18	−.35/.36	.07	.23	−.41/.47	.03	.32	−.61/.63
Number of switches	.69*	.19	.20/.93	.47*	.13	.16/.70	.58*	.15	.25/.80	.37	.26	−.20/.82

Note. n = number of the sample in each group; HC = healthy controls; PD = Parkinson's disease; PD-nMCI = PD patients without mild cognitive impairment; PD-MCI = PD patients with mild cognitive impairment; *SE* = standard error; CI = 95% confidence interval.
*$p < .01$.

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Table 5. Correlation (Spearman's non-parametric rank) of Verbal Fluency Test with education, Information subtest, depression, and WCST (categories), for the control group (n = 20)

	Education			Information subtest			BDI			WCST		
Variables	Rho	*SE*	CI	Rho	*SE*	CI	Rho	*SE*	CI	Rho	*SE*	CI
Letters fluency												
Total words	.14	.34	−.54/.80	.46	.22	−.12/.78	.05	.24	−.42/.52	.62*	.23	.09/.93
Mean cluster size	−.36	.26	−.80/.21	−.31	.29	−.84/.30	.03	.32	−.62/.64	−.07	.28	−.57/.58
No. of switches	.13	.29	−.44/.66	.27	.28	−.32/.76	.09	.30	−.54/.63	.41	.28	−.18/.88
Animals fluency												
Total words	.26	.19	−.18/.60	.25	.27	−.32/.73	.08	.29	−.54/.62	.33	.27	−.25/.76
Mean cluster size	.20	.30	−.43/.78	.32	.25	−.26/.73	−.09	.26	−.57/.47	−.38	.24	−.78/.12
No. of switches	.28	.21	−.21/.60	.05	.27	−.48/.54	.26	.25	−.28/.68	.52*	.22	−.02/.83

Note. *n* = number of the sample in each group; BDI = Beck Depression Inventory; WCST = Wisconsin Card Sorting Test. *SE* = standard error; CI = 95% confidence interval.
*$p < .05$.

and education, Information subtest, or BDI score. Analyses of covariance with the Information subtest as a covariate revealed significant between-group differences for the number of switches in phonemic fluency, $F(1,62) = 4.04$; $p < .023$, $\eta^2 = .13$ [covariate $F(1,62) = 11.06$; $p < .01$] and semantic fluency, $F(1,62) = 3.33$, $p < .043$, $\eta^2 = .11$ [covariate $F(1,62) = 3.94$; $p = .052$]. However, between-group difference was not significant for total words generated in phonemic fluency, $F(1,62) = 2.79$, $p = .070$ [covariate $F(1,62) = 25.98$; $p < .001$].

The utility of qualitative analysis in the VFT for classifying patients into their respective groups (PD-MCI *vs*. PD-nMCI) was evaluated using discriminant function analyses. An overall classification rate of 81.4% was found using switches variables in phonemic and semantic fluency combined, with the best classification belonging to the PD-MCI group (93%) followed by the PD-nMCI group (74.1%). Switches in phonemic fluency reached an overall classification rate of 72.1% (PD-MCI 87.5%, PD-nMCI 63%). Mean cluster size in semantic fluency and also mean cluster size variables combined (phonemic and semantic) reached an overall classification rate of 69.8%. Individual and combined discriminant function analyses can be seen in Table 7.

Stepwise logistic regression analysis was conducted to determine which VFT variables had the greatest ability to differentiate patients with and without PD-MCI. Phonemic and semantic fluency scores (total words, switches, mean cluster size) were included in the regression analysis as independent variables, whereas the diagnosis (PD-MCI *vs*. PD-nMCI) was the dependent variable. The Hosmer and Lemeshow Test was not significant ($\chi^2 = 5.33$; $p = .722$), suggesting a goodness-of-fit for the model. The analysis showed that only the number of switches in phonemic (WALD = 6.81; $p < .01$) and semantic fluency (WALD = 4.15; $p = .042$) significantly contributed to the prediction. For a differentiation between PD-MCI and PD-nMCI groups, the area under the ROC curve of switches in phonemic fluency was .819 (95% confidence interval (CI) [.70, .94]), while the area under the ROC curve of switches in semantic fluency was .759 (95% CI [.61, .91]) (Figure 1). The optimal cutoff of switches was 13.5 in

