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The Effect of Parkinson's Disease Subgroups on Verbal and Nonverbal Fluency

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Abstract

Background—Parkinson's disease (PD) leads to deficits in executive function, including verbal and nonverbal fluency, as a result of compromised fronto-striatal circuits. It is unknown whether deficits in verbal and nonverbal fluency in PD are driven by certain subgroups of patients, or how strategy use may facilitate performance.

Participants—Sixty-five non-demented individuals with PD, including 36 with right-body onset (RPD; 20 with tremor as their initial symptom, 16 non-tremor) and 29 with left-body onset (LPD; 14 with tremor as their initial symptom, 15 non-tremor), and 52 normal control participants (NC).

Measurements—Verbal fluency was assessed using the FAS and Animals tests. Nonverbal fluency was assessed using the Ruff Figural Fluency Test.

Results—Both RPD and LPD were impaired in generating words and in using clustering and switching strategies on phonemic verbal fluency, whereas different patterns of impairment were found on nonverbal fluency depending on the interaction of side of onset and initial motor symptom (tremor vs. non-tremor). Strategy use correlated with number of correct responses on verbal fluency in LPD, RPD, and NC. By contrast, on nonverbal fluency, strategy use correlated with correct responses for RPD and LPD, but not for NC.

Conclusion—Our findings demonstrate the importance of considering subgroups in PD and analyzing subcomponents of verbal and nonverbal fluency (correct responses, errors, and strategies), which may depend differently on the integrity of dorsolateral prefrontal cortex, inferior frontal cortex, and anterior cingulate cortex.

Keywords

Parkinson's disease; verbal fluency; nonverbal fluency; executive function; prefrontal cortex

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Note that this research was conducted at Boston University.

Parkinson's disease (PD) is a debilitating and progressive neurodegenerative disorder that is associated with executive dysfunction including deficits in planning, set-shifting, working memory, and response inhibition (Elgh et al., 2009; Kehagia, Barker, & Robbins, 2010; Miller, Neargarder, Risi, & Cronin-Golomb, 2013). A growing focus of research is on neurocognitive changes that vary by patient subgroups. The motor symptoms of PD typically manifest unilaterally, with onset on the left side of the body (LPD) reflecting predominant right-hemisphere dysfunction and onset on the right side (RPD) reflecting predominant left-hemisphere dysfunction (Cronin-Golomb, 2010; Djaldetti, Ziv, & Melamed, 2006; Gomez-Esteban et al., 2010; Uitti, Baba, Whaley, Wszolek, & Putzke, 2005). Greater dopamine depletion and reduction in dopamine uptake occurs in the hemisphere contralateral to the side of onset (Kim, Lee, Choe, & Kim, 1999; Marek et al., 1996). LPD is associated with impairments in cognitive abilities mediated by the right hemisphere, including global visuospatial perception and nonverbal memory, as well as unilateral neglect of left space (Amick, Grace, & Chou, 2006; Amick, Schendan, Ganis, & Cronin-Golomb, 2006; Ebersbach et al., 1996; Foster, Black, Antenor-Dorsey, Perlmutter, & Hershey, 2008; Lee, Harris, Atkinson, & Fowler, 2001; Schendan, Amick, & Cronin-Golomb, 2009), whereas RPD patients more commonly show deficits on tasks mediated by the left hemisphere, such as verbal memory (Amick, Grace, et al., 2006).

Additional PD subgroups are described by initial motor symptom, referred to as tremor-dominant (TD) and non-tremor-dominant (NTD: rigidity, akinesia, and disordered gait, posture, and balance). Relative to TD, NTD patients exhibit more pronounced visual difficulties, greater Lewy body pathology load, more extensive and rapid cognitive impairment, and heightened risk for dementia (Alves, Larsen, Emre, Wentzel-Larsen, & Aarsland, 2006; Lewis et al., 2005; Seichepine et al., 2011; Selikhova et al., 2009; Taylor et al., 2008). It is critical for researchers and clinicians to determine different neurocognitive profiles by subgroup as this would guide disease management and treatment more effectively than is possible at present.

Investigations of PD subgroup differences in executive function have generally produced mixed results (reviewed in Verreyt, Nys, Santens, & Vingerhoets, 2011), possibly because of the range of abilities considered. In the present study, we focus on fluency because both verbal and nonverbal formats exist to facilitate LPD-RPD comparisons, and because of the association between fluency and the ability to carry out instrumental activities of daily living in healthy older adults (Cahn-Weiner, Boyle, & Malloy, 2002). Understanding different patterns of executive dysfunction including fluency in PD may assist in predicting and managing functional decline.

