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Longitudinal decline in spoken word recognition and object knowledge in primary progressive aphasia

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Abstract

The premise of this study is that spoken word recognition and object knowledge are impaired in semantic variant primary progressive aphasia (PPA) (svPPA) and are spared in logopenic variant (lvPPA) and nonfluent agrammatic primary progressive aphasia (nfaPPA) at disease onset. Over time, however, there may be heterogeneity in these abilities in lvPPA and nfaPPA. We hypothesized that individuals with svPPA would demonstrate poorer performance on baseline spoken word recognition and object knowledge than those with lvPPA and nfaPPA) as documented in the literature, but that rates of decline over time on spoken word recognition and object knowledge would be similar in all 3 PPA variants because these become less distinguishable with disease progression.

The aim of this study was to investigate longitudinal patterns of decline in spoken word recognition and object knowledge across PPA variants.

Ninety-five individuals with PPA completed the Semantic Word Picture Matching and Semantic Associates tests at baseline to establish expected performance in these areas. Thirty-five individuals completed follow-up testing.

The distributions of trichotomized mean rates of decline in object knowledge were similar for lvPPA and svPPA ($P = .05$). There were weak negative correlations between symptom duration and baseline scores on Semantic Word Picture Matching ($r[37] = -0.399$, $P = .01$), and baseline scores on Semantic Associates ($r[37] = -0.394$, $P = .01$) in lvPPA.

Degradation of spoken word recognition and object knowledge occurs over time in lvPPA. Further investigation of the receptive language deficits in PPA is warranted to characterize language changes that lessen the distinctions between PPA variants with disease progression.

Abbreviations: AD = Alzheimer disease, AD-PPA = Alzheimer disease related primary progressive aphasia, lvPPA = logopenic variant primary progressive aphasia, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, PPTT = Pyramids and Palm Trees Test, SA = Semantic Associates, svPPA = semantic variant primary progressive aphasia, SWPM = Semantic Word Picture Matching.

Keywords: logopenic primary progressive aphasia, nonfluent agrammatic primary progressive, object knowledge, primary progressive aphasia, semantic variant primary progressive aphasia, spoken word recognition

1. Introduction

International consensus criteria[1] have been adopted widely and successfully for classifying the variants of primary progressive aphasia (PPA), especially in the early stages of disease before progression obscures the distinguishing characteristics of the variants.[2,3] The presentations of some individuals, however, elude classification into any 1 of the 3 clinical syndromes.[4–6] Diagnosis of PPA variant can be confounded by the seeming

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overlap of language characteristics among variants (eg, impaired naming in all variants, impaired repetition in logopenic variant PPA [lvPPA] and nfaPPA), speech and language features which are challenging for even experienced clinicians to diagnose, and variability in clinical presentation, especially in lvPPA and nfaPPA.[7]

Studies of clinical and neuroimaging characteristics of individuals with lvPPA reveal variability in this PPA subtype. Sajjadi et al[4] examined the atrophy patterns of 14 individuals diagnosed with mixed PPA defined as language deficits characteristic of more than one PPA variant or diffuse involvement of language functions, and found a pattern of left temporoparietal atrophy most similar to that seen in lvPPA. The authors concluded that Alzheimer's pathology, the underlying etiology of lvPPA, is variable, resulting in a heterogeneous language profile in a PPA subtype that is neither nfaPPA nor semantic variant PPA (svPPA). Subsequently, Hoffman et al[8] used k-means clustering to group individuals with PPA based on similar linguistic and neuropsychological profiles. They identified 3 PPA clusters: one which closely corresponded to svPPA with bilateral anterior temporal lobe atrophy (left greater than right); another which included features of both lvPPA and nfaPPA; and a mixed PPA group characterized by weak semantic abilities and severe impairments in speech production, repetition, and syntax (not attributable to more advanced disease) which does not map onto the Gorno-Tempini et al[1] criteria. In the non-svPPA groups, patterns of atrophy were widely distributed. These results suggest that svPPA is a readily defined form of PPA, whereas lvPPA and nfaPPA are less distinguishable. Consistent with this finding, Giannini et al[9] endorsed a logopenic spectrum, which includes lvPPA as defined by consensus guidelines and lvPPA+ and lvPPA– defined as clinical phenotypes that are partially consistent with consensus guidelines. More recently, Preiß et al[10] described diffuse cortical thickness reductions in the left hemisphere language network in Alzheimer disease (AD)-related PPA, including regions typically associated with nfaPPA and svPPA. The authors concluded that these neuroimaging patterns explain why the language deficit in AD-PPA is often more extensive than is captured by the consensus guidelines for diagnosing lvPPA.