Table 6. Correlation (Spearman's non-parametric rank) of Verbal Fluency Test with education, Information subtest, depression, and Wisconsin test (categories), for PD patients (n = 43)

	Education			Information subtest			BDI			WCST		
Variables	Rho	*SE*	CI	Rho	*SE*	CI	Rho	*SE*	CI	Rho	*SE*	CI
Letters fluency												
Total words	.28	.15	−.04/.57	.70**	.09	.49/.82	−.10	.17	−.41/.25	.47**	.13	.18/.69
Mean cluster size	.14	.16	−.19/.43	−.05	.15	−.36/.26	.09	.16	−.21/.41	−.05	.15	−.34/.24
No. of switches	.30	.16	−.03/.59	.60**	.11	.36/.77	−.10	.17	−.44/.25	.50**	.13	.21/.72
Animals fluency												
Total words	.07	.16	−.25/.36	.34*	.15	.03/.59	−.25	.16	−.53/.08	.16	.17	−.19/.46
Mean cluster size	−.11	.15	−.40/.18	−.10	.18	−.46/.28	−.40**	.16	−.67/−.07	−.31*	.15	−.58/.01
No. of switches	.07	.15	−.23/.36	.38*	.15	.07/.65	.23	.16	−.08/.53	.35*	.15	.03/.61

Note. *n* = number of the sample in each group; BDI = Beck Depression Inventory; WCST = Wisconsin Card Sorting Test; *SE* = standard error; CI = 95% confidence interval.
*$p < .05$.
**$p < .01$.

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Table 7. Classification rates (%) for each verbal fluency variables from discriminant function analyses

Variables	PD-nMCI ($n = 27$)	PD-MCI ($n = 16$)	Overall
Phonemic/semantic fluency combined			
Total words	70.4	75.0	72.1
Mean cluster size	88.9	37.5	69.8
Switches	74.1	93.8	81.4
Phonemic fluency			
Total words	66.7	68.8	67.4
Mean cluster size	70.4	56.3	65.1
Switches	63.0	87.5	72.1
Semantic fluency			
Total words	48.1	56.3	51.2
Mean cluster size	88.9	37.5	69.8
Switches	59.3	68.8	62.8

Note. n = number of the sample in each group; PD-nMCI = PD patients without mild cognitive impairment; PD-MCI = PD patients with mild cognitive impairment.

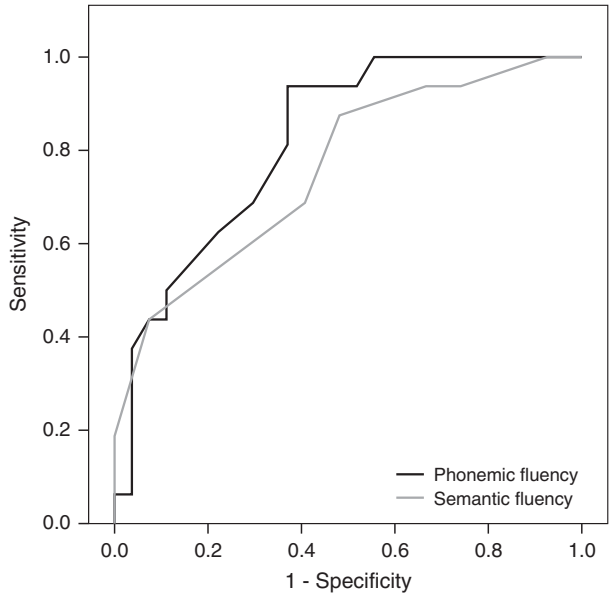

Fig. 1. ROC curves of switches in phonemic and semantic fluency for PD-MCI.

phonemic fluency (sensitivity .938, specificity .630) and 4.5 in semantic fluency (sensitivity .875, specificity .519).

DISCUSSION

The aim of this study was to investigate the clustering and switching strategies in the VFT in patients with PD-MCI. In addition, there was an analysis about which of the qualitative variables related to the VFT are better predictors for the PD-MCI diagnosis. In the present study, 37.2% of patients were diagnosed with PD-MCI according to MDS criteria. This result is coincident with previous studies that found percentages of PD-MCI between 24% and 35% in newly diagnosed PD patients (Broeders et al., 2013; Stefanova et al., 2015) and 42.6% and 60.5% in samples of PD patients with a moderate degree of neurological impairment (Domellöf et al., 2015; Galtier et al., 2016).