Previous studies have established that PD affects verbal fluency (Auriacombe et al., 1993; Fama et al., 1998; Henry & Crawford, 2004b). Because verbal fluency is mediated by the left frontal lobe including dorsolateral prefrontal cortex and inferior frontal gyrus (Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001; Elfgren & Risberg, 1998; Phelps, Hyder, Blamire, & Shulman, 1997), it would be expected that RPD patients would show deficits on this task relative to LPD. Some studies to date have found LPD-RPD differences (Tomer, Levin, & Weiner, 1993), and others have found no difference (Finali, Piccirilli, & Rizzuto, 1995; Foster et al., 2008; St. Clair, Borod, Sliwinski, Cote, & Stern, 1998; Verreyt et al.,

2011). Different results may reflect small sample sizes, differing proportions of LPD and RPD or TD and NTD, or differential performance on various aspects of the test, which may be discerned from analyzing, for example, perseverative errors. Numerous prior studies have not reported perseverative errors, though there is behavioral and neuroimaging evidence that the ability to self-monitor and inhibit responses is distinguishable from response generation in verbal fluency tasks (e.g., anterior cingulate vs. left inferior frontal gyrus and dorsolateral prefrontal cortex, respectively; Azuma, 2004; Fu et al., 2002; Phelps et al., 1997; Weiss et al., 2003).

A further limitation of studies on fluency in PD, particularly when contrasting performance of subgroups, is that nonverbal (design) fluency typically has not been examined. Using the Ruff Figural Fluency Test (RFFT; Ruff, Light, & Evans, 1987), Fama et al. (1998) and Goebel, Atanassov, Kohnken, Mehdorn, and Leplow (2012) found PD patients to be impaired in the number of unique designs produced; the latter investigators also found greater perseverative errors in PD than healthy control adults. No study to date has examined nonverbal fluency, or the relative impairment of verbal and nonverbal fluency, by PD subgroup.

The first goal of the present study was to directly compare non-demented individuals with LPD and RPD on verbal and nonverbal fluency. The hypothesis was that the RPD group (but not LPD) would perform more poorly (fewer correct responses and more perseverative errors) than normal control adults (NC) on verbal fluency, whereas the LPD group (but not RPD) would perform more poorly than NC on nonverbal fluency because nonverbal fluency is primarily mediated by right prefrontal cortex (Robinson, Shallice, Bozzali, & Cipolotti, 2012). Additionally, we predicted that the initial symptom experienced by patients (TD or NTD) would interact with side of onset, such that NTD patients would perform especially poorly.

A second goal was to investigate how PD subgroups used planning and strategizing to maximize their performance on fluency tests. Qualitative scoring of fluency tests allows researchers to determine *how* respondents use organizational strategies to maximize their performance. On verbal fluency, several studies have shown that strategically clustering consecutive words (e.g., words that begin with the same sound, rhyme, or share semantic subcategories) and switching between these strategic clusters correlates with a greater number of words generated (Hughes & Bryan, 2002; Lanting, Haugrud, & Crossley, 2009; Troyer, 2000; Troyer, Moscovitch, & Winocur, 1997). On the nonverbal RFFT, respondents can strategically build on a design by adding or subtracting a line in the design, or can strategically rotate a design (Ross, Foard, Hiott, & Vincent, 2003). On verbal fluency tests, Donovan, Siegert, McDowall, and Abernethy (1999) found a small sample of PD patients to be impaired in switching between strategic clusters (but unimpaired in the mean size of clusters), whereas Tröster et al. (1998) found that only PD patients with dementia were impaired (see also Koerts et al. (2013)). On the RFFT, Goebel et al. (2012) found PD patients used fewer strategic clusters as a proportion of their total responses. None of these studies analyzed strategy use by PD subgroups. We hypothesized that PD patients would use fewer strategic clusters than NC, with this effect driven primarily by the LPD group on the RFFT and by the RPD group on verbal fluency. We additionally determined whether

strategy use would be associated with generating more correct responses and fewer errors. We hypothesized that LPD patients would show fewer performance benefits from strategy use on the RFFT, and RPD patients would show fewer benefits on verbal fluency.

Methods

Participants

Participants included 36 RPD, 29 LPD, and 52 NC matched on age, education, and male:female ratio (Table 1). Of the RPD group, 20 had tremor as their initial symptom (RPD-TD) and 16 had non-tremor (RPD-NTD). Of the LPD group, 14 had tremor (LPD-TD) and 15 non-tremor (LPD-NTD). PD participants were recruited from the Boston Medical Center and PD support groups in the greater Boston area. NC participants were recruited from the community. Exclusion criteria for both groups included any serious chronic medical, neurological, or psychiatric illness, mental retardation, history of intracranial surgery, history of traumatic brain injury, current or previous substance or alcohol abuse, history of eye disease, and use of psychoactive substances (other than antidepressants, anxiolytics, and sleep aids in the PD group). All participants were native speakers of English, in good health (other than a diagnosis of PD), and were living at home. All participants were screened for dementia using the Columbia Modified Mini Mental State Examination (mMMSE; Stern, Sano, Paulson, & Mayeux, 1987). Depression and anxiety were assessed using the Beck Depression Inventory – 2nd edition (BDI-II) and Beck Anxiety Inventory (BAI). Tests of near visual acuity (Snellen eye chart, distance of 16 inches) and motor dexterity/psychomotor speed (Purdue Pegboard Test) were administered to control for the contribution of vision and motor function to performance on the RFFT.

Side of PD motor symptom onset and initial symptom were determined by patient self-report and neurological records when available. Patients were medicated and were tested in the “on” state. Levodopa equivalent dosage was calculated using a standard formula (Tomlinson et al., 2010). Clinical severity and motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS). All PD participants were in a mild-moderate disease stage (Hoehn & Yahr 1-3). LPD and RPD participants were matched for disease severity and stage.