Similarly, some have proposed that there is variability in nfaPPA, specifically a subset that exhibits single word comprehension deficits in addition to apraxia of speech and/or agrammatism.[11–13] Schaeverbeke et al[14] found that 7 of 12 individuals with a priori diagnosis of nfaPPA (symptom duration 6–131 months) demonstrated single word comprehension deficits, consistent with a mixed variant PPA. Those with this mixed variant showed additional deficits on object knowledge and object recognition relative to healthy controls, although to a lesser degree than those with svPPA.

Studies of nonlinguistic auditory processing lend support to the entity of mixed PPA or an expansion of the criteria that define nfaPPA. Grube et al[15] investigated nonlinguistic auditory processing in 18 individuals with PPA (disease duration 6–72 months) who were classified according the international consensus criteria.[1] They found, however, that 3 of 6 individuals with nfaPPA presented with word comprehension deficits and 2 presented with object recognition difficulty, consistent with mixed PPA. Cope et al[16] found that individuals with nfaPPA performed more poorly than those with stroke aphasia in processing a tone-based language and attributed this finding to the auditory processing deficit in nfaPPA reported by Grube et al.[15] In a related case report, Utianski et al[17] described the evolution of disproportionate difficulty with comprehension of spoken compared to written language, and difficulty perceiving environmental sounds and common musical tunes, in a 65-year-old woman with PPA and apraxia of speech whose clinical presentation became characteristic of nfaPPA.

In this study, we investigated the rate of decline over time in spoken word recognition and object knowledge in the variants of PPA. The premise of our study is that individuals with svPPA will demonstrate poorer baseline performance on spoken word recognition and object knowledge than those with lvPPA and nfaPPA, as expected. Despite these baseline differences, we hypothesized that rates of decline would be similar in all three PPA variants because these become less distinguishable with neurodegeneration, obscuring PPA classification. Confirmation of this hypothesis would contribute to understanding the challenges of classifying PPA variants, identification of therapy targets, and aid in patient/family counseling regarding compensatory strategies.

2. Methods

2.1. Participants

The Johns Hopkins University School of Medicine Institutional Review Board approved this study as exempt research for which consent is not required (IRB00241582). We located the clinical charts of individuals who were seen in an outpatient cognitive neurology clinic (between January 2012 and November 2018) and extracted the following information into a secured, deidentified spreadsheet: age, sex, PPA variant, symptom duration, and language test scores. Of the 294 screened patients, 55 patients did not have a PPA diagnosis and 28 were diagnosed with PPA-NOS (ie, not classified into a subtype at the time of the recorded visit). Of the remaining 211 individuals, 95 with PPA (M age = 68.98 ± 7.78 years; M education [n = 91] = 15.88 ± 2.55 years; M symptom duration = 44.84 ± 22.77 months; 55% female) completed baseline testing with our measures of interest. This population included 39 individuals with lvPPA, 24 individuals with nfaPPA, and 32 individuals with svPPA.

Thirty-five individuals (M age = 67.49 ± 7.32 years; M education = 15.80 ± 2.81 years; M symptom duration = 49.77 ± 24.08 months; 63% female) completed follow-up testing from 3 to 47 months post-baseline (M = 14.26 ± 10.60 months). This subset included 15 with lvPPA, 11 with nfaPPA, and 9 with svPPA.

PPA subtype was identified based on history, comprehensive neurological examination, imaging, and a battery of cognitive/language tests at baseline. Inclusion and exclusion criteria from the international consensus[1] were used to diagnose PPA. PPA variant was diagnosed based on expressive and receptive language characteristics, specifically impaired repetition in lvPPA, agrammatism and/or apraxia of speech in nfaPPA, and impaired semantic knowledge in svPPA. Testing was completed based on participant tolerance. Testing included the following: Benson Figure Copy, Benson Complex Figure Delay (Recall) and Benson Figure Recognition[18,19]; Phonemic Verbal Fluency; Oral Word Reading (regular and irregular words); Johns Hopkins University Anagram Task; Sentence Repetition Test; short form of the Pyramids and Palm Trees Test (PPTT)[20,21]; Kissing and Dancing Test[22]; Noun and Verb Naming Tests[23]; Sentence Reading Test; Spelling to Dictation; short form of the Boston Naming Test[24,25]; Hopkins Assessment of Naming Actions; Picture Word Verification[26]; and Cookie Theft description from the Boston Diagnostic Aphasia Battery.[27] This battery (including unpublished subtests) is an expansion of the FTLD Module to the Uniform Data Set, of