Concerning VFT, PD-MCI patients generated fewer words and switches in phonemic fluency, compared to the PD-nMCI and control group. However, PD patients and healthy participants did not differ in mean cluster size. On the other hand, the results of semantic fluency show that, although no differences were found between groups in total words, PD-MCI patients generated fewer switches, compared to the PD-nMCI patients and healthy controls. Concerning semantic cluster size, although differences did not reach statistical significance, PD-MCI patients produced larger clusters, compared to the PD-nMCI patients and controls.

In others words, PD-MCI patients presented a deficient use of shift strategies, but this difficulty did not have an effect on the quantitative production in semantic fluency (total words), probably because the word generation within each cluster was maximized. Therefore, this result would be interpreted as a compensatory mechanism to minimize the deficient use of search and shift strategies that, in normal conditions, allows a rapid change of cluster and, therefore, a more efficient performance. There are no previous studies that have reported similar results, and this is not surprising, given that the present study is the first to explore the qualitative components of VFT in PD-MCI patients.

On the other hand, as expected, the performance in the WCST was highly associated with switches in phonemic and semantic fluency, linked to frontal lobe processes. Mean cluster size in semantic fluency, more related to verbal memory and word storage, also correlated to Wisconsin categories, although the association was low. In addition, the analyses of covariance demonstrated that differences between-groups in the VFT were not explained by the differences observed among patients with and without PD-MCI in estimated IQ. Other authors that studied VFT in PD patients also reported impairment in phonemic fluency together with normal execution in semantic fluency (Epker et al., 1999), although other investigations showed opposite results (Koerts et al., 2013). Recent studies also showed differences between PD-MCI and PD-nMCI patients in phonemic fluency but not in semantic fluency (Galtier et al., 2016). Other investigations with PD-MCI patients only examined phonemic fluency and reported an altered performance (Broeders et al., 2013; Santangelo et al., 2015).

As regards qualitative components of the VFT, clustering and switching strategies were studied in PDD and PDND; initial investigations suggested that deficits in these qualitative components of verbal fluency are limited to demented patients, with a normal performance in PDND (Tröster et al., 1998; Troyer, Moscovitch, Winocur, Leach, et al., 1998). However, other studies demonstrated that qualitative measures of VFT are not only sensitive to patients with very advanced cognitive impairments, but also to the cognitive decline of PDND patients group. The PDND group showed differences compared to controls in the number of switches in

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phonemic (Epker et al., 1999) and semantic fluency (Koerts et al., 2013) and also in the cluster size in phonemic fluency (Epker et al., 1999).

The discrepancies in the results regarding PDND can be interpreted as a consequence of the methodological limitations of the previous studies; information relative to clinical characteristics of PD patients are insufficient; data of neurological impairment or motor symptoms are not detailed, nor is information about the duration of illness or age at diagnosis. Moreover, comprehensive neuropsychological assessment was not included in most of the previous studies (Epker et al., 1999; Tröster et al., 1998; Troyer, Moscovitch, Winocur, Leach, et al., 1998). Consequently, detailed information about clinical variables and the cognitive status of PD patients was not available and patients with different degrees of impairment may have been included in the studies. Therefore, discrepancies in the results of the investigations available are a reflection of the heterogeneity observed in some aspects of the neuropsychological profile classically associated with PD. Cognitive impairment can be present even in the early stages of the disease and multiples factors have been related to the progression of cognitive dysfunction in this pathology, including the degree of neurological impairment, duration of illness, or educational level, among others.

One exception is the study of Koerts et al. (2013); they included a PD sample with a greater control of clinical and cognitive variables. The results showed that PD patients differed to the control group in total words and switches in semantic fluency. A trend toward significance was found in total words on phonemic fluency, whereas no differences between groups were observed in the number of switches. Mean cluster size was not analyzed. These results partially coincide with the present study given that differences were also found here in the number of switches in semantic fluency. Differences regarding phonemic fluency can be explained by the PD sample characteristics; in the study of Koerts et al. (2013) PD patients had minor disease duration (mean 5 years) and motor impairment, according to the UPDRS. Moreover, 68% of PD patients were in the early stages, according to the Hoehn and Yahr Scale. If the neurological impairment and disease duration are considered risk factors associated to cognitive impairment and PD-MCI, it is to be expected that the PD patients included in the study of Koerts et al. (2013) presented less cognitive impairment, including measures of VFT.