Procedures

Procedures were approved by the Boston University Institutional Review Board following the guidelines of the Declaration of Helsinki.

Verbal Fluency—Participants were administered either the traditional verbal fluency test (FAS and Animals) or the FAS and Animals subtests from the verbal fluency portion of the Delis-Kaplan Executive Functioning System (D-KEFS Verbal Fluency). FAS is a test of phonemic fluency, in which participants must name as many unique words as possible that begin with the letters F, A, and S in separate trials. Animals is a test of semantic fluency, in which participants must name as many unique animals as possible. Each condition has a time limit of 60 seconds. Repeated words are scored as perseverative errors. The outcome measures, calculated separately for FAS (summed across F, A, and S trials) and Animals,

were *correct responses*, *perseverative errors*, and *error ratio* (calculated by dividing the number of perseverative errors by correct responses). Although the instructions for both versions of the test are highly similar, D-KEFS Verbal Fluency includes additional specifications (e.g., naming numbers is not allowed). We conducted independent samples t-tests comparing results for the two versions and found no differences on number of correct responses or errors, on FAS or Animals (all p 's > .05). Accordingly we pooled results across versions for further analysis.

Strategy variables were determined per Abwender, Swan, Bowerman, and Connolly (2001) and Troyer, Moscovitch, and Winocur (1997). On FAS, strategic clusters were defined by two or more consecutively generated words that (1) began with the same first two letters (“flip” and “fleet”); (2) rhymed (“span” and “scan”); (3) had the same first and last sounds and differed only by a vowel sound in the middle (“seat” and “soot”); and (4) were homonyms (“fair” and “fare”). On Animals, strategic clusters were defined by two or more consecutively generated words belonging to the same subcategory (e.g., African animals, farm animals, water animals; see Troyer et al. [1997] for the full list). Perseverative errors were counted as part of strategic clusters, as long as the same word was not repeated twice within a cluster (e.g., in a sample response of “flick, flame, flick” the second “flick” is not counted as part of a strategic cluster. If “flame” was said earlier in the test, it is still counted as part of this specific cluster). Using these rules, we calculated *total strategic clusters* and *mean cluster size* for each of FAS and Animals. Following Abwender et al. (2001), we also examined three variables that assessed the degree to which participants switched between words/clusters. *Cluster switches* were defined as transitions between adjacent clusters (e.g., on FAS “flip, fleet, fair, fare”; on Animals “lion, tiger, cow, horse”). *Hard switches* were defined as a transition between two isolated (non-clustered) words (e.g., on FAS “fix, far”; on Animals “cat, butterfly”) or between a cluster and an isolated word (e.g., on FAS “flip, fleet, far”; on Animals “lion, tiger, butterfly”). *Total switches* were the sum of the cluster switches and hard switches. The *proportion of words incorporated into clusters* was calculated by dividing the total number of words used in clusters by total output.

Nonverbal Fluency—All but seven (one LPD-NTD, one RPD-TD, five NC) of those who participated in the verbal fluency assessment were also administered the RFFT, and one participant (LPD-TD) received the RFFT but not verbal fluency. The RFFT has five trials with a time limit of 60 seconds each. On each trial, an array of squares is displayed, each containing an identical arrangement of five dots. Subsequent trials include distracting elements (e.g., diamonds and lines) and asymmetrically arranged dots (Ruff, 1996; Ruff, Allen, Farrow, Niemann, & Wylie, 1994). Participants are instructed to create as many unique designs or figures as possible by connecting two or more dots and using straight lines. Squares containing a unique design are scored as correct. Squares containing repetitions of previous designs are scored as perseverative errors. The outcome measures are *unique designs*, *errors*, and *error ratio* (errors divided by unique designs). The error ratio is an index of efficiency that accounts for the fact that two participants may have the same number of errors, but one may have a much greater number of unique designs.

To index the degree to which participants used planning to facilitate performance on the RFFT, two types of strategic clusters were calculated, following Ruff (1996) and Ross,

Foard, Hiott, and Vincent (2003). A rotation strategy was counted when a participant spatially rotated the same figure (i.e., the same number of dots and lines in the same arrangement) for at least three consecutive squares. An enumerative strategy was counted when a participant built on a foundational design by systematically adding to or deleting one line from the preceding figure for at least three consecutive squares. Perseverative errors were counted as part of strategic clusters, as long as participants did not repeat a design within a cluster (Ross et al., 2003). That is, if in the middle of a strategic cluster the participant repeated a design from earlier in the test, it did not negate the cluster; however, if a perseveration occurred within that same strategic cluster, it was not counted as part of the cluster. Rotation strategies and enumerative strategies were combined to yield *total strategic clusters*. Following Ross et al., the *mean cluster size* and *proportion of designs incorporated into clusters* were also calculated, the latter by dividing the total number of designs incorporated into strategic clusters by the overall participant output (unique designs plus perseverations).

