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Lexical-Semantic Search Related to Side of Onset and Putamen Volume in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is characterized by dopaminergic cell loss and reduced striatal volume. Prior studies have demonstrated striatal involvement in access to lexical-semantic knowledge and damage to this structure may be evident in the lexical properties of responses. Semantic fluency task responses from early stage, non-demented PD participants with right (PD-R) or left (PD-L) lateralizing symptoms were compared to matched controls on lexical properties (word frequency, age of acquisition) and correlated with striatal volumes segmented from T1-weighted brain MR images. PD-R participants produced semantic fluency responses of a lower age of acquisition than

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PD-L and control participants ($p < 0.05$). PD-R age of acquisition responses correlated positively with putamen volume ($p < 0.05$), while age of acquisition of responses correlated negatively with caudate volume in controls ($p < 0.05$). Findings provide evidence for a role of the striatum in lexical-semantic access and qualitative changes in lexical access in select PD patients.

Keywords

Parkinson's disease; motor asymmetry; cognition; Voxel-based morphometry; striatal matter volume

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the insidious onset of resting tremor, rigidity, akinesia and postural instability (Fekete & Jankovic, 2014). Symptoms often present asymmetrically and are associated with dopaminergic cell loss in the substantia nigra and ventral tegmental area, and accompanied by atrophic changes affecting the putamen and caudate head (Djaldetti, Ziv, & Melamed, 2006; Pitcher et al., 2012). These structures receive both nigral dopaminergic input and excitatory projections from multiple cortical areas and, in turn, relay information to other subcortical and cortical structures (Alexander, DeLong, & Strick, 1986). Specifically, the caudate receives inputs from the prefrontal cortex and the temporal and parietal lobes and has been implicated in executive function, language and other tasks such as directing attention, inhibition, and response switching (Eslinger & Grattan, 1993; Grahn, Parkinson & Owen, 2008). Although the putamen traditionally has been linked to motor function, its role in higher cognition has increasingly been acknowledged (Sefcsik et al., 2009; van Beilen & Leenders, 2006). Investigations using various imaging techniques have supported a broader connectivity of both structures to cortical cognitive networks (Postuma & Dagher, 2006; Ystad et al., 2011).

Individuals with PD typically develop cognitive deficits as the disease progresses (Dirnberger & Jahanshahi, 2013; Muslimovic, Post, Speelman, & Schmand, 2005; Rodríguez-Ferreiro, Cuetos, Herrera, Menendez, & Ribacoba, 2010). One area of investigation has focused on access of the lexical-semantic system. A few studies have indicated loss of excitation in lexical decision tasks when dopaminergic medications are withheld from PD participants but normal performance when medicated (Angwin, Chenery, Copland, Murdoch, & Silburn, 2007). In studies where dominant and subordinate meanings of a word are contrasted, both PD and control participants appear to engage in automatic processing early in the task, but differ as the decision time is varied, with activations of both meanings prolonged in PD participants relative to the controls (Copland & Angwin, 2014). These studies suggest that dopamine may play a role in modulating efficient access of the lexical-semantic system by suppressing subordinate word meanings and enhancing primary meanings. Evidence for this position is further supported by similar studies where task performance is faster for controls under the influence of dopaminergic agents versus those in a placebo group (Kischka, et al., 1996; Roesch-Ely, et al., 2006).

A more direct way of accessing organizational features of the lexical-semantic system is through verbal fluency (VF) measures. VF tasks engage both executive function and word retrieval processes by requiring participants to generate words beginning with a particular letter or that are members of a semantic category under a time constraint (Strauss, Sherman, & Spreen, 2006). In a survey of studies including VF performance, reports have cited lower performance in PD participants relative to controls on both verbal fluency tasks; however, the semantic fluency tasks are impaired more often (Henry & Crawford, 2004). While the number or quantity of words generated is the established metric for VF tasks, qualitative methods have been developed for examining access characteristics of lexical-semantic knowledge and may reveal information about the underlying cognitive processes. For example, individuals with PD have been found to produce a smaller number of continuous items from a subcategory (i.e. clustering), suggesting an inefficient search strategy for semantic memory (Raskin, Sliwinski, & Borod, 1992; Troyer, 2000). Another method is to evaluate the frequency of the words produced. With respect to the VF tasks, the frequency of the exemplars produced reflects the subject's level of effort as well as their facility with lexical-semantic search (Crowe, 1998).

