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Rapid rate on quasi-speech tasks in the semantic variant of primary progressive aphasia: A non-motor phenomenon?

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This study examined the rate of producing alternating motion rates, sequential motion rates (SMRs), and repeated words in 27 individuals with the semantic variant of Primary Progressive Aphasia (svPPA). Only the rate of producing SMRs was significantly elevated in svPPA compared to controls. This may be associated with concomitant neuropsychiatric symptoms in svPPA, as correlation analysis showed a relationship between increased SMR rate and the Neuropsychiatric Inventory Questionnaire, which documented anxiety and disinhibition. Future studies will assess these findings in a larger cohort and work to better understand if this phenomenon is a manifestation of behavioral and/or motor changes. © *2018 Acoustical Society of America*.
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I. INTRODUCTION

The semantic variant of Primary Progressive Aphasia (svPPA), or semantic dementia, is a neurodegenerative disease characterized by difficulties with confrontation naming, reduced comprehension of single words, impaired object knowledge, and surface dyslexia (Gorno-Tempini *et al.*, 2011; Warrington, 1975). In addition to loss of semantic knowledge, there are well-documented behavioral changes, including prominent disinhibition in a subset of patients (Edwards-Lee *et al.*, 1997; Rohrer and Warren, 2010; Singh *et al.*, 2015). Generally, svPPA is associated with the absence of apraxia of speech and dysarthria. In fact, spared motor speech production is an element of the diagnostic criteria for svPPA under the current consensus criteria (Gorno-Tempini *et al.*, 2011).

A recent review synthesized studies that assessed motor speech abilities in the variants of PPA among other frontotemporal dementias (Poole *et al.*, 2017). They describe that among 16 studies, only one reported motor speech disruption in patients with svPPA (Thompson *et al.*, 2012). Studies of connected speech have reported decreased speech rate, which was attributed to pauses for word finding and increased non-specific fillers (Ash *et al.*, 2013; Fraser *et al.*, 2014). Other studies have incidentally noted elevated speaking rates in svPPA (Catani *et al.*, 2013; Mesulam *et al.*, 2012), but the findings have not been fully explained. No studies to date have looked at the performance of patients with svPPA in quasi-speech tasks (i.e., oral diadochokinetic rates) that are typically utilized in the assessment of motor speech function.

In our research cohort, among 27 classified as svPPA, none were judged to have a motor speech disorder. Nonetheless, we subjectively observed in some patients an increased speaking rate during quasi-speech tasks consisting of alternating motion rates (AMRs) and sequential motion rates (SMRs). It is conceivable that quasi-speech tasks might be a vehicle for quantifying rate while controlling other linguistic influences, providing a more accurate estimate of performance. Therefore, the primary aim of this study was to quantify speech rate in svPPA compared to neurologically normal controls. Our secondary aim was to identify possible mechanisms for any observed differences between patients with svPPA and controls through correlation of rate findings with measures reflective of cognitive, behavioral, and motor function.

II. METHODS

A. Participants

Twenty-seven patients who met clinical criteria for svPPA (Botha *et al.*, 2015; Gorno-Tempini *et al.*, 2011) were recruited into an NIH-funded study between October 2011 and April 2018. All patients underwent a standard protocol of neurological, speech, language, and neuropsychological assessments. All patients consented to have their data utilized for research and the Mayo Clinic Institutional Review Board approved the study.