Two raters independently scored strategic clusters for each participant. Differences in scoring were resolved by consensus discussion. There was a high degree of agreement between raters for most variables. On the RFFT, Pearson correlation coefficients between raters for each strategy variable exceeded .96, echoing previous research that has demonstrated strong inter-rater reliability for the RFFT (Ross et al., 2003). On FAS, correlations between raters for each variable exceeded .74, except for mean cluster size ($r = .23$). Given the low inter-rater reliability for mean cluster size, and the absence of group differences on this variable, we excluded it from further analysis. On *Animals*, correlations between raters exceeded .74.

Statistical Analyses—One-way analyses of variance (ANOVAs) and Tukey's post-hoc tests were conducted to examine differences between LPD, RPD, and NC on verbal and nonverbal fluency (correct responses, perseverative errors, error ratio, and strategy variables). To examine the interaction between side of onset (LPD-RPD) and initial symptom (TD-NTD), we conducted 2×2 ANOVAs with follow-up independent samples t-tests. Analysis of covariance (ANCOVA) was performed to covary for motor dexterity/psychomotor speed, where appropriate. To account for the number of analyses and correlations between our outcome variables (e.g., correct responses and errors), we used a conservative alpha level of .01. To examine the relation between strategy use and fluency, and whether this relation differed by group, we conducted Pearson correlations between the strategy variables and the main fluency outcome variables (correct responses and errors), again using a conservative alpha level of .01. Effect sizes are reported using partial eta squared (η_p^2).

Results

Participant characteristics (Table 1)

The three groups did not differ in age ($F(2, 114) = .11$, $MSE = 67.9$), education ($F(2, 114) = .64$, $MSE = 4.5$), near visual acuity ($F(2, 105) = 1.6$, $MSE = .02$), or in male:female ratio ($\chi^2 = 2.0$, $p = .37$). Although nine participants (two RPD-NTD, three RPD-TD, one LPD-

NTD, three NC) were missing visual acuity data, there was no difference in fluency (unique designs and errors for the RFFT) between participants who did and did not have acuity data (all p 's $> .05$). Significant group differences emerged on the BDI-II ($F(2, 114) = 12.2$, $MSE = 17.1$, $p < .01$, $\eta_p^2 = .18$) and BAI ($F(2, 114) = 23.4$, $MSE = 17.1$, $p < .01$, $\eta_p^2 = .29$). Post-hoc analyses revealed that the LPD and RPD groups each showed greater symptom severity (though below established cutoffs for clinically significant levels of depression and anxiety) than the NC group on the BDI-II (each $p < .01$) and the BAI (each $p < .01$), with no differences between LPD and RPD. Group differences also emerged on the Purdue Pegboard for the dominant hand ($F(2, 114) = 37.1$, $MSE = 4.2$, $p < .01$, $\eta_p^2 = .39$). Post-hoc analyses showed that LPD and RPD placed significantly fewer pegs than did the NC participants (p 's $< .01$), with no LPD-RPD difference. LPD and RPD did not differ on UPDRS motor score ($t(63) = .65$, $p = .52$), Hoehn and Yahr stage (Kolmogorov-Smirnov $Z = .92$, $p = .36$), or levodopa equivalent dosage ($t(60) = -1.45$, $p = .15$).

To determine whether motor dexterity/psychomotor speed, depression, or anxiety were associated with verbal and nonverbal fluency, Pearson correlations were conducted separately for the PD and NC groups (alpha set to .01). In the PD group only, the Purdue Pegboard score correlated significantly with unique designs on the RFFT ($r = .36$) and so was included as a covariate when subsequently analyzing the effect of group on this measure. The BDI-II and BAI did not correlate significantly with correct responses or errors on verbal and nonverbal fluency for any group with the exception of BDI-II and error ratio on Animals in NC ($r = .36$). Because of the overall lack of significant correlations between depression and anxiety in relation to verbal and nonverbal fluency, and because mean scores on the BDI-II and BAI fell in the normal range for clinical severity, depression and anxiety were not included as covariates in subsequent analyses.

Because we sought to determine whether side of onset interacted with initial symptom (TD or NTD), we conducted a series of 2×2 ANOVAs to ensure that PD subgroups were appropriately matched (Table 1). There were no significant interactions between side of onset and initial symptom on any of the participant characteristics (all F 's $< .55$, p 's $> .46$). There was no significant difference in male:female ratio ($\chi^2 = .92$, $p = .82$) or in Hoehn & Yahr stage (Kruskal-Wallis $H(3) = 4.8$, $p = .19$).

Verbal Fluency

One-way ANOVAs were conducted to determine whether performance on FAS and Animals varied by group (RPD, LPD, NC). As shown in Figure 1, a significant group difference emerged on FAS correct responses ($F(2, 113) = 15.5$, $MSE = 121.3$, $p < .01$, $\eta_p^2 = .22$). Post-hoc tests revealed that the LPD and RPD groups each generated significantly fewer correct responses than NC (p 's $< .01$), with no significant difference between LPD and RPD. There were no differences by group on FAS perseverative errors ($F(2, 113) = .33$, $MSE = 3.7$) or error ratio ($F(2, 113) = 1.3$, $MSE = .002$) or for Animals on correct responses ($F(2, 114) = 2.3$, $MSE = 27.9$), perseverative errors ($F(2, 114) = 1.1$, $MSE = 1.0$), or error ratio ($F(2, 114) = 1.4$, $MSE = .002$). We additionally conducted 2×2 ANOVAs to determine whether side of onset (RPD vs. LPD) interacted with initial symptom (TD vs. NTD). There were no significant interactions between side of onset and initial symptom for correct

responses, perseverative errors, or error ratio for either FAS or Animals (all F 's < 2.5, p 's > .11).

