Research Article

Evaluation of Linguistic Markers of Word-Finding Difficulty and Cognition in Parkinson's Disease

Kara M. Smith,^{a,b} Sharon Ash,^c Sharon X. Xie,^d and Murray Grossman^c

Purpose: Early cognitive symptoms such as word-finding difficulty (WFD) in daily conversation are common in Parkinson's disease (PD), but studies have been limited by a lack of feasible, quantitative measures. Linguistic analysis, focused on pauses in speech, may yield markers of impairment of cognition and communication in PD. The objective of this study was to evaluate the relationship of linguistic markers in semistructured speech to WFD symptoms and cognitive function in PD.

Method: Speech recordings of description of the Cookie Theft picture in 53 patients with PD without dementia and 23 elderly controls were analyzed with Praat software. Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), category naming fluency, and confrontation naming tests were administered. Questionnaires rating WFD symptoms and cognitive instrumental activities of daily living were completed. We determined the relationships between (a) pause length and location, (b) MoCA score, and (c) WFD symptoms, using Pearson's correlations and multivariate regression models.

Results: Compared with controls, patients with PD had more pauses within utterances as well as fewer words per minute and a lower percentage of well-formed sentences. Pauses within utterances differed significantly between PD–mild cognitive impairment and normal cognition ($p < .001$). Words per minute and percentage of well-formed sentences were predictive of MoCA in multivariate regression models. Pauses before verbs were associated with patient-reported severity of WFD symptoms ($p = .006$).

Conclusions: Linguistic markers including pauses within utterances distinguish patients with PD with mild cognitive symptoms from elderly controls. These markers are associated with global cognitive function before the onset of dementia. Pauses before verbs and grammatical markers may index early cognitive symptoms such as WFD that may interfere with functional communication.

Supplemental Material: <https://doi.org/10.23641/asha.6615401>

Cognitive impairment is a frequent complication in Parkinson's disease (PD) and has a dramatic impact on mortality and quality of life (Leroi, McDonald, Pantula, & Harbisetar, 2012; Oosterveld et al., 2015). At the time of diagnosis, about one third of patients have mild cognitive impairment (MCI; Yarnall

et al., 2014), and over a typical disease duration, up to 80% of patients will develop dementia (Williams-Gray et al., 2013). However, current methods to diagnose and monitor cognitive impairment in PD are fraught with limitations, and improved methods to obtain detailed, objective data on cognitive function are greatly needed. Speech and language analysis may reveal information about the presence and underlying neurobiology of cognitive function. Most individuals with PD will experience difficulty with communication (Ackermann & Ziegler, 1991; Miller et al., 2007). A multitude of changes in voice, speech, and language occur in PD, and novel analytical methods may allow these changes to be used as an easy-to-detect proxy of cognitive function. There is evidence to suggest that speech and language and cognitive changes may be interrelated in PD, considering the frequent reporting of symptoms such as word-finding difficulty (WFD; Matison, Mayeux, Rosen, & Fahn, 1982) and deterioration of performance on language tasks with an increased cognitive load (Grossman, Lee, Morris, Stern, & Hurtig, 2002; Huber, Darling, Francis,

^aParkinson Disease and Movement Disorders Center, Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia

^bDepartment of Neurology, University of Massachusetts Memorial Medical Center/UMass Medical School, Worcester

^cDepartment of Neurology and the Penn Frontotemporal Degenerative Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia

^dDepartment of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia

Correspondence to Kara M. Smith: karasmi@gmail.com

Editor-in-Chief: Sean Redmond

Editor: Charles Ellis

Received August 15, 2017

Revision received December 5, 2017

Accepted March 5, 2018

https://doi.org/10.1044/2018_JSLHR-L-17-0304

Disclosure: The authors have declared that no competing interests existed at the time of publication.

& Zhang, 2012). This study focuses on language production with the objective of identifying linguistic markers of cognitive impairment in PD. Because language production is a complex and cognitively demanding process, it may manifest changes concurrently with early, mild cognitive dysfunction. Linguistic markers have several potential advantages over current cognitive assessment tools. They are noninvasive and could be collected and processed inexpensively with the use of remote technology and automated signal processing. The ever-increasing access to mobile devices would also allow for frequent symptom monitoring outside the traditional clinic setting. Such data-driven health care technology has generated growing interest and investment and will be most useful when guided by the needs of patients and clinicians. We have therefore designed our study focusing on WFD and other functional cognitive impairments that impact individuals with PD. As a first step toward the identification of linguistic markers of cognitive impairment in PD, we chose to evaluate WFD and its relationship to measurable linguistic changes in a brief semi-structured speech task. WFD is a common symptom in PD that remains understudied and poorly understood (Matison et al., 1982). Prior research has been limited by a lack of adequate assessment tools. Neuropsychological tests of verbal fluency and confrontational naming have been utilized as markers of WFD, but the relationship between these tests and functional impairment in continuous speech is unknown. Indeed, verbal fluency or naming measures may not adequately reflect continuous speech, which requires multiple simultaneous cognitive processes (e.g., lexical retrieval, grammatical and syntactical structuring, organization of narrative and thematic roles) occurring in real time (Grossman, 1999). Therefore, quantitative analysis of continuous speech may better assess WFD than neuropsychological testing and help elucidate the relationship of this symptom to other linguistic and cognitive changes in PD.