the National Alzheimer's Coordinating Center (2013; alz.washington.edu) from the National Institute on Aging (NIA, a US Government Health Institute). Some patients were also administered the Apraxia Battery for Adults[28]; in others, assessment of speech and limb praxis was done as a part of the comprehensive neurological examination. Symptom duration was ≥24 months (M = 44.84 ± 22.77 months, median = 36 months, range 24–144 months). Patients were classified using international consensus criteria for each variant.[1]

2.2. Language assessment

Semantic Word Picture Matching (SWPM)[29] and the Semantic Associates (SA) test from the Northwestern Naming Battery, experimental edition[23] were administered at baseline and at follow up. Spoken word comprehension at the single word level is assessed on SWPM; object knowledge is assessed on SA.

On SWPM, participants point to pictures that match orally presented object labels. Each display has 4 pictures of semantically related objects that are counterbalanced across all trials. There are five 4-picture displays, each presented 4 times in pseudorandomized order (once with each picture as the target) for a total of 20 trials. The total score is the sum of correctly identified pictures (0–20).

On the SA, participants point to the pair of related pictures of animals and tools from a choice of 2 pairs (eg, squirrel-nuts vs squirrel-eggs; saw-log vs saw-bread) to assess object knowledge. The total is the sum of all correct 8 animal and 8 tool associations (0–16).

Assessment of single word comprehension and semantics were not contingent on our measures of interest as other tests captured these domains (ie, PPTT[20,21]; Kissing and Dancing Test[22]; Picture Word Verification[26]).

2.3. Statistical analysis

We defined symptom duration as number of months between participants and/or caregivers first noticing symptoms and the time of assessment. We defined *decline* the number of points loss between baseline and follow up test scores divided by the baseline score multiplied by 100. We defined *rate of decline* as decline divided by the number of months between initial and final test sessions. Mean rates of decline on SWPM were trichotomized into mean decline "≥−1.44," "between −1.43 and 0," and ">0." Mean rates of decline on SA were trichotomized into mean decline "≥−2.07," "between −2.06 and 0," and ">0." We used means and standard deviations to determine these groupings. Given the wide standard deviation for SA, we did not include one outlier in our calculations to determine groupings for this test. We tested differences in mean baseline test scores between PPA variants and differences in mean rate of decline between PPA variants using ANOVA. We computed Pearson product–moment correlation coefficients to assess the relationship between symptom duration in months and scores on the SWPM and SA. We used Fisher exact test to identify associations between PPA variants and trichotomized scores on SWPM and SA. In the analyses, $P < .05$ was accepted as statistically significant. IBM SPSS Statistics (version 26) was used (SPSS Inc, Chicago, IL).

3. Results

Tables 1 and 2 show the age, sex, education, and symptom duration for individuals tested at baseline and at follow-up. At baseline for the full set, the groups were not significantly different on these characteristics (age: $F_{2,92} = 1.81$, $P = .17$; education: $F_{2,88} = 2.91$, $P = .06$; symptom duration: $F_{2,92} = 0.42$, $P = .66$; sex: $\chi^2 = 0.291$, $P = .87$). For the subset who were tested at follow-up, there were no significant differences for these characteristics (age:

Table 1

Age, sex, education, and symptom duration for PPA variants and for participants overall.

Variant	Age, y, M (SD)	Education, y, M (SD)†	Symptom duration, mo, M (SD)	Sex (F) N (%)
lvPPA (n = 39)	70.21 (6.74)	16.47 (2.70)	45.00 (25.61)	22 (56)
nfaPPA (n = 24)	69.79 (9.95)	16.00 (2.36)	47.96 (23.02)	12 (50)
svPPA (n = 32)	66.88 (6.91)	15.00 (2.31)	42.31 (18.99)	18 (56)
Overall (n = 95)	68.98 (7.78)	15.88 (2.55)	44.84 (22.77)	52 (55)
*P**	.17	.06	.66	.87

F = female, lvPPA = logopenic primary progressive aphasia, M = mean, mos = months, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, SD = standard deviation, svPPA = semantic variant primary progressive aphasia.