Verbal Fluency – Strategies

One-way ANOVAs were conducted to examine group differences in strategy use (LPD, RPD, NC). On FAS, a group difference emerged on total strategic clusters ($F(2, 113) = 6.4$, $MSE = 12.2$, $p < .01$, $\eta_p^2 = .10$) and total switches ($F(2, 113) = 7.1$, $MSE = 79.8$, $p < .01$, $\eta_p^2 = .11$). Post-hoc tests revealed that LPD produced fewer strategic clusters than NC ($p < .01$). There was no difference between LPD and RPD ($p = .69$), or between RPD and NC ($p = .03$). The LPD and RPD groups each produced fewer total switches than NC (p 's < .01). There was no difference between LPD and RPD ($p = .98$) on total switches. There was no difference by group on cluster switches ($F(2, 113) = 4.2$, $MSE = 5.3$), hard switches ($F(2, 113) = 4.2$, $MSE = 88.0$), or proportion of words incorporated into clusters ($F(2, 113) = 1.5$, $MSE = .02$). Using 2x2 ANOVAs to investigate the interaction between side of onset and initial symptom, we found no significant interaction effects across any of the strategy variables (all F 's < 1.1, p 's > .30). On Animals, there was a group difference on total switches ($F(2, 113) = 6.5$, $MSE = 9.7$, $p < .01$, $\eta_p^2 = .10$). Post-hoc tests showed that LPD had fewer total switches than NC ($p < .01$), with no difference between RPD and NC, or between LPD and RPD. There were no significant differences in number of clusters ($F(2, 113) = 1.0$, $MSE = 2.7$), mean cluster size ($F(2, 113) = .95$, $MSE = .62$), cluster switches ($F(2, 113) = .06$, $MSE = 2.7$), hard switches ($F(2, 113) = 4.4$, $MSE = 13.2$), or proportion of words in clusters ($F(2, 113) = 1.7$, $MSE = .02$). We found no significant interaction effects between side of onset and initial symptom across any of the strategy variables (all F 's < 2.7, p 's > .10).

We examined correlations between strategy use and performance on verbal fluency within group (see Table 2; all significant correlations at $p < .01$). On FAS, number of strategic clusters correlated with correct responses for each group (RPD $r = .77$; LPD $r = .61$; NC $r = .69$). Hard switches correlated with correct responses for each group (RPD $r = .75$; LPD $r = .57$; NC $r = .63$), with perseverative errors for each group (RPD $r = .49$; LPD $r = .56$; NC $r = .40$), and with error ratio for LPD only ($r = .48$). Total switches correlated with correct responses for each group (RPD $r = .87$; LPD $r = .70$; NC $r = .75$), with perseverative errors for each group (RPD $r = .45$; LPD $r = .62$; NC $r = .40$), and with error ratio for LPD only ($r = .52$). On Animals, number of clusters correlated with correct responses for each group (RPD $r = .71$; LPD $r = .70$; NC $r = .65$), cluster switches correlated with correct responses for all groups (RPD $r = .52$; LPD $r = .60$; NC $r = .42$), total switches correlated with correct responses for NC ($r = .54$), and proportion of words in clusters correlated with correct responses for LPD ($r = .48$). There were no significant correlations between strategy variables and perseverative errors or error ratio on Animals.

Nonverbal Fluency

One-way ANOVAs were conducted to determine whether performance on the RFFT varied by group. A significant group difference was found on RFFT unique designs ($F(2, 107) = 4.9$, $MSE = 382.6$, $p < .01$, $\eta_p^2 = .08$). Post-hoc tests demonstrated that RPD had fewer unique designs than NC ($p = .01$), with no difference between LPD and NC, or between

LPD and RPD. When Purdue Pegboard score for the dominant hand was entered as a covariate in an analysis of covariance (ANCOVA), the effect of group on unique designs was no longer significant ($F(2, 106) = 1.4, p = .26$), suggesting that motor dexterity/psychomotor speed was primarily responsible for the RPD vs. NC difference. We then conducted a 2×2 ANOVA to examine the interaction between side of onset and initial symptom on unique designs. We found a trend towards an interaction ($F(1, 59) = 4.4, MSE = 310, p = .04, \eta_p^2 = .06$), with a similar trend towards an interaction after co-varying for Purdue Pegboard score for the dominant hand ($F(1, 58) = 3.9, MSE = 292.9, p = .05, \eta_p^2 = .05$). As shown in Figure 2, post-hoc t-tests showed that LPD-TD had a greater number of unique designs than LPD-NTD, RPD-TD, and RPD-NTD (all p 's $< .01$).