Although there is a wide range of communication deficits that can be seen in PD, involving voice, speech, production and processing of language, and auditory and affective processing (Miller, 2017), we focused on linguistic output in our analyses. Language deficits in PD are often overlooked in the clinical setting or misinterpreted as motor speech symptoms. Hypokinetic dysarthria, characterized by decreased loudness, slow and inaccurate articulation, and dysprosody, is the best recognized motor speech impairment in PD (Duffy, 2012). However, studies demonstrating language comprehension abnormalities in individuals with PD suggest that there is a distinct language impairment separate from motor speech function. Various deficits in language production in PD may have a cognitive–linguistic basis (Auclair-Ouellet, Lieberman, & Monchi, 2017). Specifically, deficits in complex grammar and syntax processing and production have been consistently reported and have been linked to executive function and working memory (Colman, Koerts, Stowe, Leenders, & Bastiaanse, 2011; Grossman et al., 2003, 2012; Hochstadt, 2009; Hochstadt, Nakano, Lieberman, & Friedman, 2006; Kemmerer, 1999; Lee, Grossman, Morris, Stern, & Hurtig, 2003). Additional

expressive language deficits have been observed in organization and cohesiveness of narrative discourse (Ellis, Crosson, Gonzalez Rothi, Okun, & Rosenbek, 2015). The underlying mechanism of these language deficits is unknown but may be related to striatal dopaminergic deficiency leading to impaired function of frontostriatal circuits. One notable limitation of this body of work is that language was studied in a restricted laboratory or clinic environment using structured experimental paradigms rather than natural spontaneous speech. In addition, detailed linguistic analysis requires significant time and expertise and so may not be scalable to larger populations of patients. To address these gaps, we analyzed brief spontaneous speech for quantifiable measures that could potentially become automated such as speech rate and pausing.

Decreased speech rate and increased pausing have been described in PD and may have both motor and cognitive influences. Our prior work has shown that language production in Lewy body spectrum disorders (PD and dementia with Lewy bodies) can be distinguished from controls by reduced speech rate and impaired grammar. These differences were present even in patients with PD without dementia, who demonstrated an increased duration of pauses between utterances compared with controls (Ash et al., 2012). In this study, we expanded on this work using similar linguistic analysis techniques to examine pauses within utterances (rather than between utterances). Pauses within utterances have been associated with impaired lexical retrieval (Levelt, 1983) and may allow for detailed, quantitative measurement of WFD. Pause location may also be useful to distinguish motor speech (e.g., hypokinetic dysarthria) impairment from cognitive–linguistic impairment, as hypokinetic dysarthria would be expected to have a global rather than word-type–specific effect. Moreover, depending on the location of a pause, for example, before a verb or noun, its significance may extend beyond difficulty retrieving a single word. There are several differences between verbs and nouns including semantic representation, grammatical roles in sentences, lexical functions, and morphological structure (Tyler, Bright, Fletcher, & Stamatakis, 2004). A neurobiological separation between noun and verb production has also been suggested, with verbs localizing to the left frontal cortex and nouns to the left temporal cortex (Damasio & Tranel, 1993). We therefore hypothesize that a pause before a verb may reflect difficulty planning and constructing a sentence (Grossman, Zurif, et al., 2002) and may be more affected in PD because of frontostriatal dysfunction, whereas a pause before a noun may reflect lexical retrieval and may be relatively spared in PD.

Analysis of linguistic markers including pause locations may provide a quantifiable measurement of online language processing within the context of natural speech that could be detected easily and automatically with technologic advances. To identify linguistic markers of cognitive impairment in PD, we evaluated semistructured speech in patients with PD without dementia. Our goal was to determine the relationship of linguistic characteristics to patient-reported

WFD symptoms and functional cognitive impairment in activities of daily living (IADLs). We also evaluated associations between linguistic markers and well-validated standard neuropsychological test performance. We hypothesized that pause location before a noun or verb would be related to patient-reported WFD symptoms. We hypothesized that linguistic markers would be associated with cognitive function even in patients with PD with mild cognitive difficulties.

Method

Participants

We studied 53 patients with PD enrolled in the Morris K. Udall Center research program at the Perelman School of Medicine at the University of Pennsylvania (Table 1). PD was diagnosed according to published criteria (Hughes, Daniel, Kilford, & Lees, 1992). Participants with PD in the Udall program undergo annual clinical and neuropsychological assessments. Data from 33 of these participants with PD were collected prospectively since implementation of this study protocol and partial data were available on 20 patients retrospectively. Data on 23 elderly healthy controls (HCs) were retrospectively obtained from the University of Pennsylvania Integrated Neurodegenerative Disease database. For both patients with PD and HCs, participants were included if they provided neuropsychological assessments and language samples within 6 months of each other. Participants with dementia were excluded. For retrospective data, patients with dementia were excluded based on Montreal Cognitive Assessment (MoCA) score < 24 (Nasreddine et al., 2005). For prospective participants, MCI and dementia were diagnosed by a consensus evaluation of two independent raters reviewing neurologic history, neurologic examination, and detailed cognitive testing based on International Parkinson and Movement Disorders Society (MDS) criteria (Dubois et al., 2007; Litvan et al., 2012). Motor deficits were characterized by

MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) obtained within 6 months of testing. Participants with PD were assessed in the "on-medication" state.

All subjects completed an informed consent procedure in accordance with the Declaration of Helsinki and approved by the institutional review board of the University of Pennsylvania.

Assessments

Neuropsychological assessments included letter-guided category naming fluency (FAS, total number of nonrepeated words produced in 1 min that begin with each letter), semantic category naming fluency (total animal names produced in 1 min; Benton, Hamsher, & Sivan, 1994), and confrontation naming (Boston Naming Test; Kaplan, Goodglass, & Weintraub, 1983). Global cognition was assessed with the MoCA. Depressive symptoms were assessed with the Geriatric Depression Scale (Weintraub, Oehlberg, Katz, & Stern, 2006).