* *P* values were calculated using 1-way analysis of variance for age, education, and symptom duration and using χ^2 for sex.

† n = 91.

Table 2

Age, sex, education, and symptom duration for PPA variants and for participants tested at follow-up.

Variant	Age, y, M (SD)	Education, y, M (SD)	Symptom duration, mo, M (SD)	Sex (F) N (%)
lvPPA (n = 15)	69.80 (6.89)	16.60 (2.92)	54.60 (26.55)	11 (73)
nfaPPA (n = 11)	65.27 (8.66)	15.64 (2.66)	44.82 (21.50)	4 (36)
svPPA (n = 9)	66.33 (5.72)	14.67 (2.65)	47.78 (23.88)	7 (78)
Overall (n = 35)	67.49 (7.32)	15.80 (2.81)	49.77 (24.08)	22 (63)
*P**	.26	.26	.58	.09

F = female, lvPPA = logopenic primary progressive aphasia, M = mean, mos = months, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, *SD* = standard deviation, svPPA = semantic variant primary progressive aphasia.

* *P* values were calculated using 1-way analysis of variance for age, education, and symptom duration and using χ^2 for sex.

$F_{2,32}=1.39$, $P=.26$; education: $F_{2,32}=1.39$, $P=.26$; symptom duration: $F_{2,32}=0.55$, $P=.58$; sex: $\chi^2=4.870$, $P=.09$).

Baseline test results on cognitive/language measures are documented in Tables 3 to 6.

3.1. Study premise: baseline differences

As expected based on classification criteria for the variants, the PPA variants were significantly different on performance on SWPM ($F_{2,92}=11.61$, $P < .001$) and on performance on SA ($F_{2,92}=19.81$, $P<.001$). On both tests, those with svPPA scored significantly lower on SWPM than those with lvPPA (Tukey HSD, $P<.001$) and nfaPPA (Tukey HSD, $P<.001$) (Table 7).

3.2. Receptive language and symptom duration correlations

There were weak negative correlations between symptom duration in months and SPWM score for lvPPA (r[37]=−0.399, $P=.01$), and between symptom duration in months and SA score for lvPPA (r[37])=−0.394, P=.01). There were no

Table 3

Test scores on cognitive/language testing for PPA variants and for participants overall at baseline.

Variant	Benson figure copy, M (SD) (maximum score=17)	Benson delay, M (SD) (maximum score=17)	Benson recognition, #correct/n (% correct)
lvPPA	15.26 (3.55)	6.42 (4.81)	33/38 (87)
nfaPPA	15.50 (3.60)	10.13 (5.67)	19/24 (79)
svPPA	13.25 (5.12)	5.52 (5.60)	19/30 (63)
Overall	14.64 (4.24)	7.08 (5.57)	71/92 (77)
	$F_{2,91}=2.72$	$F_{2,90}=5.58$	X^2 (1,92)=5.33
P^*	.07	.01	.07
Tukey HSD		lvPPA vs nfaPPA .02	
		lvPPA vs svPPA .74	
		nfaPPA vs svPPA .01	

HSD = honestly significant difference, lvPPA = logopenic primary progressive aphasia, M = mean, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA=primary progressive aphasia, SD = standard deviation, svPPA = semantic variant primary progressive aphasia.

* P values were calculated using 1-way analysis of variance and χ^2.

Table 4

Test scores on cognitive/language testing for PPA variants and for participants overall at baseline.

Variant	Berndt, M (SD) (maximum score=60)	Pyramids and palm trees, M (SD) (maximum score=14)	Kissing and dancing, M (SD) (maximum score=15)
lvPPA	51.91 (8.65)	13.51 (0.970)	12.51 (2.08)
nfaPPA	56.89 (4.15)	13.79 (0.415)	14.13 (1.10)
svPPA	41.86 (10.31)	10.66 (3.64)	10.72 (3.26)
Overall	52.42 (8.86)	12.62 (2.61)	12.30 (2.70)
	$F_{2,47}=10.43$	$F_{2,92}=19.12$	$F_{2,91}=13.93$
P^*	<.001	<.001	<.001
Tukey HSD	lvPPA vs nfaPPA .10	lvPPA vs nfaPPA .87	lvPPA vs nfaPPA. 03
	lvPPA vs svPPA .01	lvPPA vs svPPA. 001	lvPPA vs svPPA .01
	nfaPPA vs svPPA .001	nfaPPA vs svPPA .001	nfaPPA vs svPPA .001

HSD = honestly significant difference, lvPPA = logopenic primary progressive aphasia, M = mean, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA=primary progressive aphasia, SD = standard deviation, svPPA = semantic variant primary progressive aphasia.