There were no significant differences between RPD, LPD, and NC on errors ($F(2, 107) = 2.4, MSE = 123.5$) or error ratio ($F(2, 107) = 2.9, MSE = .02$). 2×2 ANOVAs with side of onset and initial symptom as the between-subjects factors showed significant interaction effects for errors ($F(1, 59) = 10.3, MSE = 144.3, p < .01, \eta_p^2 = .14$) and error ratio ($F(1, 59) = 12.2, MSE = .03, p < .01, \eta_p^2 = .17$). On errors, LPD-NTD produced more errors than LPD-TD at a trend level ($p = .03$) and significantly more errors than RPD-NTD ($p = .01$), while RPD-TD produced more errors than RPD-NTD at a trend level ($p = .03$). A similar pattern emerged on error ratio, as shown in Figure 3. LPD-NTD had a larger error ratio than RPD-NTD ($p = .02$) and LPD-TD ($p = .02$) at a trend level. RPD-TD had a larger error ratio than RPD-NTD ($p = .03$) and LP-DTD ($p = .03$) at a trend level.

Nonverbal Fluency – Strategies

One-way ANOVAs were conducted to investigate group differences in strategy use. There were no significant differences by group in total strategic clusters ($F(2, 107) = .68, MSE = 23.0$), mean cluster size ($F(2, 107) = .60, MSE = 1.7$), or proportion of designs incorporated into clusters ($F(2, 107) = 1.1, MSE = .05$). Using 2×2 ANOVAs to investigate the interaction between side of onset and initial symptom, we found no significant interaction effects in total strategic clusters ($F(2, 107) = 1.1, MSE = 20.2$), mean cluster size ($F(2, 107) = .01, MSE = 1.7$), or proportion of designs incorporated into clusters ($F(2, 107) = .90, MSE = .04$). To determine the relation between strategy use and performance on nonverbal fluency, we conducted Pearson correlations within group (all significant correlations at $p < .01$). Within the RPD and LPD groups, the total number of strategic clusters correlated with unique designs ($r = .55$ and $r = .49$, respectively). Within the NC group, there were no significant correlations between the strategy variables and unique designs. There were no significant correlations between strategy variables and perseverative errors or error ratio in RPD, LPD, or NC.

Discussion

This study investigated the relation between PD subgroup (side of motor symptom onset and initial motor symptom) and verbal and nonverbal fluency in PD. Our results showed that PD patients (LPD and RPD) generated significantly fewer words than a normal control group on a test of phonemic verbal fluency, whereas on a test of nonverbal fluency, performance depended on PD side of onset and initial symptom, as well as on the dependent variable of

interest (unique designs vs. perseverative errors). Specifically, we found that LPD patients with tremor as their initial symptom generated significantly more unique designs than all other groups. In regard to initial symptom of tremor, this finding echoes previous research suggesting that this PD subgroup may have sparing of cognition relative to non-tremor dominant PD (Alves et al., 2006; Katzen, Levin, & Weiner, 2006; Lewis et al., 2005). For example, Katzen et al. (2006) found that RPD patients with tremor outperformed other subgroups of PD on semantic fluency, verbal memory, visuospatial function, and executive function. Although our findings differ in that LPD patients, but not RPD patients, with tremor outperformed other subgroups, the studies converge in suggesting that tremor symptoms may moderate the relation between asymmetric onset of PD and lateralized cognitive deficits. The initial symptom of tremor did not appear to have a protective effect in RPD as in LPD; in RPD, it is possible that patients performed poorly because, despite intact right hemisphere function, they were unable to “verbalize” their designs (e.g., drawing a “diamond” or a “star”). This possibility is suggested by research indicating that the left frontal lobes may also be involved in nonverbal fluency (Baldo et al., 2001).

A different interaction pattern emerged when analyzing perseverative errors on nonverbal fluency, for which we expected worse performance of LPD than RPD and non-tremor than tremor subgroups. We found that LPD patients with non-tremor symptoms made more perseverative errors than either LPD patients with tremor or RPD patients with non-tremor symptoms. This result appears to reflect an additive effect of relative right hemisphere impairment in LPD and initial non-tremor symptoms that may result in a particularly pronounced deficit in self-monitoring and inhibiting perseverative responses on nonverbal fluency (see Wylie et al., 2012 for evidence of greater motor impulsivity in non-tremor compared to tremor PD). This finding is in line with previous research indicating greater cognitive impairment and risk for dementia in non-tremor PD (Alves et al., 2006; Lewis et al., 2005; Selikhova et al., 2009). Our results also demonstrated that RPD patients with initial symptom of tremor made more perseverative errors than both RPD non-tremor patients and LPD tremor patients. It is unclear why RPD patients with tremor would perform particularly poorly in regard to errors, though again this may be due to a possible role for left frontal lobe function even in nonverbal fluency tasks (Baldo et al., 2001). Overall, our findings demonstrate that the interaction between side of onset and initial symptom may play a role in fluency in mild to moderate stages of PD.