We assessed functional communication symptoms in daily life from both the patient and caregiver perspectives, focusing on WFD. As an exploratory descriptive assessment, participants with PD were asked if they experienced WFD in daily life and to rate the impact of this symptom by marking on a line labeled 0 (no impact) to 100 (spanning 25 cm). For only patients with PD, a knowledgeable informant completed validated questionnaires (the Perceptions of Conversation Index in Dementia of the Alzheimer Type [PCI-DAT; Orange, Lubinski, Johnson, Purves, & Small, 2009] and the Penn Parkinson's Daily Activities Questionnaire [PDAQ; Brennan et al., 2016]). The single item on the PCI-DAT assessing severity of WFD in daily conversation was used in analysis. The scale for this item is 0–7, with 7 representing a very serious problem. The PDAQ is an item response theory-based tool for rating cognitive IADLs in PD, demonstrating reliability and validity across a range of daily functions. Because these questionnaires were recently added to the Udall study visit

Table 1. Demographic and cognitive characteristics of patients with PD and HCs.

Variable	Patients with PD (<i>n</i> = 53)	HCs (<i>n</i> = 23)	Mean difference (<i>SE</i>)	<i>p</i> ^a
	<i>M</i> (<i>SD</i>) or %	<i>M</i> (<i>SD</i>) or %		
Age	66.6 (7.3)	68.0 (6.9)	1.43 (1.80)	.33
Sex	74.8% male	47.8% male	0.18 (0.12)	.14
Education	16.1 (2.5)	16.3 (2.7)	0.13 (0.64)	.76
MoCA ^b	26.9 (2.2)	n/a	n/a	n/a
UPDRS III ^b	21.3 (11.0)	n/a	n/a	n/a
PD duration ^b (years)	8.9 (5.0)	n/a	n/a	n/a
BNT ^b	57.1 (3.9)	n/a	n/a	n/a
Letter verbal fluency (FAS)	44.7 (14.7)	43.2 (13.2)	–1.50 (3.89)	.71
Category verbal fluency (animals)	18.0 (6.0)	20.4 (6.5)	2.41 (1.68)	.32

Note. PD = Parkinson's disease; HCs = healthy controls; MoCA = Montreal Cognitive Assessment; n/a = not applicable; UPDRS III = MDS-Unified Parkinson's disease Rating Scale Part III (motor); BNT = Boston Naming Test; FAS = total number of words produced in 1 min that begin with each letter.

^aMann–Whitney *U* test for continuous data and Pearson chi-square for categorical data. ^bData not available or not applicable in controls.

protocol, a subset of 30 pairs of participants with PD and knowledgeable informants provided questionnaire data.

A semistructured language sample was elicited from patients with PD and controls by asking them to describe the Cookie Theft picture (Kaplan et al., 1983) “using as much detail as possible,” given a 90-s time limit. This task was selected because it is widely used in both clinical and research settings, allowing comparisons to be drawn between different populations with PD and other neurological disorders. This picture description is also relatively brief and therefore amenable to frequent and automated analysis of certain linguistic features. In addition, this picture description task was found to provide comparable linguistic information with a longer and more complex task involving narration of a story from a wordless picture book (Ash et al., 2013). Language samples were recorded digitally, and recordings were transcribed by previously defined convention (Supplemental Material S3; Ash et al., 2012, 2006) using the signal processing software Praat (v5.3.72, www.praat.org). A single rater performed all language sample analyses. Utterances were defined as one independent clause and all clauses or phrases dependent on it (Hunt, 1965). A series of three independent clauses conjoined by *and* is counted as three utterances. Well-formed sentences were defined as containing a predicate for each subject, excluding sentence fragments and sentences without a clear subject identified. Pauses of at least 1-s duration within an utterance were considered clinically relevant (Goldman-Eisler, 1972). Only silent pauses were measured, excluding filled pauses or speech errors such as stuttering or mazes. Pauses were classified according to their position immediately before a noun or verb. Only lexical verbs were counted, unless the only verb in the utterance was an auxiliary verb. Linguistic measures were normalized to 100 words of speech output to control for differences in both the total quantity of speech output and speech rate. Modified words per minute was calculated by subtracting the total duration of pauses from the total sample duration.

Statistical Analysis

Descriptive statistics were calculated for demographic, clinical, and neuropsychological characteristics. Because linguistic measures were not normally distributed, nonparametric statistical tests were used. Patients with PD and HCs, as well as patients with PD with MCI and normal cognition, were compared using Mann–Whitney *U* test. Clinical, neuropsychological, and linguistic variables were assessed for correlation with patient-reported WFD using Spearman’s rho. Patient-reported WFD was not normally distributed and so was log-transformed before inclusion in the models (Kolmogorov–Smirnov $p = .13$). From this screening process, variables with suggestion of potential correlation ($p \leq .25$) with the outcome of interest were entered into linear regression models. We evaluated the capacity for linguistic markers to predict patient-reported WFD and global cognitive function. First, we assessed

each predictor with univariate linear regressions, and significant variables were incorporated into multivariate linear regressions. Stepwise linear regression models were then created for patient-reported WFD and MoCA, controlling for age and UPDRS. All statistical tests were two sided. Statistical significance was set at $p \leq .05$. Because our study was exploratory rather than confirmatory, multiple testing adjustment was not performed (Bender & Lange, 2001). Analyses were conducted with IBM SPSS Statistics (Version 22.0).

Results

Baseline characteristics of the 53 patients with PD and 23 HCs are shown in Table 1. Patients with PD had mild motor symptom severity on average (Martinez-Martin et al., 2015). There were no significant differences in clinical characteristics or neuropsychological measures in patients with PD compared with HCs. Baseline characteristics of the subgroup with PD-MCI are shown in Supplemental Material S1.

Linguistic Markers in Patients With PD and Elderly HCs

Compared with HCs, participants with PD produced significantly fewer words per minute (raw and modified) and a lower percentage of well-formed sentences (Table 2). Participants with PD had, on average, twice the number of pauses within utterances (per 100 words) compared with HCs. Participants with PD had significantly more pauses before nouns and verbs compared with HCs, correcting for the number of nouns and verbs used. This difference was larger for pauses before verbs than for pauses before nouns.