* P values were calculated using 1-way analysis of variance.

Table 5

Test scores on cognitive/language testing for PPA variants and for participants overall at baseline.

Variant	Boston naming test, M (SD) (maximum score=30)	Hopkins assessment of naming actions, M (SD) (maximum score=30)	Verbal fluency (#words/min)
lvPPA	13.49 (7.48)	13.28 (8.09)	13.00 (8.61)
nfaPPA	19.42 (9.90)	,20.21 (8.42)	8.41 (5.51)
svPPA	6.50 (6.51)	8.00 (7.49)	8.03 (6.98)
Overall	12.63 (9.24)	13.61 (9.16)	10.25 (7.72)
	$F_{2,92}=18.87$	$F_{2,86}=14.54$	$F_{2,86}=4.57$
P^*	<.001	<.001	.01
Tukey HSD	lvPPA vs nfaPPA .01	lvPPA vs nfaPPA .01	lvPPA vs nfaPPA .06
	lvPPA vs svPPA .001	lvPPA vs svPPA .03	lvPPA vs svPPA .02
	nfaPPA vs svPPA .02	nfaPPA vs svPPA .001	nfaPPA vs svPPA .90

HSD = honestly significant difference, lvPPA = logopenic primary progressive aphasia, M = mean, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, SD = standard deviation, svPPA = semantic variant primary progressive aphasia.

* P values were calculated using 1-way analysis of variance.

significant correlations between symptom duration in months and either test for nfaPPA, svPPA, or for participants overall (Tables 8 and 9; Figures 1 and 2).

3.3. Decline in spoken word recognition and semantic associates

Participants' mean rates of decline on SWPM were significantly different ($F_{2,32}=19.84$, $P<.001$). Individuals diagnosed with svPPA had significantly greater mean rates of decline on SWPM than those with lvPPA and nfaPPA (Tukey HSD, $P<.001$). There were no significant differences in mean rates of decline on SA between the PPA variants ($F_{2,32}=1.15$, $P=.33$) (Table 10).

When mean rates of decline on SWPM were trichotomized into performance "≥−1.44," "between −1.43 and 0," and ">0," patterns of performance were significantly different ($\chi^2=19.167$, $P < .001$). No individuals with lvPPA or nfaPPA had decline "≥−1.44" whereas 56% of those with svPPA had this rapid rate of decline (Table 11).

On SA, the distributions of trichotomized mean rates of decline were also statistically different ($\chi^2=7.707$, P=.05). Twenty percent of those with lvPPA and 33% of those with svPPA had decline "≥−2.07,'" whereas none of the nfaPPA group demonstrated this rapid rate of decline (Table 12).

4. Discussion

The PPA variants were distinguishable by different patterns of performance on spoken word recognition and object knowledge at baseline, with the svPPA group demonstrating poorer performance than the other variants. This finding is consistent with the literature and offers complementary evidence in a relatively large sample with similar durations of symptom onset. Those with svPPA also demonstrated greater decline on spoken word recognition than lvPPA and nfaPPA. Significant distinctions between the variants were not seen in object knowledge decline, perhaps because deficits in object knowledge emerge later and less consistently in svPPA. However, when decline scores were

Table 6

Test scores on cognitive/language testing for PPA variants and for participants overall at baseline.

Variant	Oral word reading, M (SD) (maximum score = 30)	Sentence reading, M (SD) (maximum score = 5)	Sentence repetition, M (SD) (maximum score = 5)
lvPPA	25.74 (7.15)	4.13 (1.61)	2.36 (2.02)
nfaPPA	25.00 (9.00)	3.67 (1.71)	3.13 (2.05)
svPPA	22.90 (8.01)	3.38 (1.79)	2.74 (1.90)
Overall	24.62 (7.65)	3.76 (1.71)	2.68 (1.99)
	$F_{2,91}=1.41$	$F_{2,91}=1.76$	$F_{2,91}=1.13$
P^*	0.32	0.18	0.33

lvPPA = logopenic primary progressive aphasia, M = mean, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, SD = standard deviation, svPPA = semantic variant primary progressive aphasia.
* *P* values were calculated using 1-way analysis of variance.

Table 7

Test scores on semantic word picture matching and semantic associates for PPA Variants and for participants overall at baseline.