On a test of phonemic fluency, but not semantic fluency, both RPD and LPD generated significantly fewer words than NC. Contrary to our initial hypothesis, we did not find disproportionate impairments in RPD patients relative to LPD, or an interaction between side of onset and initial symptom. With a larger sample size, our finding is in line with previous research that has shown a lack of subgroup differences in verbal fluency (Dirksen, Howard, Cronin-Golomb, & Oscar-Berman, 2006; Erro et al., 2013), suggesting that tests of verbal fluency may not be sensitive enough to detect subtle differences between LPD and RPD, at least in the mild to moderate stages of the disease. It is possible that subgroup differences in verbal fluency may not manifest until a later disease stage. The finding of a greater deficit in phonemic than semantic fluency is consistent with prior research suggesting that phonemic word retrieval relies more heavily on strategic search processes mediated by the dorsolateral and lateral inferior frontal cortex than does semantic fluency,

which depends more heavily on temporal lobe function (Birn et al., 2010; Henry & Crawford, 2004a; Jurado, Mataro, Verger, Bartumeus, & Junque, 2000). Finally, the lack of group differences on verbal fluency with respect to perseverative errors indicates that neither LPD nor RPD at this disease stage are impaired in self-monitoring and inhibition of responses on verbal fluency.

We examined how healthy adults and PD patients use strategies to facilitate their performance on verbal and nonverbal fluency, investigating for the first time whether strategy use on fluency tasks differs by side of onset in PD in accordance with test modality. Overall, our findings suggested that PD patients and healthy adults use strategies in similar ways to benefit performance, with some deficits in PD on verbal fluency, and possible compensatory strategy use by PD on nonverbal fluency as suggested by the correlation between strategy use and number of unique designs in the PD groups but not in the control group.

On a test of phonemic verbal fluency, we found that LPD (and RPD at a trend level) produced fewer strategic clusters and switched between strategies/words less often than NC, suggesting a deficit in the ability to organize word retrieval in a strategic manner. PD as a group generated fewer correct responses, and strategy use was associated with correct responses, together suggesting that a deficit in strategic clustering and switching may contribute to decreased verbal fluency in PD. These findings are in line with previous research indicating that fronto-striatal impairments lead to difficulties in phonemic switching, such as in Huntington's disease (Ho et al., 2002). For all groups, strategy variables correlated with the number of words generated, but not with perseverative errors, indicating that the use of strategies in PD patients as well as healthy adults was associated with a greater ability to retrieve words and generate responses, but did not appear to help inhibit perseverative errors. Moreover, hard switches correlated positively with errors in each group, suggesting that hard switching may reflect the ability of older adults to simply generate more words, regardless of whether the words are novel or repeated.

Although LPD showed fewer total switches than NC, overall we found similar results for LPD, RPD, and NC on semantic fluency, who all showed significant positive correlations between number of clusters and correct responses, and between cluster switching and correct responses. These results corroborate the findings of Tröster et al. (1998) who showed that non-demented PD patients did not exhibit group differences in strategy use, as well as of Ho et al. (2002), who showed stable and unimpaired semantic switching in Huntington's disease patients with fronto-striatal compromise. We extend their finding by documenting that the correlation between strategy use and performance is similar in LPD, RPD, and NC. Deficits in strategy use that differentially affect LPD and RPD may become more apparent at later stages of the disease, perhaps only after onset of dementia (Tröster et al., 1998).

On nonverbal fluency, we found no group differences across strategy variables. The lack of PD impairment differs from the findings of Goebel et al. (2012), possibly due to their smaller sample size; as well, these investigators did not report results by subgroup (side or type of initial motor symptom) and may have had unequal proportions of LPD, RPD, TD, and NTD, which presumably would have affected their results. We also found different

associations between strategy use and performance depending on the group. The number of strategic clusters correlated positively with unique designs in the LPD and RPD group, but not in the NC group. NC apparently are able to achieve the same level of unique designs regardless of strategy use, whereas PD patients may need to use strategies in order to achieve normal performance (that is, as compensation for disease effects). Strategy use did not benefit the participants in our study by reducing perseverative errors. The finding that strategy use was unrelated to perseverative tendency supports the notion that generation of unique designs and suppression of perseverative errors may depend on differing neural substrates, as noted earlier (Fu et al., 2002; Weiss et al., 2003).

Conclusions

Our results demonstrated that non-demented individuals with PD (1) were impaired in generating responses, but not inhibiting errors, on phonemic verbal fluency; (2) showed different patterns of impairment on nonverbal fluency depending on the interaction between subgroups (side of onset and initial symptom) and outcome variable (unique designs or perseverative errors); (3) produced fewer strategic clusters and switched less often than NC on phonemic verbal fluency, though the relation between strategies and correct responses was the same across groups; (4) differed from NC in that strategy use was associated with unique designs on nonverbal fluency, suggesting possible compensatory behavior in specific PD subgroups. Our large sample size relative to those reported in other studies strengthens the conclusion that LPD-RPD differences on verbal fluency measures may not appear in the mild to moderate stages of the disease, and on nonverbal fluency measures, may be apparent only when considered in tandem with initial motor symptom. These findings emphasize the importance of considering both side of onset and initial symptom when evaluating cognitive deficits in PD. In particular, we argue that PD subgroups, as well as *how* individuals generate responses on these tasks (i.e., the strategies that they use), are important factors to consider in the assessment of impaired executive function in this disorder.