Cognitive Function Questionnaires

All three questionnaires focusing on WFD symptoms (patient-reported WFD, knowledgeable informant-rated PDAQ, and PCI-DAT) were completed by 30 pairs of patients with PD and knowledgeable informants. There were no significant differences in age, sex, PD duration, UPDRS, confrontational naming (Boston Naming Test), verbal fluency (FAS), and global cognition (MoCA) between those who did and did not complete the questionnaires. WFD was common in patients with PD, with 75% of participants endorsing this symptom. The mean rating of the impact of WFD on daily life was 16.0 ($SD = 17.6$) on a scale from 0 = *no impact* to 100 = *severe impact*. Similarly, 67.6% of knowledgeable informants reported the patients with PD experienced WFD on the single item of PCI-DAT. This single-item response was significantly associated with cognitive IADL function on the more extensive PDAQ in a multivariate linear regression model controlling for age, sex, education, UPDRS, and MoCA, $\beta = -0.60 [-4.28, 1.46]$, $t(27) = -4.23$, $p < .0001$. Neither patients nor knowledgeable

Table 2. Linguistic characteristics of patients with PD and HCs.

Linguistic variable	Patients with PD (<i>n</i> = 53)	HCs (<i>n</i> = 23)	Mean difference (<i>SE</i>)	<i>p</i> ^a
	<i>M</i> (<i>SD</i>) or %	<i>M</i> (<i>SD</i>) or %		
Words per minute	126.8 (29.3)	145.9 (25.7)	19.16 (7.09)	.005
Modified words per minute	140.9 (28.7)	158.2 (25.3)	17.3 (6.6)	.02
% well-formed sentences	79.5 (18.4)	88.5 (9.2)	9.02 (4.05)	.04
Nouns per 100 words	20.5 (4.2)	18.0 (4.2)	−2.48 (1.06)	.02
Verbs per 100 words	15.1 (4.5)	13.1 (1.7)	−1.98 (0.97)	.002
Pauses ≥ 1 s per 100 words	2.4 (2.0)	1.2 (1.0)	−1.26 (0.45)	.01
Pauses before noun per 100 nouns	2.0 (2.5)	1.0 (2.6)	−1.05 (0.63)	.02
Pauses before verb per 100 verbs	2.3 (4.9)	0.4 (2.0)	−1.86 (1.06)	.03

Note. PD = Parkinson's disease; HCs = healthy controls.

^aMann–Whitney *U* test for continuous data and Pearson chi-square for categorical data.

informants reported that WFD correlated with depressive symptoms (data not shown).

Relationship Between Linguistic Markers and WFD Symptoms

Pauses within utterances before verbs correlated significantly with patient-rated WFD, as did words per minute and total pauses within utterances (Supplemental Material S2). In univariate linear regression models, words per minute, pauses ≥ 1 s per 100 words, and pauses before verbs were significantly associated with WFD (Supplemental Material S3). Only pauses before verbs remained significantly associated with WFD in a stepwise multivariate linear regression model, controlling for age and UPDRS, $\beta = 0.50$, $t(28) = 2.97$, $p = .006$ (Table 3).

The knowledgeable informant–reported WFD item score did not correlate significantly with any clinical, neuropsychological, or speech variable (Supplemental Material S2), and none of these variables was significant in the multivariate linear regression model (data not shown).

There was a trend toward a correlation between patient- and knowledgeable informant–reported WFD symptoms, but this was not statistically significant.

Relationship Between Linguistic Markers and Cognition

In the 33 participants with cognitive consensus diagnosis available, there was a significant difference between groups with PD with normal cognition ($n = 21$) and MCI ($n = 12$) in modified words per minute (Mann–Whitney $U = 58.00$, $p = .01$) and pauses within utterances ≥ 1 s per 100 words ($U = 39.00$, $p = .001$).

Several linguistic markers correlated significantly with MoCA and were entered into linear regression models (Table 4). In the stepwise multivariate linear regression model (controlled for age and UPDRS), modified words per minute and percentage of well-formed sentences, as well as education, were significantly associated with MoCA score.

Table 3. Univariate and multivariate linear regression analyses for patient-reported WFD.

Variable	<i>R</i> ²	β coefficient ^a	<i>t</i> (<i>df</i>)	95% CI	<i>p</i>
Univariate					
Age	.03	−0.17	−0.92 (30)	−0.04, 0.10	.37
MoCA	.001	−0.03	−0.14 (30)	−0.23, 0.02	.89
UPDRS	.03	−0.18	−0.97 (30)	−0.02, 0.06	.34
BNT	.05	0.22	1.18 (29)	−0.20, 0.05	.25
Words per minute	.20	0.45	2.66 (29)	−0.03, −0.004	.013
Pauses ≥ 1 s per 100 words	.23	−0.48	−2.86 (29)	0.07, 0.042	.008
Verbs per 100 words	.01	−0.10	−0.51 (29)	−0.19, 0.11	.61
Pause before noun per 100 nouns	.06	−0.25	−1.35 (29)	−0.06, 0.27	.19
Pause before verb per 100 verbs	.24	−0.49	−2.99 (29)	0.04, 0.22	.006
Multivariate					
General model ^b (overall)	.33	—	0.10 (28)	−19.65, 17.81	.44
Stepwise model ^b					
Pauses before verb per 100 verbs	.25	0.50	2.97 (28)	0.04, 0.22	.006

Note. CI = confidence interval; MoCA = Montreal Cognitive Assessment; UPDRS III = MDS-Unified Parkinson's Disease Rating Scale Part III (motor); BNT = Boston Naming Test; WFD = word-finding difficulty.

^aStandardized coefficient. ^bControlled for age, MoCA, and UPDRS.

Table 4. Univariate and multivariate linear regression analyses for MoCA.