Analysis of the word frequency of responses produced by PD participants during VF performance has produced mixed results thus far. In one study, despite no difference between normal controls and PD groups on the number of exemplars produced, the wider range of words produced by English speaking PD participants was thought to be caused by lower dopamine levels potentiating the broader excitation of the lexical-semantic network (Foster, et al., 2008). These participants were tested on optimal levels of dopamine treatment, which calls into question whether results were due to dopamine deficiency. In a second study (Herrera, Cuetos, & Ribacoba, 2012), native Spanish speaking PD participants produced words of greater frequency for a semantic VF trial in an off-medication state and showed performance nearly equal to control participants while on medication. Linguistic and cultural differences, including the choice of reference corpora used, make comparisons between these two studies difficult.

While word frequency has been considered as a factor in the organization of the lexical-semantic system (Collins & Loftus, 1975; Jescheniak & Levelt, 1994), there is growing evidence that the age at which words and concepts were acquired (or age of acquisition) may play a greater role. A review (Brysbaert & Ghyselinck, 2006) of a number of language studies, including picture naming and lexical decision tasks, demonstrated a greater effect for age of acquisition over word frequency, especially when word frequency effects were factored out. Conversely, word frequency effects were diminished when age of acquisition was controlled. Age of acquisition has been shown to better discriminate between clinical groups including those with mild cognitive impairment (Venneri et al., 2011) and Alzheimer's disease (Forbes-McKay, Ellis, Shanks, and Venneri, 2005; Sailor, Zimmerman, and Sanders, 2011) on VF tasks when effects of word frequency have been controlled for, with clinical groups routinely producing words from an earlier age of acquisition. Effects of age of acquisition have yet to be examined in VF productions of a PD sample.

In this study, we investigated the differences in VF production between PD and matched control participants without PD. PD samples were categorized by side of motor symptom

(PD-R: right motor symptoms; PD-L: left motor symptoms) and tested under a practically defined off medication state so as to empirically evaluate the behavioral effects of dopamine-related striatal differences between samples. We hypothesized that PD participants, regardless of any difference in the number of exemplars produced, would generate word responses of higher frequency and earlier age of acquisition on a semantic VF task in contrast to controls. Secondly, the production of VF exemplars with greater frequency/earlier age of acquisition were expected to be observed more so in PD-R participants given that the language-dominant left hemisphere has greater involvement in the disease process of these patients. Lastly, we hypothesized that controls and PD participants would have lower striatal volume than controls and that, because of the relationship between these structures and dopamine levels, the qualitative VF performance would correlate with striatal volume measurements in PD participants. Again, we expected this to occur more so in the PD-R participants.

Material and Methods

2.1 Participants

Thirty-four PD participants (17 right [PD-R] and 17 left [PD-L] motor symptom presentation) were selected from a subject pool of an ongoing clinical study at Pennsylvania State University Hershey Medical Center. PD participants were diagnosed by a movement disorder specialist (XH) according to published criteria (Calne, Snow, & Lee, 1992). All PD participants were treated with anti-parkinsonian medications except for one subject who had very mild symptoms and was drug naïve. PD participants were assessed in a practically defined off-state after withholding anti-Parkinsonian medications overnight (~12 hours; Langston et al., 1992). Motor symptoms were assessed with the Unified PD Rating Scale-III (UPDRS-III). UPDRS-III scores, along with Hoehn & Yahr ratings (Hoehn & Yahr, 1998), were recorded and verified by a second rater from video recording. Participants were assigned to right and left motor symptom groups based on their report of side of first symptom onset and asymmetry of symptoms that was calculated using the formula: $(\text{Right-side UPDRS} - \text{Left-side UPDRS}) \div (\text{Right-side UPDRS} + \text{Left-side UPDRS})$ (Espay, Morgante, Gunraj, Chen, & Lang, 2006). Seventeen control participants were randomly selected from a pool of controls that were part of the longitudinal study and matched to the PD groups in ratio of males to females, age and years of education.

All participants were right-handed, as indicated by a score greater than 60 on the Edinburgh Handedness questionnaire (Oldfield, 1971). As a part of standard procedures for our lab, screening examination confirmed the absence of other major and acute neurological and psychological disorders, hypothyroidism, vitamin B12 and folate deficiency, and kidney and liver disease. All participants attained a score greater than 26 on the Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975). The Hamilton Depression Scale (HAM-D; Hamilton, 1960) was used to screen for depression.

This study was approved by the Institutional Review Board/Human Subjects Protection Office (IRB/HSPO) of the Penn State Hershey Medical Center, and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants according to the IRB/HSPO guidelines.

2.2 Semantic Verbal Fluency Task

Participants were administered one trial of semantic VF, during which they were instructed to say as many animal names as possible in 60 seconds, irrespective of starting letter. Subject responses were recorded verbatim. After the trial, participants were queried regarding ambiguous responses. Total correct responses were summed for each subject.