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Figure 1. Correct Responses on Phonemic and Semantic Verbal Fluency by Condition and Side of Onset. (“*” denotes significance at $p < .01$)

On FAS, the LPD and RPD groups each generated significantly fewer words than the NC group, with no difference between LPD and RPD. There were no group differences on Animals. There were no significant interactions with initial symptom (Tremor, Non-Tremor) on FAS or Animals.

Figure 2. Nonverbal Fluency (Unique Designs) by Side of Onset and Initial Symptom. (“*” denotes significance at $p < .01$)
 The LPD-TD group generated significantly more unique designs than LPD-NTD, RPD-TD, and RPD-NTD. Mean performance by NC participants (87.2 unique designs) is shown by the dashed horizontal line as a comparison.

Figure 3. Nonverbal Fluency (Error Ratio) by Side of Onset and Initial Symptom (“+” denotes $p < .05$)

LPD-NTD had a larger error ratio than RPD-NTD and LPD-TD at a trend level ($p < .05$). RPD-TD had a larger error ratio than RPD-NTD and LPD-TD at a trend level ($p < .05$). Mean performance by NC participants (error ratio of .09) is shown by the dashed horizontal line as a comparison.

Table 1

Participant Characteristics.

Measure	RPD			LPD		NC	
	All (n = 36)	TD (n = 20)	NTD (n = 16)	All (n = 29)	TD (n = 14)	NTD (n = 15)	NC (n = 52)
Age (years)	64.8 (7.2)	65.6 (7.5)	63.8 (7.0)	63.9 (8.6)	65.8 (8.7)	62.1 (8.3)	64.2 (8.7)
Education (years)	16.9 (2.1)	16.2 (1.8)	17.8 (2.2)	17.5 (2.2)	16.9 (2.2)	18.1 (2.1)	17.2 (2.1)
Gender (M/F)	20/16	11/9	9/7	16/13	9/5	7/8	22/30
UPDRS Motor Score	21.5 (10.3)	22.3 (10.7)	20.6 (10.2)	20.0 (8.0)	22.3 (8.8)	17.9 (6.9)	–
H & Y Stage (median)	2.0	2.0	2.0	1.5	1.5	2.0	–
LED (mg/day)	595 (288)	608 (302)	576 (278)	851 (966)	799 (1282)	900 (579)	–
Near Acuity (LogMAR)	.11 (.12)	.11 (.12)	.12 (.13)	.08 (.14)	.06 (.14)	.09 (.13)	.06 (.13)
Purdue Pegboard (DH)	10.9 (2.1) *	11.0 (2.0)	10.7 (2.2)	12.3 (2.5) *	12.7 (1.9)	11.9 (2.9)	14.6 (1.8)
Beck Depression Inventory-II	7.4 (4.8) *	6.8 (5.6)	8.1 (3.6)	7.1 (4.7) *	6.1 (3.8)	8.0 (5.4)	3.5 (3.2)
Beck Anxiety Inventory	7.2 (4.9) *	7.1 (5.3)	7.4 (4.6)	7.3 (5.0) *	6.2 (3.6)	8.3 (6.0)	2.0 (2.8)

Note. RPD = right-onset Parkinson's disease; LPD = left-onset Parkinson's disease; TD = tremor-dominant; NTD = non-tremor dominant; NC = normal control participants. UPDRS = Unified Parkinson's Disease Rating Scale; H & Y = Hoehn & Yahr staging criteria; LED = Levodopa equivalent dosage; LogMAR = Log mean angle of resolution; DH = dominant hand. Values presented are means (standard deviations), unless otherwise indicated.

* Denotes significant difference when compared to NC ($p < .01$)

Table 2

Pearson Correlations between Strategy Use and Performance on Verbal Fluency by Group

Strategy Variable	FAS Correct	FAS Error Ratio	Animals Correct	Animals Error Ratio
RPD				
Total Strategic Clusters	.77*	-.18	.71*	-.18
Total Cluster Switches	.49*	-.29	.52*	-.17
Total Hard Switches	.75*	.32	.01	.23
LPD				
Total Strategic Clusters	.61*	.24	.70*	.14
Total Cluster Switches	.56*	.16	.60*	.07
Total Hard Switches	.57*	.48*	-.01	.04
NC				
Total Strategic Clusters	.69*	-.08	.65*	-.10
Total Cluster Switches	.24	-.18	.42*	-.16
Total Hard Switches	.63*	.23	.29	.13

* denotes significance at $p < .01$

Table 3
Pearson Correlations between Strategy Use and Performance on Nonverbal Fluency by Group

Strategy Variable		Unique Designs	Error Ratio
RPD	Total Strategic Clusters	.55*	-.37
	Mean Strategy Size	.28	-.37
	Proportion of Designs Used in Strategies	.33	-.37
LPD	Total Strategic Clusters	.49*	-.24
	Mean Strategy Size	.40	-.32
	Proportion of Designs Used in Strategies	.36	-.40
NC	Total Strategic Clusters	.19	-.17
	Mean Strategy Size	.17	-.08
	Proportion of Designs Used in Strategies	-.06	-.22

* denotes significance at $p = .01$