As mentioned above, the MDS criteria for PD-MCI hope to advance the understanding and characterization of cognitive impairment in PD; the present study is the first that has focused on the analysis of the qualitative components of the VFT in a sample of PD-MCI patients. The other objective of the present investigation has been to study clustering and switching strategies in the VFT as predictors for PD-MCI diagnosis. The results of the presents study show that the number of switches is a good predictor of PD-MCI (overall classification rate of 81.4%) and is better than total words generated in the VFT (overall classification rate of 72.1%). Logistic regression and ROC curves reinforce this affirmation considering that the number of switches in phonemic and semantic fluency significantly contributed to the prediction of PD-MCI.

These results are especially relevant considering that PD-MCI patients performed poorly in phonemic fluency, but no differences were found in semantic fluency. The analysis of switching strategies in PD might provide a sensitive measure of cognitive status in PD which is more sensitive than the total number of words. Therefore, even without an altered performance in the VFT (total words generated), qualitative components of the execution (switches) can be considered as a useful predictor of PD-MCI.

There are no previous studies that have focused on studying the clustering and switching strategies in the VFT as a risk factor for PD-MCI diagnosis. Other authors reported that executive dysfunction was associated with the progression of cognitive impairment. The results available showed that impairment on mental flexibility, inhibition, or form abstract concepts were associated with an increased risk of developing dementia (Domellöf et al., 2015; Lee et al., 2014; Williams-Gray et al., 2007, 2009). For example, Domellöf et al. (2015) reported that PD-MCI patients who developed PDD in a 5-year follow up study performed poorly at the base line, when compared to PD-MCI patients who remained stable, in different tests including measures of executive functions such as TMT-B and VFT.

Similarly, Lee et al. (2014) stated that PD-MCI patients who converted to PDD showed poor performance in the VFT and the Stroop test (color-word score), among other cognitive measures. Lee et al. (2014) also reported that PD-MCI patients who converted to PDD presented more atrophy in the frontal lobe, which correlated with executive measures. Therefore, the results relate executive dysfunction in PD-MCI with the development of dementia, and are coincident with the present study, considering that switches strategies is the most strongly qualitative component of the VFT related to frontal lobe processes (Troyer et al., 1997; Troyer, Moscovitch, Winocur, Alexander, et al., 1998).

The results of the present investigation are especially relevant considering that the VFT is one of the most widely used tests to evaluate executive functions, commonly used in scientific studies and also by the clinicians. Numerous investigations have been conducted to explore possible predictors of cognitive impairment in PD patients. The National Institute of Neurological Diseases and Stroke (NINDS) established the Parkinson Disease Biomarkers Program (PDBP), a consortium of 11 research projects with the aim of identifying biomarkers for PD and also PDD (Rosenthal et al., 2015).

Another project is the Parkinson Progression Marker Initiative (PPMI), a 5-year international multicenter study, designed to identify PD progression biomarkers. One crucial objective for investigations in the context of PPMI will be to examine biological predictors of cognitive impairment in PD (Marek et al., 2011). However, some of the results related to the biomarker use, although highly relevant, are sometimes difficult to incorporate in daily clinical practices, unlike the VFT that is a brief instrument which is easy to apply and

interpret. The incorporation of qualitative analyses in the VFT would provide relevant information for the PD-MCI diagnostic process.

Certain limitations of the present study need to be acknowledged: (1) the sample size is relatively small and (2) a sample of PDD patients was not included. Further studies with larger samples and which include PDD patients would be able to confirm these findings.

In summary, the present investigation is the first to study the clustering and switching strategies in the VFT in PD-MCI and provides relevant data on the process of characterization of PD-MCI, according to the MDS criteria. PD-MCI patients differ in terms of the quantitative and qualitative components of VFT, when compared to PD-nMCI patients and healthy subjects. A lesser use of switching strategies can be considered as a useful predictor of PD-MCI.

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