B. Clinical measures

Clinical measures of neurologic, neuropsychiatric, and language functioning were administered and included: the Western Aphasia Battery- Revised (WAB) as an index of overall language ability, with particular attention paid to the

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fluency subtest (naming animals) (Kertesz, 2007); Pyramids and Palm Trees Test (PPTT) as a measure of semantic access (Howard and Patterson, 1992); reading and writing of irregular and non-words (supplementary tests from the WAB) to probe for surface dyslexia; the 15-item Boston Naming Test (BNT) as a sensitive measure of confrontation naming ability (Lansing *et al.*, 1999); the composite of the aforementioned tests was utilized in the judgment of aphasia severity (1 = mild; 4 = severe); Montreal Cognitive Assessment (MoCA) as an assessment of general cognition (Nasreddine *et al.*, 2005); a test of Famous Faces Recognition (Josephs *et al.*, 2008); the Neuropsychiatric Inventory Questionnaire (NPI-Q) as a measure of neuropsychiatric features (Kaufer *et al.*, 2000); and the Movement Disorders Society-sponsored version of the Unified Parkinson's Disease Rating Scale motor subsection (MDS-UPDRS III) as a measure of motor impairments (Goetz *et al.*, 2008). Importantly, the NPI-Q is administered via interview with a caregiver who is instructed to rate the magnitude of behaviors relative to a change from baseline. This version of the NPI-Q also records perceived caregiver distress associated with the behavior but those ratings were not evaluated in the current study. Additionally, the UPDRS-III was developed and validated for Parkinson's disease as a global assessment of motor abilities with a focus on parkinsonism; speech impairment is judged via a single item on the UPDRS-III. Additional judgments of speech functioning included supplementary motor tasks, including alternating and sequential motion rates and examination of the oral mechanism, which were reviewed and agreed upon by at least two speech-language pathologists.

C. Acoustic measurements

Responses to several supplementary speech task items were measured acoustically to quantify the temporal characteristics of speech output. Consistent with past studies (Duffy *et al.*, 2017; Duffy *et al.*, 2015), patients were instructed to repeat a series of words three times. For this study, the word *catastrophe* was selected, as it has previously been found to be the most sensitive for separating individuals with apraxia of speech from controls and other forms of PPA (Duffy *et al.*, 2017). Patients were also instructed to repeat "as fast and steadily as you can" a series of each of "puh," "tuh," and "kuh" (alternating motion rates or AMRs), and sequences of "puh tuh kuh" (sequential motion rates or SMRs). Imitative speech tasks were used to minimize the influence or frequency of pause, hesitation, and restart occurrences that can be associated with aphasia during non-imitative utterances. Recordings were collected via an audio-video recording (Panasonic WV-SC384) in a quiet clinical examination room. The audio component utilized a TOA UHF (WM-4310) wireless microphone with Shure SCM 268 mixer. Audio recordings (16-bit, 32.768 kHz, with a maximum input level of 120 dB sound pressure level) were saved separately for analysis.

The speech analysis software PRAAT (version 6.0.18) (Boersma and Weenink, 2014) was used for all acoustic measures. Durations were measured from the initial stop release to cessation or marked reduction of acoustic energy at the end of the response. Syllable rates for *catastrophe* reflect the three repetition average. Syllables per second rates were derived by dividing the number of syllables (in the case of *catastrophe*, four) by its duration. AMR data reflect the average syllable rate per second across "puh," "tuh," and "kuh" on the basis of the first ten consecutive successful repetitions of each syllable. SMR data reflect the syllable rate per second across the total duration of the first three successful consecutive repetitions of "puh tuh kuh" (i.e., a total of nine syllables).

D. Acoustic measurement reliability

To assess reliability of the acoustic measurements, a second author (J.R.D.) independently measured the duration of responses for 25% of the patients with svPPA (n = 6). Intra-class correlations between the two judges across all measures ranged from 0.94 to 0.99. Reliability was thus considered high. The primary author's measurements were utilized in all subsequent analyses.

E. Normative acoustic data

Eleven participants served as normal speech controls for acoustic measure comparisons. These individuals had no evidence of speech or language difficulty. Further details are provided in a previous report (Duffy *et al.*, 2017).

F. Statistical analysis

Statistical analyses were performed using JMP computer software (version 13.0.0; SAS Institute, Inc.). Wilcoxon signed-rank tests were used to compare continuous data. Significance was assessed at $p \leq 0.05$, adjusted for multiple comparisons with the Bonferroni correction. Non-parametric correlations (Spearman's ρ) between statistically significant acoustic measures and behavioral measures were calculated within the cohort of individuals with svPPA and adjusted for multiple comparisons with the Bonferroni correction.