Variable	R ²	β coefficient ^a	t (df)	95% CI	p
Univariate					
Age	.23	−0.48	−3.06 (32)	−0.24, −0.05	.005
Education (years)	.11	−0.33	−1.92 (32)	−0.68, 0.02	.06
UPDRS III	.19	−0.44	−2.71 (32)	−0.14, −0.02	.01
Modified WPM	.30	0.54	3.61 (32)	0.02, 0.05	.001
% well-formed sentences	.21	0.45	2.83 (32)	0.02, 0.10	.008
Pauses ≥ 1 s per 100 words	.14	−0.38	−2.28 (32)	−0.66, −0.04	.03
Pause before noun per 100 nouns	.19	−0.43	−2.68 (32)	−0.58, −0.08	.01
Multivariate					
General model ^b (overall)	.56	—	5.50 (32)	17.20, 37.82	< .0001
Stepwise model ^b					
Modified WPM	.50	0.41	2.68 (32)	0.01, 0.05	.01
% well-formed sentences	.50	0.32	2.06 (32)	0.000, 0.08	.05

Note. CI = confidence interval; MoCA = Montreal Cognitive Assessment; UPDRS III = MDS-Unified Parkinson's Disease Rating Scale Part III (motor); WPM = words per minute.

^aStandardized coefficient. ^bControlled for age and UPDRS.

Discussion

In semistructured language samples, there were significant differences between patients with PD and age-matched controls in multiple linguistic markers, including more pauses within utterances, both before nouns and verbs, in patients with PD. These linguistic characteristics also differed significantly between patients with PD with and without MCI. Modified words per minute and percentage of well-formed sentences were independently associated with global cognitive performance.

We explored the relationship of linguistic markers to WFD symptoms and cognitive IADL function. Questionnaire-based assessment of WFD in everyday communication revealed that this symptom was prevalent in patients with PD without dementia, as assessed by both patients and knowledgeable informants. Although neuropsychological tests of verbal fluency and confrontation naming are routinely used to assess word-finding abilities, these tests did not correlate with participant- or knowledgeable informant-rated WFD in everyday communication. The clinical importance of WFD symptoms to functional cognitive status is supported by the fact that knowledgeable informant-reported WFD was an independent predictor of cognitive IADL function on the extensive and validated PDAQ.

We focused on pausing before content words within utterances to represent lexical retrieval difficulty in continuous speech that comprises WFD. We found that pausing before verbs occurred more frequently in patients with PD than HCs and was the single predictive factor for patient-reported WFD in our model. These findings are consistent with prior reports of verb production and comprehension impairment in patients with PD (Colman et al., 2009; Peran et al., 2003; Silveri et al., 2012). These differences are most notable when verbs are utilized in complex syntactic formulations (Grossman, 1999) and have therefore been attributed to a greater cognitive demand required for verb use. Patients with PD in our cohort also had a

lower percentage of well-formed sentences overall compared with controls. Previous research in spontaneous speech for PD without dementia has also shown decreased grammatical correctness and complexity (Murray, 2000) and difficulty processing complex syntax (Colman et al., 2011; Grossman et al., 2003, 2012; Hochstadt, 2009; Hochstadt et al., 2006; Kemmerer, 1999; Lee et al., 2003). In terms of macro-structure of discourse, impairments in cohesiveness and organization have been identified in PD (Ellis et al., 2015). The link between these language deficits in PD is their reliance on the frontal lobe and associated areas, involving planning, set-shifting, and other aspects of executive function, as well as working memory, which are often impaired from early stages in PD (Williams-Gray et al., 2013). Frontostriatal dysfunction is thought to occur in PD because of lack of dopaminergic activity in the striatum, leading to impairment of the cognitive and associative striatal circuits. The linguistic deficits in PD therefore deserve further study to assess their ability to detect and predict early cognitive change and to better understand the mechanism of cognitive decline. Further study of verb and noun processing may also help elucidate mechanisms of cognitive dysfunction in PD. Lesional and functional neuroimaging studies, despite some mixed results, suggest distinct neuroanatomical localizations, with verb processing localizing to the frontal lobe and noun processing localizing to the temporoparietal lobes (Bak, O'Donovan, Xuereb, Boniface, & Hodges, 2001; Damasio & Tranel, 1993; Shapiro, Moo, & Caramazza, 2006). Specifically, the left inferior frontal and prefrontal regions are activated during inflected verb processing, but not during inflected noun processing (Longe, Randall, Stamatakis, & Tyler, 2007; Tyler et al., 2004). Future studies including neuroimaging are required to confirm the structural and functional separation between verbs and nouns in PD and to evaluate the relationship between these networks and pausing in speech.

One major limitation of our study was the lack of established instruments to measure WFD symptoms

in PD. This study was not designed to create a validated assessment tool, so we utilized a combination of patient and knowledgeable informant questionnaires to evaluate cognitive symptoms. A validated instrument would help distinguish WFD in PD from that which occurs in normal aging. There are no available reports on the prevalence of WFD symptoms in the general elderly population to enable comparison with our cohort with PD. Of note, age did not correlate with severity of WFD impact on the patient questionnaire, supporting a distinct WFD deficit in PD. Future instrument development and assessment should also address discrepancies between patient and knowledgeable informant reporting of cognitive symptoms. Another limitation was the use of the MoCA as our primary cognitive outcome. Although the MoCA is a screening test that is not sensitive to small change, it was selected in this study to provide a single, global cognitive measure. Exploration of relationships between linguistic characteristics and individual neuropsychological tests was not performed given the relatively small sample size.