Word frequency and age of acquisition norms were applied to task responses. Words that violated the rules of the task were not included. Compound responses (ex. “Piliated woodpecker”), while not prohibited in the instructions for the VF task, were also not included as they could not be properly accounted for (2.4% of the total responses). Word frequency counts from Francis and Ku era (1982) were then applied to the remaining responses, expressed as the frequency of the exemplar per million words. Exemplars not appearing in the frequency norms were dealt with using Laplace smoothing by adding a value of one to all responses. In this way, the rarity of these exemplars could be acknowledged, and still be included in the analysis (Brysbaert & Diependaele, 2013). Application of age of acquisition norms (Kuperman, Stadthagen-Gonzalez, & Brysbaert, 2012) were treated in a different manner due to the way in which these norms were calculated. While word frequency is determined by the number of times a word appears in a representative corpus (for further discussion, please refer to Francis & Ku era, 1982), age of acquisition norms are derived by having participants in the norming study estimate the age at which they learned words. As such, responses not included in the age of acquisition norms were not included in the analysis (0.5% of the total responses). This was limited to five responses – two generated by control participants and three such responses from the PD-R group. Mean word frequency and age of acquisition of responses were calculated for each subject.

2.3 Magnetic Resonance Imaging and Volume Extraction

High-resolution T1- and T2-weighted MRI images were acquired for all participants on a 3T scanner (Trio, Siemens Magnetom, Erlangen, Germany) with an 8-channel phased array head coil. A magnetization-prepared rapid acquisition gradient echo sequence was used to obtain T1-weighted images with TR = 1540 ms, TE = 2.34 ms, field-of-view = 256 mm, matrix = 256 × 256, slice thickness = 1 mm (with no gap), and slice number = 176. T2-weighted images were collected using a fastspin-echo sequence with TR = 2500, TE = 316, and the same resolution configuration as that for T1-weighted images.

The process used for measuring striatal volumes has been detailed elsewhere (Sterling, et al., 2013). Bilateral caudate and putamen volumes were processed initially using Autoseg, a fully-automatic probabilistic atlas-based segmentation pipeline (University of North Carolina NeuroImage Analysis Laboratory (UNC Chapel Hill, NC) that features N4 bias field correction, expectation-maximization tissue segmentation, skull stripping, and probabilistic atlas-based segmentation of subcortical structures (Gouttard, et al., 2007). Further correction of the caudate and putamen volumes were performed manually by an investigator (NS) blinded to subject diagnosis using ITK-SNAP 2.2.0 (www.itksnap.org; Yushkevich et al., 2006). Corrections followed the anatomical guidelines in the UNC NeuroImage Analysis Lab Manual (2007) to establish consistent boundaries of the caudate

and putamen and exclude surrounding structures. This semi-automated process was repeated using a mirrored version of the original image set after a delay of four weeks to avoid potential left–right rater bias and to increase the consistency of the final regions of interest.

2.4 Statistical Analyses

Demographic and clinical characteristics (i.e., age, education, HAM-D, MMSE, and UPDRS-III) of the control and two PD groups were compared using one-way analysis of variance (ANOVA) with post hoc Tukey's t-tests where needed. PD subgroups were compared using t-tests.

Between-group differences for raw responses on the VF task were examined with a one-way ANOVA. Pearson's correlations were carried out to explore the relationship between the word frequency and age of acquisition as it pertained to the entire sample and the clinical groups. The average word frequency and age of acquisition of each subject's responses across the VF trial were calculated and analyzed with one-way ANOVA. Additionally, two one-way ANCOVAs were undertaken to determine group differences on each measure with the other included as a covariate. The first ANCOVA examined between group differences on the age of acquisition ratings in which word frequency was included as a covariate. A second ANCOVA was performed looking at group differences based on word frequency ratings with age of acquisition ratings as a covariate.

The effects of total intracranial volume (TIV), age, and sex were included as covariates when comparing volumetric measures of the caudate and putamen using one-way ANCOVAs. Spearman correlations were carried out between derived residuals and the age of acquisition of the VF task with effects of frequency controlled for each group and striatal volume measures with effects of TIV, age, and sex held constant. All tests were performed with SPSS, version 24 (IBM Corp, 2016).

Results

3.1 Demographics

PD subgroups and controls did not differ significantly on sex ratio, age, educational attainment, handedness, or MMSE score (Table 1). Groups differed significantly on UPDRS III ratings, $F(2, 48) = 19.68$, $p < 0.001$, $\eta_p^2 = 0.451$, with both PD groups demonstrating a greater number of motor symptoms than controls ($p < 0.001$) and little difference between PD groups despite a moderate effect size ($p = 0.112$, $d = 0.577$). HAM-D scores were marginally higher for PD participants, $F(2, 48) = 2.87$, $p = 0.070$, $\eta_p^2 = 0.107$, due to a trend difference between controls and PD-L participants ($p = 0.054$, $d = 0.309$). PD-R participants did not differ from controls in regards to depression symptoms ($p = 0.340$). PD subgroups did not differ significantly in duration of illness and Hoehn and Yahr rating. There was a significant difference in the asymmetry index for these groups, supporting the initial onset classification according to subject recall, $t(7.97)$, $p < 0.001$, $d = 2.772$.