III. RESULTS

A. Clinical measures

Demographic, and relevant neurologic, neuropsychological, and language data for the total cohort, and separately for those who performed SMRs with a faster-than-expected rate and those who performed SMRs similar to controls, are detailed in Table I. The entire svPPA cohort (55% male) had a median age of 67 years old with median disease duration of 3 years. All but five patients were right-handed. Median education was 16 years. Median WAB-AQ was 86.8/100, suggesting mild-moderate aphasia. Median number of animals named in a fluency task was 8 and median PPTT was 42/52, both suggesting reduced semantic access. Median accuracy was 8/10 for reading irregular words and 8/10 non-words. Median accuracy was 4/10 for writing irregular words and 7/10 for non-words. For those who received the Boston Naming Test, the median score was

TABLE I. Demographic, neurologic, and neuropsychological information. Patients for whom rate of production of sequential motion rates was greater than one standard deviation above the mean of the neurologically normal controls are presented first. Note: F = female, M = male, ambi = ambidextrous. Maximum score noted in column header, when appropriate.

ID	Sex	Age at exam	Years since onset	Handedness	Education	MoCA (/30)	MDS-UPDRS III (/120)	Famous faces recognition (/10)	NPI-Q (/36)	WAB-AQ (/100)
1	F	70	4	Right	12	14	4	0	6	63.5
2	F	75	1	Right	12	14	8	1	11	84.2
3	M	69	4	Left	17	18	2	4	2	77.4
4	F	77	3	Right	12	20	7	1	4	83.9
5	F	68	6	Left	16	15	7	3	13	70.5
6	M	64	2	Right	14	20	0	10	14	89.6
7	F	60	1.5	Right	18	24	2	9	1	95.2
8	F	58	5	Right	16	27	2	10	0	92.2
9	M	62	1	Right	16	25	1	10	5	98.4
10	M	69	2	Right	18	24	2	7	4	93.4
11	M	67	14	Right	18	26	4	3	9	95
12	F	57	5	Left	15	18	0	7	2	72.8
13	F	68	3	Right	13	26	0	0	13	86.8
Faster cohort median		68	3		16	20	2	4	5	86.8
14	F	79	3	Left	12.5	24	0	10	2	91.6
15	M	64	3	Right	16	17	4	7	7	85.7
16	M	51	4	Right	16	24	0	1	9	88.4
17	F	78	2	Right	12	23	9	2	3	95.8
18	M	56	6	Right	14	12	0	3	21	67.4
19	M	69	2	Right	16	20	2	10	7	82.4
20	M	75	8	Right	15	9	0	0	5	45
21	F	60	4	Right	16	23	0	9	5	93.3
22	M	55	2	Right	13	19	0	10	1	82.3
23	M	63	5	Right	16	20	0	7	3	91.5
24	M	72	5	Right	22	23	0	10	4	90.4
25	F	72	3	Right	17	22	1	10	4	85.9
26	M	67	5	Right	18	29	3	0	8	91.2
27	M	44	2	Ambi	14	21	2	7	7	80.4
Control-like cohort median		65.5	3.5		16	21.5	0	7	5	87.15
Total cohort median		67	3		16	21	2	7	5	86.8

3/15; performance for all participants was below average. Median overall aphasia severity was 1.5/4, suggesting mild-moderate impairment. Median MoCA was 21/30. Median recognition of famous faces was 7/10, suggesting reduced ability to recognize famous faces. Median score on NPI-Q was 5/36, consistent with the presence of neuropsychiatric symptoms. Median MDS-UPDRS III, Motor Section score was 2/120, suggesting no Parkinsonism.