Other limitations include the generalizability of our results, given the relatively high educational level in our population with PD and recruitment at a tertiary movement disorder center. Our population with PD also had mild motor severity, indicating well-controlled motor symptoms, and no dementia nearly 10 years into their disease course. This may be one reason that we found no difference in letter-guided category fluency between patients with PD and HCs, which was unexpected for a group of patients with PD with several years of disease duration. Our findings must be replicated in broader cohorts including earlier PD and examined longitudinally to include patients who develop dementia over the first decade of disease. In addition, evaluation of speech and language on and off PD medications would be informative. We assessed participants in the “on-medication” state, which may have impacted motor speech and cognition. Dopaminergic therapy has been shown to increase overall speech rate in some (Ho, Bradshaw, & Iansek, 2008) but not all studies (Fabbri et al., 2017), and the effects on detailed measures such as pausing are unknown. The literature on cognitive effects of dopaminergic therapy is inconsistent, with some studies reporting worsened verbal memory or other deficits that may impact cognitive–linguistic abilities (Hanna-Pladdy, Pahwa, & Lyons, 2015; Molloy et al., 2006). We did not assess speech errors (e.g., palilalia) in this preliminary study, but this could be useful as a quantifiable measure of motor speech function. Another limitation is that a single rater coded and analyzed all speech samples. A second rater would have strengthened the reliability of our linguistic markers. The time limit for the picture description may also have impacted the results, but nearly all speakers completed the task within the 90-s limit, and there was no significant difference in the total time of the speech sample between groups with MCI and normal cognition.

Speech and language changes in PD likely involve a complex interplay of auditory and language perception and discrimination, speech motor control, and cognitive

function. We attempted to focus on the cognitive component by controlling our models for motor severity and evaluating specific linguistic characteristics thought to have more cognitive than motor influence. However, we acknowledge that further work is needed to disentangle the relative motor and cognitive contributions to specific linguistic marker profiles, to improve the clinical and research utility of linguistic analysis. Other neurodegenerative diseases including Alzheimer’s disease (Fraser, Meltzer, & Rudzicz, 2016), frontotemporal lobar degeneration (Ash et al., 2009), and dementia with Lewy bodies (Ash et al., 2011) may also impact pausing and other linguistic characteristics and should be studied concurrently to determine which characteristics are specific to PD.

In conclusion, linguistic markers including pausing within utterances and before verbs in semistructured speech may be a useful quantitative method to detect and monitor cognitive changes in PD. This approach could be implemented using mobile technology, allowing frequent detailed and objective assessments of cognitive function during real-life daily experiences.

Acknowledgments

This study was funded by a Morris K. Udall Parkinson’s Disease Research Center of Excellence grant from the National Institute of Neurological Disorders and Stroke (NS-053488). K. S. was supported by an unrestricted educational grant from Medtronic, Inc. S. X. was supported by NINDS (NS-053488) and National Institutes of Health Grant AG10124. S. A. was supported by NINDS (NS-053488). M. G. was supported by National Institutes of Health (NS-053488, AG017586, AG038490, and AG053940) and was an investigator on the BMS CN002003 Study.

References

- Ackermann, H., & Ziegler, W. (1991). Articulatory deficits in parkinsonian dysarthria: An acoustic analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, 54(12), 1093–1098. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/1783924>
- Ash, S., Evans, E., O’Shea, J., Powers, J., Boller, A., Weinberg, D., . . . Grossman, M. (2013). Differentiating primary progressive aphasia in a brief sample of connected speech. *Neurology*, 81(4), 329–336. <https://doi.org/10.1212/WNL.0b013e31829c5d0e>
- Ash, S., McMillan, C., Gross, R. G., Cook, P., Gunawardena, D., Morgan, B., . . . Grossman, M. (2012). Impairments of speech fluency in Lewy body spectrum disorder. *Brain and Language*, 120(3), 290–302. <https://doi.org/10.1016/j.bandl.2011.09.004>
- Ash, S., McMillan, C., Gross, R. G., Cook, P., Morgan, B., Boller, A., . . . Grossman, M. (2011). The organization of narrative discourse in Lewy body spectrum disorder. *Brain and Language*, 119(1), 30–41. <https://doi.org/10.1016/j.bandl.2011.05.006>
- Ash, S., Moore, P., Antani, S., McCawley, G., Work, M., & Grossman, M. (2006). Trying to tell a tale: Discourse impairments in progressive aphasia and frontotemporal dementia. *Neurology*, 66(9), 1405–1413. <https://doi.org/10.1212/01.wnl.0000210435.72614.38>
- Ash, S., Moore, P., Vesely, L., Gunawardena, D., McMillan, C., Anderson, C., . . . Grossman, M. (2009). Non-fluent speech in