3.2 Preliminary Analyses

An ANOVA was performed on the number of semantic fluency responses to determine group differences in performance and to explore whether this should be considered as a covariate in later analyses. This did not show a statistically significant difference between groups (Controls: $M = 21.41$, $SD = 5.59$; PD-R: $M = 21.71$, $SD = 8.69$; PD-L: $M = 21.53$, $SD = 6.63$; $F(2, 50) = 0.008$, $p = 0.992$).

Exploratory analysis revealed a significant outlier in the data set. This outlier, a PD-L subject, demonstrated an average frequency of response that was greater than two standard deviations from the mean and was due to the extremely low frequency of the exemplars produced by this subject. As a result, this subject was withheld from the set prior to further analysis of the age of acquisition and word frequency scores. In addition, both the average age of acquisition and frequency scores for the data set showed a right skew for the distribution of both scores. This was corrected, in both cases, by introducing a log transformation.

Pearson correlations between the average word frequency and average age of acquisition of each subject's responses indicated a significant inverse correlation between these two ratings ($r = -0.50$, $p < 0.001$). Based on this result, we used word frequency as a covariate when examining differences between groups based on the age of acquisition of their responses and vice versa. Further analysis examined this correlation per each group. The correlations for the average age of acquisition and average frequency ratings for exemplars produced by the two PD groups were significant (PD-R: $r = -0.56$, $p = 0.018$; PD-L: $r = -.51$, $p = 0.046$), while the correlation for controls revealed a trend ($r = -0.40$, $p = 0.108$). A test for the homogeneity of slopes was performed in SPSS to ensure that the differences between groups did not violate this assumption in the planned ANCOVAs. This test confirmed the appropriateness of including word frequency as a covariate for age of acquisition and vice versa with a p-value of 0.958.

3.3 Analysis of Semantic Fluency Responses

Comparison of the average age of acquisition of responses demonstrated a significant difference between-groups (Controls: $M = 5.51$, $SD = 0.44$; PD-R: $M = 5.03$, $SD = 0.40$; PD-L: $M = 5.21$, $SD = 0.52$; $F(2, 47) = 5.08$, $p = 0.010$, $\eta_p^2 = 0.178$). Post-hoc analyses revealed that PD-R participants produced words of earlier age of acquisition than controls ($p = 0.008$, $d = 1.142$). Although not significant, differences between the control and PD-L groups showed a moderate effect size ($p = 0.179$, $d = 0.623$). There was no difference noted between the two PD subgroups ($p = 0.745$). An ANCOVA procedure was carried out to control for the effects of word frequency on age of acquisition. Word frequency contributed significantly to this analysis ($p < 0.001$) and raised the predictive value of the model from an adjusted R^2 of 0.143 to 0.338. The group differences for the age of acquisition of semantic VF responses remained significant after accounting for the effects of word frequency, $F(2, 46) = 4.75$, $p = 0.013$, $\eta_p^2 = 0.171$). Post-hoc comparisons continued to show significant differences between the PD-R and control groups ($p = 0.012$, $d = 1.142$) and, while not significant, the difference between the PD-L and control groups had a moderate effect size

($p = 0.156$, $d = 0.623$). There were no significant difference between the average age of acquisition of responses between the PD subgroups (0.953). See Figure 1.

ANOVA for the word frequency ratings of semantic VF responses failed to show significant differences between groups (Controls: $M = 18.15$, $SD = 3.90$; PD-R: $M = 19.90$, $SD = 4.98$; PD-L: $M = 19.04$, $SD = 5.79$; $F(2, 47) = 0.458$, $p = 0.635$). An ANCOVA controlling for effects of age of acquisition on the word frequency of responses indicated no significant group differences occurred; $F(2, 46) = 0.263$, $p = 0.770$. In any case, the effect of age of acquisition was significant to the analysis ($p < 0.001$) and improved the adjusted R^2 value from -0.023 to 0.211 .