B. Acoustic measures

There were no statistically significant differences in the rate of producing *catastrophe* ($p = 0.772$) or AMRs ($p = 0.772$) between svPPA cohort and controls. There was a significant difference in the rate of producing SMRs ($p = 0.016$), where the svPPA cohort produced SMRs at a faster rate. Comparisons with controls are visualized in Fig. 1.

Acoustic measurements for each individual with svPPA are presented in Fig. 1. The mean rate of production of the word *catastrophe* was 4.84 syllables/s [standard deviation (SD) = 0.41] for controls and 4.79 syllables/s (SD = 0.70) for svPPA. Rate of production of *catastrophe* for five svPPA patients was faster than 1 SD above the mean rate of production observed in controls. The mean rate of production of the AMRs was 6.06 syllables/s (SD = 0.54) for controls and 5.98 syllables/s (SD = 0.71) for svPPA. Rate of production of AMRs for seven svPPA patients was faster than 1 SD above the mean rate of production observed in controls. The mean rate of production of the SMRs was 5.32 syllables/s (SD = 1.32) for controls and 6.35 syllables/s (SD = 0.99) for svPPA. Rate of production of SMRs for 13 svPPA patients (8 female) was faster than 1 SD above the mean rate of production observed in controls. Within the svPPA cohort, SMR was moderately correlated with *catastrophe* ($\rho = 0.69$, $p < 0.0001$). AMRs were not correlated with SMRs ($\rho = 0.13$, $p = 0.53$) or *catastrophe* ($\rho = 0.21$, $p = 0.29$).

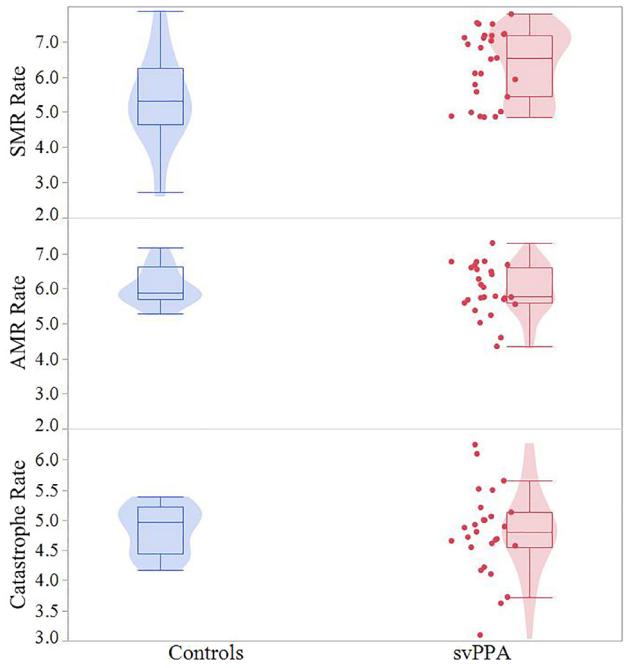

FIG. 1. (Color online) Data for rate of production (syllables/s) of *catastrophe* (bottom panel), AMRs (middle panel), and SMRs (top panel) for the svPPA and cognitively unimpaired controls. Box plots of the interquartile range and a shaded contour, or violin plot, offer two visualizations of the distribution of the raw data, which is overlaid for the svPPA cases.

These same relationships held true within the control cohort, where SMR was moderately correlated with *catastrophe* ($\rho = 0.75$, $p = 0.0085$) and AMRs were not correlated with SMRs ($\rho = 0.10$, $p = 0.77$) or *catastrophe* ($\rho = 0.32$, $p = 0.34$).