- frontotemporal lobar degeneration. *Journal of Neurolinguistics*, 22(4), 370–383. <https://doi.org/10.1016/j.jneuroling.2008.12.001>
- Auclair-Ouellet, N., Lieberman, P., & Monchi, O. (2017). Contribution of language studies to the understanding of cognitive impairment and its progression over time in Parkinson's disease. *Neuroscience & Biobehavioral Reviews*, 80, 657–672. <https://doi.org/10.1016/j.neubiorev.2017.07.014>
- Bak, T. H., O'Donovan, D. G., Xuereb, J. H., Boniface, S., & Hodges, J. R. (2001). Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 in the motor neurone disease-dementia-aphasia syndrome. *Brain*, 124(Pt. 1), 103–120. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/11133791>
- Bender, R., & Lange, S. (2001). Adjusting for multiple testing—When and how? *Journal of Clinical Epidemiology*, 54(4), 343–349. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/11297884>
- Benton, A. L., Hamsher, K., & Sivan, A. B. (1994). *Multilingual aphasia examination*. Iowa City, IA: AJA Associates.
- Brennan, L., Siderowf, A., Rubright, J. D., Rick, J., Dahodwala, N., Duda, J. E., ... Weintraub, D. (2016). Development and initial testing of the Penn Parkinson's Daily Activities Questionnaire. *Movement Disorders*, 31(1), 126–134. <https://doi.org/10.1002/mds.26339>
- Colman, K. S., Koerts, J., Stowe, L. A., Leenders, K. L., & Bastiaanse, R. (2011). Sentence comprehension and its association with executive functions in patients with Parkinson's disease. *Parkinson's Disease*, 2011, 213983. <https://doi.org/10.4061/2011/213983>
- Colman, K. S., Koerts, J., van Beilen, M., Leenders, K. L., Post, W. J., & Bastiaanse, R. (2009). The impact of executive functions on verb production in patients with Parkinson's disease. *Cortex*, 45, 930–942. <https://doi.org/10.1016/j.cortex.2008.12.010>
- Damasio, A. R., & Tranel, D. (1993). Nouns and verbs are retrieved with differently distributed neural systems. *Proceedings of the National Academy of Sciences, U.S.A.*, 90(11), 4957–4960. <https://doi.org/10.1073/pnas.90.11.4957>
- Dubois, B., Burn, D., Goetz, C., Aarsland, D., Brown, R. G., Broe, G. A., ... Emre, M. (2007). Diagnostic procedures for Parkinson's disease dementia: Recommendations from the movement disorder society task force. *Movement Disorders*, 22(16), 2314–2324. <https://doi.org/10.1002/mds.21844>
- Duffy, J. (2012). *Motor speech disorders: Substrates, differential diagnosis, and management* (3rd ed.). St. Louis, MO: Elsevier Mosby.
- Ellis, C., Crosson, B., Gonzalez Rothi, L. J., Okun, M. S., & Rosenbek, J. C. (2015). Narrative discourse cohesion in early stage Parkinson's disease. *Journal of Parkinson's Disease*, 5(2), 403–411. <https://doi.org/10.3233/JPD-140476>
- Fabbri, M., Guimaraes, I., Cardoso, R., Coelho, M., Guedes, L. C., Rosa, M. M., ... Ferreira, J. J. (2017). Speech and voice response to a levodopa challenge in late-stage Parkinson's disease. *Frontiers in Neurology*, 8, 432. <https://doi.org/10.3389/fneur.2017.00432>
- Fraser, K. C., Meltzer, J. A., & Rudzicz, F. (2016). Linguistic features identify Alzheimer's disease in narrative speech. *Journal of Alzheimer's Disease*, 49(2), 407–422. <https://doi.org/10.3233/JAD-150520>
- Goldman-Eisler, F. (1972). Pauses, clauses, sentences. *Language and Speech*, 15(2), 103–113. <https://doi.org/10.1177/002383097201500201>
- Grossman, M. (1999). Sentence processing in Parkinson's disease. *Brain and Cognition*, 40(2), 387–413. <https://doi.org/10.1006/brcg.1999.1087>
- Grossman, M., Cooke, A., DeVita, C., Lee, C., Alsop, D., Detre, J., ... Hurtig, H. I. (2003). Grammatical and resource components of sentence processing in Parkinson's disease: An fMRI study. *Neurology*, 60(5), 775–781. <https://doi.org/10.1212/01.WNL.0000044398.73241.13>
- Grossman, M., Gross, R. G., Moore, P., Dreyfuss, M., McMillan, C. T., Cook, P. A., ... Siderowf, A. (2012). Difficulty processing temporary syntactic ambiguities in Lewy body spectrum disorder. *Brain and Language*, 120(1), 52–60. <https://doi.org/10.1016/j.bandl.2011.08.007>
- Grossman, M., Lee, C., Morris, J., Stern, M. B., & Hurtig, H. I. (2002). Assessing resource demands during sentence processing in Parkinson's disease. *Brain and Language*, 80(3), 603–616. <https://doi.org/10.1006/brln.2001.2630>
- Grossman, M., Zurif, E., Lee, C., Prather, P., Kalmanson, J., Stern, M. B., & Hurtig, H. I. (2002). Information processing speed and sentence comprehension in Parkinson's disease. *Neuropsychology*, 16(2), 174–181. <https://doi.org/10.1037/0894-4105.16.2.174>
- Hanna-Pladdy, B., Pahwa, R., & Lyons, K. E. (2015). Paradoxical effect of dopamine medication on cognition in Parkinson's disease: Relationship to side of motor onset. *Journal of the International Neuropsychological Society*, 21(4), 259–270. <https://doi.org/10.1017/S1355617715000181>
- Ho, A. K., Bradshaw, J. L., & Iansek, R. (2008). For better or worse: The effect of levodopa on speech in Parkinson's disease. *Movement Disorders*, 23(4), 574–580. <https://doi.org/10.1002/mds.21899>
- Hochstadt, J. (2009). Set-shifting and the on-line processing of relative clauses in Parkinson's disease: Results from a novel eye-tracking method. *Cortex*, 45(8), 991–1011. <https://doi.org/10.1016/j.cortex.2009.03.010>
- Hochstadt, J., Nakano, H., Lieberman, P., & Friedman, J. (2006). The roles of sequencing and verbal working memory in sentence comprehension deficits in Parkinson's disease. *Brain and Language*, 97(3), 243–257. <https://doi.org/10.1016/j.bandl.2005.10.011>
- Huber, J. E., Darling, M., Francis, E. J., & Zhang, D. (2012). Impact of typical aging and Parkinson's disease on the relationship among breath pausing, syntax, and punctuation. *American Journal of Speech-Language Pathology*, 21(4), 368–379. [https://doi.org/10.1044/1058-0360\(2012/11-0059\)](https://doi.org/10.1044/1058-0360(2012/11-0059))
- Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery & Psychiatry*, 55(3), 181–184. <https://doi.org/10.1136/jnnp.55.3.181>
- Hunt, K. (1965). *Grammatical structures written at three grade levels*. Champaign, IL: National Council of Teachers of English.
- Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston Diagnostic Aphasia Examination*. Philadelphia, PA: Lea & Febiger.
- Kemmerer, D. (1999). Impaired comprehension of raising-to-subject constructions in Parkinson's disease. *Brain and Language*, 66(3), 311–328. <https://doi.org/10.1006/brln.1999.2022>
- Lee, C., Grossman, M., Morris, J., Stern, M. B., & Hurtig, H. I. (2003). Attentional resource and processing speed limitations during sentence processing in Parkinson's disease. *Brain and Language*, 85(3), 347–356. [https://doi.org/10.1016/S0093-934X\(03\)00063-4](https://doi.org/10.1016/S0093-934X(03)00063-4)
- Leroi, I., McDonald, K., Pantula, H., & Harbisetar, V. (2012). Cognitive impairment in Parkinson disease: Impact on quality of life, disability, and caregiver burden. *Journal of Geriatric*