3.4 Between-Groups Comparisons of Striatal Volume Measurements

Average striatal volumes and results of post-hoc tests are presented in Table 2. Group differences were significant for bilateral volume measurements of the putamen after controlling for TIV, age, and sex. Regarding the left putamen ($F(2, 45) = 9.26$, $p < 0.001$, $\eta_p^2 = 0.292$), volume measurements of control participants were larger than those of the PD-R group ($d = 0.692$). Differences between controls and the PD-L group approached significance ($d = 0.396$). The same pattern was obtained for the right putamen volume measurements ($F(2, 45) = 5.66$, $p = 0.006$, $\eta_p^2 = 0.201$). The putamen volumes of controls were larger than those of the PD-R group ($d = 0.605$), and while there was no significant difference between the controls and the PD-L groups, this comparison was of a mild to moderate effect size ($d = 0.427$). There were no significant differences for the left or right putamen volume measurements between the PD-R and PD-L groups. See Figure 2.

ANCOVA comparisons revealed no significant group differences in volume measurements for the left ($F(2, 45) = 2.04$, $p = 0.142$, $\eta_p^2 = 0.083$) and right caudate ($F(2, 45) = 2.04$, $p = 0.142$, $\eta_p^2 = 0.083$).

3.5 Correlations between Semantic VF age of acquisition and Subcortical Volume Measurements

Spearman correlations carried out between age of acquisition of semantic VF responses controlled for frequency effects and volume measurements of the caudate and putamen volumes for each group. PD-R participants demonstrated a strong positive relationship between average age of acquisition of semantic VF responses and volume measurements for both the left ($r = 0.55$, $p = 0.021$) and right putamen ($r = 0.50$, $p = 0.041$). See Figure 3. Relationships between caudate volumes and average age of acquisition were not significant for this group (left caudate: $r = 0.39$, $p = 0.119$; right caudate: $r = 0.37$, $p = 0.149$). Conversely, strong negative relationships were detected between average age of acquisition of semantic VF responses and left caudate ($r = -0.52$, $p = 0.034$) and right caudate ($r = -0.65$, $p = 0.005$) volumes in the control sample; however, there were no significant correlations for putamen volumes (left putamen: $r = -0.17$, $p = 0.504$; right putamen: $r = -0.23$, $p = 0.384$). See Figure 4. There were no observed relationships between volume measures of the caudate (left caudate: $r = 0.00$, $p = 1.000$; right caudate: $r = -0.17$, $p = 0.542$) or the putamen (left putamen: $r = -0.11$, $p = 0.680$; right putamen: $r = -0.06$, $p = 0.837$) and average age of acquisition of semantic VF responses in the PD-L group.

Discussion

Results demonstrated that PD-R participants accessed lexical responses of an earlier age of acquisition than the control group despite the fact that all groups generated a similar number of lexical responses and items of similar frequency. Furthermore, the PD-R participants showed a positive correlation between the age of acquisition of their lexical responses and volume of the putamen, more robustly for the left putamen than the right. The results support the hypothesis that there is an identifiable association between side of motor onset in PD and efficient access within the lexical-semantic system, which may be mediated in part by the putamen. More specifically, the data suggest that early changes in lexical access may emerge in patients with right motor onset symptoms that may be associated with structural changes in the putamen.

4.1 Age of acquisition in lexical-semantic knowledge

We predicted that if qualitative differences were observed in our sample, either due to the frequency or age of acquisition of responses to the VF task, that they would be most demonstrable in the PD-R group. We hypothesized that PD participants with right motor symptom onset would have a greater likelihood of language fluency dysfunction than those with left motor symptom onset because the left hemisphere is both language dominant and exercises contralateral motor control. Our findings are consistent with the trend towards PD-R participants having greater difficulty with assessments of language function than those with left onset symptoms as reported in a number of studies (as reviewed in Verreyt, Nys, Santens, & Vingerhoets, 2011).

Unlike the preceding study that examined qualitative differences in VF task performance between controls and PD participants (Herrera et al., 2012), our groups differed on the age of acquisition and not the frequency of words produced during the semantic VF task. There is often a significant inverse correlation between word frequency and age of acquisition, and it has been speculated that the two measures are somehow one and the same (cumulative frequency: Lewis, Gerhand, & Ellis, 2001). Studies utilizing a variety of tasks, however, have shown that age of acquisition accounts for much of the frequency effect and controlling for age of acquisition often significantly weakens or negates the effect of frequency, particularly in regards to tasks of semantic retrieval (Brysbaert, Van Wijnendaele, & De Deyne, 2000); although effects may vary depending upon the task (Brysbaert & Ghyselinck, 2006). This line of research suggests that age of acquisition may have a greater role in determining the organization of the lexical-semantic network (Ghyselinck, Lewis, & Brysbaert, 2004). Our findings are consistent with this reasoning given the high degree of inverse correlation that we observed between the word frequency and age of acquisition ratings of the exemplars produced by our sample and the better fit as exemplified by increases in adjusted R^2 when word frequency was controlled (while not significant, this effect of better fit was also observed when examining differences between groups on word frequency and the age of acquisition effect was accounted for). Returning to Herrera et al (2012), although they examined the frequency of exemplars produced and not age of acquisition, it is possible that, given the inverse relationship between word frequency and age of acquisition (greater frequency generally equates to earlier age of acquisition), the

responses produced by their PD participants could have also had an earlier age of acquisition as well.