C. Cognitive/behavioral correlates

Given that SMRs were statistically significantly faster in svPPA compared to controls, non-parametric correlations (Spearman's ρ) between SMR rate and behavioral measures were calculated in order to explore possible contributors into the phenomenon of increased rate of production of SMRs. There were no statistically significant correlations between SMR rate and disease duration ($\rho = -0.36$, $p = 0.06$), age ($\rho = -0.22$, $p = 0.28$), or education ($\rho = 0.09$, $p = 0.64$). The only cognitive/ behavioral measure that was statistically correlated with SMR rate was the total score on the NPI-Q ($\rho = 0.41$, $p = 0.03$). See Fig. 2. Neither the MOCA ($\rho = 0.02$, $p = 0.9275$) nor the WAB-AQ ($\rho = 0.01$, $p = 0.97$) correlated with SMR rate, suggesting this observation is not associated with severity of cognitive or language deficits. Individual scores for items on the NPI-Q are reported in Table II. The most commonly reported symptom was depression, followed by apathy, anxiety, disinhibition, and irritability.

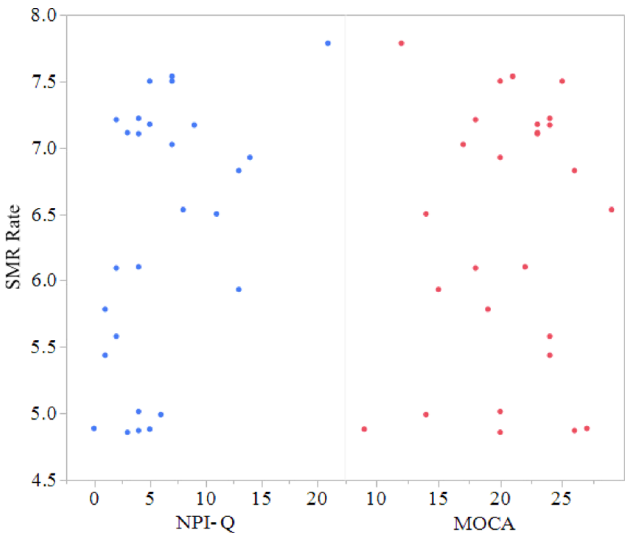

FIG. 2. (Color online) Scatterplot of the total score on the NPI-Q; maximum of 36 points, where higher scores indicate more severe impairment, and MoCA; maximum of 30 points, where a maximum scores is consistent with no cognitive impairment, relative to rate of SMR; syllables/s for the svPPA cohort.

IV. DISCUSSION

This is the first study to assess speech rate in quasi-speech tasks in svPPA. It revealed that patients with svPPA produced sequential motion rates, but not alternating motion rates or repeated words, more rapidly than neurologically normal controls. Because SMR rate correlated with a measure of neuropsychiatric symptoms, it may possibly be related to concomitant behavioral symptoms, such as disinhibition or anxiety (Mendez *et al.*, 2017; Mendez *et al.*, 2006). The aforementioned behavioral symptoms are well documented in patients with svPPA and not unlike those seen in patients with the behavioral variant of frontotemporal dementia (bvFTD) [see Modirrousta *et al.* (2013) for a review].

The current cohort of patients with svPPA met the existing consensus diagnostic criteria in that all patients presented with a pronounced anomia and loss of word meaning, without dysarthria or apraxia of speech (Gorno-Tempini *et al.*, 2011). The group had a median WAB-AQ that was consistent with a mild-moderate aphasia, with prominently reduced semantic memory, as reflected in reduced performance on the Pyramids and Palm Trees Test. Performance on animal fluency was consistent with past reports of performance in svPPA (Wilson *et al.*, 2010). The patients performed poorly on the recognition of famous faces, consistent with past reports of prosopagnosia in svPPA (Josephs *et al.*, 2008). Scores on the NPI-Q were low overall; only 7/27 patients scored above the threshold for definite behavioral issues, but, importantly, only 1/27 reported zero behavioral symptoms. The most commonly reported symptom was depression, followed by apathy, anxiety, disinhibition, and irritability. These findings are consistent with other reports of svPPA, where behaviors comparable to those seen in frontotemporal dementia were reported (Bozeat *et al.*, 2000; Snowden *et al.*, 2001). Notably, patients had no evidence of parkinsonism, evidenced by low scores on the motor section of the MDS-UPDRS III. Taken together, the data suggest this rapid rate phenomenon is not attributable to differences in motor function.