- Psychiatry and Neurology*, 25(4), 208–214. <https://doi.org/10.1177/0891988712464823>
- Levitt, W. J. (1983). Monitoring and self-repair in speech. *Cognition*, 14(1), 41–104. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/6685011>
- Litvan, I., Goldman, J. G., Troster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., ... Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Movement Disorders*, 27(3), 349–356. <https://doi.org/10.1002/mds.24893>
- Longe, O., Randall, B., Stamatakis, E. A., & Tyler, L. K. (2007). Grammatical categories in the brain: The role of morphological structure. *Cerebral Cortex*, 17(8), 1812–1820. <https://doi.org/10.1093/cercor/bhl099>
- Martinez-Martin, P., Rodriguez-Blazquez, C., Mario, A., Arakaki, T., Arillo, V. C., Chaná, P., ... Merello, M. (2015). Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. *Parkinsonism & Related Disorders*, 21(1), 50–54. <https://doi.org/10.1016/j.parkreldis.2014.10.026>
- Matison, R., Mayeux, R., Rosen, J., & Fahn, S. (1982). "Tip-of-the-tongue" phenomenon in Parkinson disease. *Neurology*, 32(5), 567–570. <https://doi.org/10.1212/WNL.32.5.567>
- Miller, N. (2017). Communication changes in Parkinson's disease. *Practical Neurology*, 17(4), 266–274. <https://doi.org/10.1136/practneurol-2017-001635>
- Miller, N., Allcock, L., Jones, D., Noble, E., Hildreth, A. J., & Burn, D. J. (2007). Prevalence and pattern of perceived intelligibility changes in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 78(11), 1188–1190. <https://doi.org/10.1136/jnnp.2006.110171>
- Molloy, S. A., Rowan, E. N., O'Brien, J. T., McKeith, I. G., Wesnes, K., & Burn, D. J. (2006). Effect of levodopa on cognitive function in Parkinson's disease with and without dementia and dementia with Lewy bodies. *Journal of Neurology, Neurosurgery & Psychiatry*, 77(12), 1323–1328. <https://doi.org/10.1136/jnnp.2006.098079>
- Murray, L. L. (2000). Spoken language production in Huntington's and Parkinson's diseases. *Journal of Speech, Language, and Hearing Research*, 43(6), 1350–1366. <https://doi.org/10.1044/jslhr.4306.1350>
- Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, 53(4), 695–699. <https://doi.org/10.1111/j.1532-5415.2005.53221.x>
- Oosterveld, L. P., Allen, J. C., Jr., Reinoso, G., Seah, S. H., Tay, K. Y., Au, W. L., & Tan, L. C. (2015). Prognostic factors for early mortality in Parkinson's disease. *Parkinsonism & Related Disorders*, 21(3), 226–230. <https://doi.org/10.1016/j.parkreldis.2014.12.011>
- Orange, J. B., Lubinski, R., Johnson, A. F., Purves, B., & Small, J. (2009). *Validity analyses of a measure of conversation in dementia*. Paper presented at the Clinical Aphasiology Conference, Keystone, CO.
- Peran, P., Rascol, O., Demonet, J. F., Celsis, P., Nespoulous, J. L., Dubois, B., & Cardebat, D. (2003). Deficit of verb generation in nondemented patients with Parkinson's disease. *Movement Disorders*, 18, 150–156. <https://doi.org/10.1002/mds.10306>
- Shapiro, K. A., Moo, L. R., & Caramazza, A. (2006). Cortical signatures of noun and verb production. *Proceedings of the National Academy of Sciences, U.S.A.*, 103(5), 1644–1649. <https://doi.org/10.1073/pnas.0504142103>
- Silveri, M. C., Ciccirelli, N., Baldonero, E., Piano, C., Zinno, M., Soleti, F., ... Daniele, A. (2012). Effects of stimulation of the subthalamic nucleus on naming and reading nouns and verbs in Parkinson's disease. *Neuropsychologia*, 50(8), 1980–1989. <https://doi.org/10.1016/j.neuropsychologia.2012.04.023>
- Tyler, L. K., Bright, P., Fletcher, P., & Stamatakis, E. A. (2004). Neural processing of nouns and verbs: The role of inflectional morphology. *Neuropsychologia*, 42(4), 512–523. <https://doi.org/10.1016/j.neuropsychologia.2003.10.001>
- Weintraub, D., Oehlberg, K. A., Katz, I. R., & Stern, M. B. (2006). Test characteristics of the 15-item geriatric depression scale and Hamilton depression rating scale in Parkinson disease. *American Journal of Geriatric Psychiatry*, 14(2), 169–175. <https://doi.org/10.1097/01.JGP.0000192488.66049.4b>
- Williams-Gray, C. H., Mason, S. L., Evans, J. R., Foltyniec, T., Brayne, C., Robbins, T. W., & Barker, R. A. (2013). The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *Journal of Neurology, Neurosurgery & Psychiatry*, 84(11), 1258–1264. <https://doi.org/10.1136/jnnp-2013-305277>
- Yarnall, A. J., Breen, D. P., Duncan, G. W., Khoo, T. K., Coleman, S. Y., Firbank, M. J., ... Burn, D. J. (2014). Characterizing mild cognitive impairment in incident Parkinson disease: The ICICLE-PD study. *Neurology*, 82(4), 308–316. <https://doi.org/10.1212/WNL.0000000000000066>