Investigations of word generation capacities in patients with mild cognitive impairment who were APOE $\epsilon 4$ carriers (Venneri, et al., 2011) and Alzheimer's disease (Forbes-McKay et al., 2005; Sailor et al., 2011) have shown that they produce words of an earlier age of acquisition than controls. These findings both support the idea of age of acquisition as an organizing principle for semantic knowledge as well as point to a breakdown of lexical-semantic knowledge and the neuroanatomical structures that support it (Venneri et al., 2008). The neurodegenerative process of Parkinson's disease is different as it affects primarily subcortical connections early in the disease process and prior to the onset of dementia symptoms. The present findings appear to be more congruent with difficulties in access and retrieval processes than the erosion of semantic knowledge per se. This hypothesis is supported by the fact that members of both PD subgroups in our study performed as well as controls in the number of words generated. The activity of producing words under time constraint is demanding and the fact the PD-R participants generated words from an earlier age of acquisition in this task may indicate a changing ability that compensates by accessing some of the more salient representations in the lexical-semantic system. Differences between PD participants and controls in cluster formation of exemplars on the semantic VF task (Raskin et al., 1992) also add support to this idea.

4.2 Role of the putamen in lexical semantic knowledge

In contrast to the idea that the putamen has only connections from the motor area (Alexander, et al, 1986), the putamen has been shown to have a vast number of cortical connections, particularly with the frontal lobes, and to participate in a variety of higher level cognitive functioning including working memory (Cairo, Liddle, Woodward, & Ngan, 2004; Chang, Crottaz-Herbette, & Mennon, 2007) cognitive control (Monchi, Petrides, Petre et al., 2001; Monchi, Petrides, Strafella et al., 2006), and motor output in executive function tasks when linked to decision-making (van Beilen & Leenders, 2006). The relationship of left putamen injury and deficits in response selection and generation has been illustrated in a case study (Troyer, Black, Armilio, & Moscovitch, 2004). Discrete connections from Broca's area, including both the pars opercularis and the pars triangularis, to the anterior-superior one third of the putamen have been mapped in controls using diffusion weighted imaging (Ford et al., 2013).

Our findings suggest that the putamen may be involved in the access of lexical-semantic knowledge, with greater putamen volume predicting access to words of later age of acquisition in the semantic VF task. Rossell et al. (2001) noted activity in the left putamen during trials of a lexical discrimination task where word pairs were concordant in their meaning and in the right putamen when word pair meanings were discordant, indicating a possible role for the putamen in response selection specific to semantic knowledge. Crosson et al. (2003) also discovered bilateral activation of the putamen during word generation tasks and ascribed differential inhibitory and facilitative roles for the right and left putamen, respectively. Other studies have suggested roles for the putamen in inhibitory processing and

the accentuation of information relevant to lexical decision and retrieval tasks (Copland, 2003; Crescentini, Shallice & Macaluso, 2010).

It has been theorized that retrieval during the VF task may involve the same intentional system that is active in motor planning and the execution of self-initiated movements (Crosson, Benjamin, & Levy, 2007). This system necessarily involves the striatum along with the medial (SMA and pre-SMA) and lateral frontal cortices and is involved in response selection through the enhancement and suppression of competing programs. This action would apply broadly to the production of exemplars during the VF task through the enhancement and suppression of responses modulated by dopaminergic action through D1 and D2 receptors, respectively. Loss of D1 receptors, as noted in PD, may result in an inability to enhance responding for all but the strongest stimulus. If the organization of the lexical-semantic network is determined by the age at which words and concepts are learned, then it is the earliest learned concepts that have the most salient representation in this system and the greatest potential for retrieval.

Connectivity of the caudal portions of the putamen as a result of PD progression has been observed in a number of studies (Guttman et al. 1997; Nurmi et al. 2001; Bruck et al. 2006) and may be connected to volume loss for this structure. A recent study showed remodeling of the connectivity of the putamen in the anterior section, leading to a greater influence of the anterior putamen to cortical areas usually connected to the posterior putamen, including posterior cortical areas (Helmich, Derikx, Bakker, Scheeringa, Bloem, & Toni, 2010). This increased overlap in function may cause a “neural bottleneck,” impairing functions of intention as attentional resources are depleted in coordination of both the planning and execution of tasks. There is evidence of greater posterior cortical activation in lexical decision trials that involve words of an earlier age of acquisition (Fiebach, Friederici, Müller, von Cramon, & Hernandez, 2003) and the greater availability of exemplars from an earlier age of acquisition may be the result of volumetric and associated functional changes in the putamen of the right motor onset PD group.