The current study demonstrated that over half of the patients with svPPA performed SMRs faster than

TABLE II. Individual scores for: severity rating on the MDS-UPDRS III, Motor section rating of speech impairment, where 1 = "loss of modulation, diction or volume" and 2 = "loss of modulation, diction, or volume, with a few words unclear"; selected item scores from the NPI-Q, where 1 = mild, 2 = moderate, and 3 = severe (omitted subtests included delusions, hallucinations, and nighttime and eating disturbances). Empty cells reflect a rating of no detected abnormality; count reflects the number of patients with non-zero scores. Patients for whom rate of production of sequential motion rates was greater than one standard deviation above the mean of the neurologically normal controls are presented first.

		NPI-Q							
Patient	MDS-UPDRS III speech	Agitation/ aggression	Dysphoria/ depression	Anxiety	Euphoria/ elation	Apathy/ indifference	Disinhibition	Irritability/ lability	Aberrant motor behaviors
1	2					2			2
2	1		2	2		2		1	
3				1		1			
4						1	2		1
5				2		2	2	1	1
6		3	3	3		1		3	
7			1						
8									
9			2			2			
10				1	1		1		
11				3			2		2
12			1	1					
13			2	2		2	2	3	
Faster cohort count	*2*	*1*	*6*	*8*	*1*	*8*	*5*	*4*	*4*
14			1	1					
15				2			2	1	1
16		2	1			1	2	1	1
17			1	1		1			
18		1		2	3	3	3		2
19		1	1	1		1		1	1
20		1				1	1	2	
21		2	1	1			1		
22			1						
23			2					1	
24			1				1	1	
25	1	1	1					2	
26	1					2	2		2
27		1	2		1	1		1	
Control-like cohort count	2	7	10	6	2	7	7	8	5
Total cohort count	*4*	*8*	*16*	*14*	*3*	*15*	*12*	*12*	*9*

neurologically normal controls (defined as higher than one standard deviation above the mean). Interestingly, the rate of producing SMRs correlated with that of *catastrophe* for svPPA, but AMRs correlated with neither SMRs nor *catastrophe*. These relationships held true within the control cohort. When comparing these findings to a study of the other variants of PPA, it was noted that patients with svPPA produced *catastrophe* mildly faster than patients with the nonfluent/agrammatic and logopenic variants of PPA, and notably faster than patients with Primary Progressive Apraxia of Speech (Duffy *et al.*, 2017). The difference in findings between tasks (speech and quasi-speech) is interesting. In fact, prior research has demonstrated differences between speech and quasi-speech tasks in adults with cerebral palsy and dysarthria, where executive dysfunction was thought to interfere with performance on the non-speech, but not the speech, tasks (Schölderle *et al.*, 2018). Although these findings reflect a different underlying etiology and motor speech process, it is an example of cognitive/behavioral influences on such tasks, which may help to explain the pattern we found here.

The current study did not assess the rate of connected speech in svPPA. This decision was made for several methodological reasons, the most important of which was to overcome the linguistic demand required in spontaneous speech tasks. Nonetheless, comparing findings of the current study to those of connected speech may be insightful. The results of the current study concur with a prior study in which patients with svPPA had a slightly elevated speech rate compared to controls (Mesulam *et al.*, 2012); this difference was attributed to excessive talking and circumlocution. Another study reported rates for svPPA that were higher compared to

other variants of PPA (Catani *et al.*, 2013). In contrast, reduced speech rate has also been reported in svPPA, but, again, this difference was attributed to increased pauses for word finding (Ash *et al.*, 2013; Fraser *et al.*, 2014). Reported rates of connected speech in svPPA were, interestingly, comparable to patients with dysexecutive features (Ash *et al.*, 2009). In another study, mean speaking rate of svPPA was reduced, but maximum speech rate was normal (Wilson *et al.*, 2010); these findings offer further support for the notion that reported differences in connected speech rate were not reflective of motor speech difficulties, but, rather, linguistic (i.e., pauses) or cognitive (i.e., dysexecutive) processes. The findings of the current study, including a modest correlation with the NPI-Q in the context of lacking correlations with the MDS-UPDRS III score, disease duration, natural maturation (age), and severity (as indexed by the WAB-AQ and MOCA), also suggest a behavioral, rather than motor, underpinning.