4.3 Role of the caudate in lexical-semantic knowledge

In the present study, we found an inverse correlation of the age of acquisition of responses generated from semantic VF and caudate volume in controls. In fMRI studies of healthy adults, bilateral activity has been detected in the caudate during semantic discrimination tasks (Abdullaev & Melnichuk, 1997) and during monitoring and switching between languages in bilinguals (Garban et al., 2011; Abutalebi et al., 2008). Studies employing fMRI during verbal generation and decision tasks have revealed activity in both the caudate and putamen (Crosson et al., 2003; Hart et al., 2013; Rossell et al., 2001). Crosson et al. (2003) speculated that the activation of the right caudate in their study was of an inhibitory nature, allowing cognitive resources to be focused by the language-dominant left hemisphere. Whereas correlations between age of acquisition and caudate volume were significant for both left and right structures, the correlation was strongest for the right caudate. Therefore, greater volume may imply greater inhibition during the search process, limiting the subject to the most salient items in the category. Alternatively, lesser right caudate volume in comparison to performance levels (as reported in our sample) may

suggest a more holistic search process, given the evidence of coarse semantic processing with initial broad excitation of the semantic system occurring within the right hemisphere (Beeman et al., 1994). This may allow for the greater likelihood of generating divergent exemplars with lesser word frequency/late age of acquisition.

4.4 PD-L group performance

While we did not find significant differences between the PD groups for quantitative or qualitative VF performance, we discovered a trend towards differences between PD-L and control groups on the age of acquisition of responses. Although we thought there might be differences between the PD groups and controls, we hypothesized that this would be most likely observed in the PD-R group given the involvement of the language-dominant left hemisphere. Even though the findings are not statistically different than controls, we project that differences may emerge in this group as the disease progresses and symptoms take on a symmetrical presentation.

Additionally, we did not find differences based on striatal volumes or relations between qualitative VF performance and those measurements in the PD-L group. While not significant, we point out that trend level differences exist in our PD-L sample relative to the control group for the striatal volumes measures, especially for putamen volumes. We did not hypothesize differences in striatal volume between PD groups, but feel compelled to comment. There are reports of PD participants having different disease trajectories based on side of onset (Bauman et al., 2013; Katzen et al., 2006; Tomer et al., 1993) and, as such, the disease process for each group may be subtly different and involve not just the striatum, but other brain structures as well. For example, other workers have recently found that the volume of the hippocampus best distinguished onset groups (Feis, Pelzer, Timmermann, & Tittgemeyer, 2015). Volume may not be the best discriminating factor between onset groups. Differences in dopamine uptake during functional scanning have proven to correlate with side of symptom onset (Filippi, et al., 2005).

4.5 Limitations

We did not collect VF performance in our PD sample while they were on dopamine medication and this limits how much we may be able to generalize our findings to dopamine effects. However, based on findings of Herrera et al. (2012) and the inverse correlation demonstrated between word frequency and age of acquisition, we speculate that PD-R participants would perform at an equivalent level with respect to controls on dopaminergic medications. We administered only one trial of semantic fluency. Performance of these groups may vary under different conditions including the category used. The animals category is rather broad and it has been suggested that exemplars from this category may be learned at an earlier age and shaped by individual proclivities (Gleason, 2014). Other categories that have fewer exemplars may require greater effort exemplified by spreading activation beyond the language dominant hemisphere (Meinzer et al., 2012). While Francis and Kuera (1982) remains a popular source for word frequency norms, there are criticisms regarding the use of this source such as the size, composition, and the relevance of the source corpus (Brysbaert & New, 2009). Likewise, the applicability of the age of acquisition norms, despite demonstrated stability across studies (Łuniewska et al., 2016) is limited by

not only the potential subjective nature of the measure but also the method used to gather data in the norming study which may have favored a younger cohort. Differences in age of acquisition ratings between younger and older participants might reflect disparities of generational experience and the advance of technology (Bird, Franklin, & Howard, 2001; De Deyne & Storms, 2007). Confirmation of the applicability of these norms to an older sample such as used in this study as could be garnered by having participants provide estimates of the age at which they had learned some of the more frequent terms. Although other linguistic aspects such as imageability, familiarity, or concreteness were not explored in this study, these linguistic qualities may have provided systematic influence and may be worthy of exploration in future studies. While our current design suggests differences between groups based on dopaminergic innervation of the striatum, we cannot address the possible involvement of mesocortical projections.

4.6 Conclusions

Results revealed a relationship between reduced left putamen volume in PD participants with right motor symptoms and reduced range of responses on a task of verbal semantic retrieval. We speculate that this impairment of initiation of retrieval mechanisms may be analogous to the impairment of intentional systems that also drive selection of motor movements in PD. Although we did not observe quantitative differences on the VF tasks, we conjecture that these qualitative differences are nascent behavioral shifts that correspond to early striatal change, with standard quantitative changes in the VF tasks becoming prominent as the disease progresses. While greater putamen volume was associated with production of words of later age of acquisition for our PD-R group, we also observed that greater caudate volume predicted a reduced range of responses in controls. We theorize that the putamen and caudate work together in tasks of semantic retrieval, such that the putamen is involved in a network mediating the generation of possible responses. This is limited by the subject's vocabulary and ability to retrieve from this store. The caudate is involved in gating the expression of these responses and inhibiting those responses that are not typical to the category.

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Statement of Significance

Recent lexical-semantic network models have implicated concept acquisition order as an organizing factor, but lack neuroanatomical underpinnings. We explored this in semantic fluency responses in control and Parkinson's participants and drew relations basal ganglia structures. Our study adds to the literature on semantic access in Parkinson's and striatal language function.

Figure 1.

Average age of acquisition of responses produced on the semantic fluency task (animal naming). PD-R sample produced words from an earlier age of acquisition than controls ($p < 0.050$), even after controlling for effects of word frequency. No differences were noted between the PD groups or PD-L sample and controls ($p > 0.050$). Error bars reflect standard error.

Figure 2.

Putamen volume measurements, after controlling for effects of age, sex, and TIV, of the control group were larger than the PD-R group, regardless of side (** $p < .005$). There were no significant differences between PD groups. Error bars reflect standard error.

Figure 3.

Average age of acquisition of semantic VF productions demonstrated positive significant correlations with left (top left, $p = 0.007$) and right (bottom left, $p = 0.030$) putamen volume measurements in the PD-R group. Volume measurements for both structures were controlled for age, sex, and TIV. Age of acquisition of responses was controlled for effects of word frequency.

Figure 4.

Significant negative correlations were noted for average age of acquisition and left ($p = 0.031$) and right ($p = 0.003$) caudate volume measurements for controls. Volume measurements for both structures were controlled for age, sex, and TIV. Age of acquisition of responses was controlled for effects of word frequency.

Table 1.

Group Demographics

	Control n = 17	PD-R n = 17	PD-L n = 17	p-value
Male/Female	8/9	8/9	8/9	
Age	60.4 ± 8.5	57.6 ± 7.7	61.2 ± 7.5	0.370
Education Years	15.7 ± 2.8	15.4 ± 2.8	15.0 ± 2.8	0.743
EHQ	94.0 ± 12.1	91.8 ± 10.7	90.0 ± 14.6	0.653
MMSE	29.4 ± 1.0	29.4 ± 1.1	28.9 ± 1.4	0.487
HAM-D	4.1 ± 3.2	6.0 ± 4.5	7.3 ± 3.9	0.066
UPDRS-III	1.2 ± 1.4	18.7 ± 8.6	27.4 ± 19.5	<0.001
Asymmetry Index	--	0.56 ± 0.4	-0.42 ± 0.3	<0.001
Duration of Illness (Months)	--	38.11 ± 28.8	52.52 ± 57.5	0.361
Hoehn & Yahr	--	1.6 ± 0.6	1.8 ± 0.7	0.320

All analyses were considered statistically significant at $p < .05$. [EHQ = Edinburg Handedness Questionnaire; MMSE = Mini Mental State Exam; HAM-D = Hamilton Depression Scale; UPDRS = Unified Parkinson's Disease Rating Scale III]

Table 2.

Striatal Volumes

Structure	Controls	PD-R (Mean $\pm$ SD)	PD-L	p - Values		
				Control v PD-R	Control v PD-L	PD-R v PD-L
Left Putamen	4486.76 $\pm$ 558.4	4136.65 $\pm$ 447.7	4264.44 $\pm$ 564.9	<0.001 *	0.052	0.205
Right Putamen	4505.09 $\pm$ 565.4	4199.29 $\pm$ 438.3	4281.97 $\pm$ 476.8	0.006 *	0.111	0.704
Left Caudate	3185.68 $\pm$ 322.8	3134.03 $\pm$ 332.7	3060.32 $\pm$ 264.4	0.297	0.235	1.000
Right Caudate	3342.47 $\pm$ 334.4	3284.82 $\pm$ 396.0	3195.21 $\pm$ 289.5	0.346	0.208	1.000

Means are expressed as mm³. p-values reflect Bonferroni-corrected post-hoc tests.

* All analyses were considered statistically significant at p<0.05.