Here, we suggest a possible relationship between speaking rate in svPPA and co-occurring disinhibition and anxiety, traits that are well documented in bvFTD (Rascovsky *et al.*, 2011). However, research has demonstrated reduced speaking rate associated with increased number and duration of pauses in connected speech (Yunusova *et al.*, 2016), while another study showed reduced rate of AMR and SMR production (Vogel *et al.*, 2017) in bvFTD compared to controls. Potential differences in both connected speech and articulation rate as markers of cognitive, behavioral and even motor symptoms are of interest in the broad spectrum of FTD.

What the findings of the current study might mean and how this information will be utilized will be better explicated with longitudinal follow-up of patients with svPPA. In the presented cohort, 9/13 patients who produced SMRs more rapidly than expected presented with either anxiety or disinhibition; 10/14 remaining patients with "normal" SMRs also presented with anxiety or disinhibition. It is possible that individuals with faster speech rates may be erroneously perceived as being anxious. Whether the change in performance in SMRs precedes the behavioral symptoms is an empirical question, but one that may guide education and counseling for patients and their families. It is also interesting that agitation/ aggression was reported for 1 "fast" patient, and noted for 7 of the patients who produced SMRs at an expected rate. It is thus possible there are subgroups of behavioral symptoms among svPPA patients. Following patients longitudinally will clarify whether there is a corollary or predictive relationship between the onset of noted behavioral and speech changes. While we are not proposing a causal relationship, it is possible the observed changes reflect the neuropsychiatric behaviors, but, more likely, they share a common underlying etiology.

The current study has some limitations. We recognize the cohort of control speakers is small; however, the novelty of the study lies in the relationship between the acoustic and behavioral measures. Of course, the NPI-Q was selected as a measure of neuropsychiatric symptoms for its wide clinical use; however, it is a measure that utilizes family report and hence is susceptible to recall and other biases. The NPI-Q is also broad in its scope and short in length, raising questions of specificity and sensitivity. Other measures of disinhibition, executive functioning and, in particular, anxiety, that are perhaps less subjective or more quantitative would be of interest. While reliability was assessed on the speech and language measures, reliability was not assessed for the neurologic measures; this will be important in future studies, particularly for judgments made on the UPDRS-III. We did not utilize connected speech, and therefore cannot correlate this to other behavioral measures or relate it directly to past research. Further, the reported measures are limited to rate in the form of syllable counts; expanded acoustic measures (e.g., envelope modulation or long term average spectra) should be considered in future research. A final limitation is the lack of neuroanatomical correlates. Identifying correlates on neuroimaging would require a larger sample of svPPA patients, but could ultimately help clarify whether this is a motor, cognitive, or behavioral phenomenon. These shortcomings will be addressed in future larger studies.

V. CONCLUSIONS

Half of this cohort of patients with svPPA produced SMRs more rapidly than neurologically normal controls. This phenomenon may be associated with concomitant neuropsychiatric symptoms in svPPA, including disinhibition and anxiety, although the findings of this small study must be interpreted with some caution. Nonetheless, SMR data may useful to quantify rate abnormalities in PPA variants, reflective of changes from sources beyond motor speech deficits or linguistic abnormalities. The observations of this study will inform hypotheses for future studies, which are necessary to validate these findings in a larger cohort and explore possible imaging biomarkers of changes in quasi-speech tasks to better understand if this observation is a manifestation of behavioral, cognitive, and/or motor changes.

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