Variant	Single word picture matching, M (SD)	Semantic associates, M (SD)
lvPPA (n = 39)	19.28 (1.30)	15.26 (1.71)
nfaPPA (n = 24)	19.71 (0.86)	15.50 (1.47)
svPPA (n = 32)	17.47 (2.88)	11.84 (3.79)
Overall (n = 95)	18.78 (2.13)	14.17 (3.04)
P^*	<.001	<.001
Tukey HSD	lvPPA vs nfaPPA .67	lvPPA vs nfaPPA .93
	lvPPA vs svPPA <.001	lvPPA vs svPPA <.001
	nfaPPA vs svPPA <.001	nfaPPA vs svPPA <.001

HSD = honestly significant difference, lvPPA = logopenic primary progressive aphasia, M = mean, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, SD = standard deviation, svPPA = semantic variant primary progressive aphasia.
* *P* values were calculated using 1-way analysis of variance.

Table 8

Pearson product–moment correlation coefficients (*r*), coefficients of determination (r^2), and percent variance between single word picture matching at baseline and symptom duration for PPA variants and participants overall.

Variant	*r*	95% Confidence interval, *r*	r^2	Percent variance	P^*
lvPPA (n = 39)	−0.399	−0.624 to −0.104	0.159	15.92	.01
nfaPPA (n = 24)	−0.027	−0.394 to 0.351	0.001	0.07	.90
svPPA (n = 32)	−0.135	−0.443 to 0.205	0.018	1.82	.46
Overall (n = 95)	−0.125	−0.314 to 0.075	0.016	1.56	.23

lvPPA = logopenic primary progressive aphasia, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, svPPA = semantic variant primary progressive aphasia.
* *P* values were calculated using Pearson product–moment correlation coefficients.

Table 9

Pearson product–moment correlation coefficients (*r*), coefficients of determination (r^2), and percent variance between semantic associates at baseline and symptom duration for PPA variants and participants overall.

Variant	r	95% Confidence interval *r*	r^2	Percent variance	*P**
lvPPA (n = 39)	−0.394	−0.618 to −0.095	0.155	15.52	.01
nfaPPA (n = 24)	0.184	−0.211 to 0.516	0.034	3.39	.39
svPPA (n = 32)	−0.091	−0.407 to 0.247	0.008	0.83	.62
Overall (n = 95)	−0.065	−0.258 to 0.135	0.004	0.42	.53

lvPPA = logopenic primary progressive aphasia, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, svPPA = semantic variant primary progressive aphasia.
* *P* values were calculated using Pearson product–moment correlation coefficients.

trichotomized into categories, decline was significantly different between the PPA variants. As expected, the svPPA group performed more poorly than the lvPPA and nfaPPA groups on single word picture matching. Less expected were the trichotomized decline scores in lvPPA on a test of semantic associates. There were weak negative correlations with decline in spoken word recognition and semantic associates with symptom duration in lvPPA. The deterioration in performance on semantic associates in lvPPA could reflect degradation of semantic knowledge or poor understanding of the task, due to a more generalized dementia that emerges in this group.

Atrophy of temporal and parietal lobes, characteristic of lvPPA, may account for impaired single word comprehension and impaired semantic knowledge. Vandenbulcke et al[30] reported that left posterior superior temporal sulcus has a critical role in mapping word form onto word meaning. In their longitudinal study of 21 individuals with lvPPA, Rohrer et al[31] reported baseline atrophy (left greater than right) of the posterior superior temporal lobe, inferior parietal lobe, posterior cingulate, and medial temporal lobe. Over time, there was involvement of other areas of the left hemisphere and atrophy in the right hemisphere that mirrored left hemisphere atrophy seen earlier in the disease course, including evidence of atrophy in the posterior cingulate/precuneus and anterior and medial temporal lobe. The anterior temporal lobe has been implicated in single word comprehension[32–36] and identified as a semantic hub.[37,38] More specifically, in their study of neural correlates of verbal and nonverbal semantic measures in semantic dementia with FDG-PET, Mion et al[39] found that hypometabolism of the most rostral portions of fusiform gyri predicted performance on semantic tests (object naming, semantic verbal fluency, non-verbal associative semantic knowledge). Rohrer et al[31] also described emergence of deficits in single word repetition, single word comprehension, and recognition memory with disease progression in their participants.

Deterioration of semantic memory is a hallmark of AD [40] which is the underlying neuropathology of lvPPA.[9,41,42] We

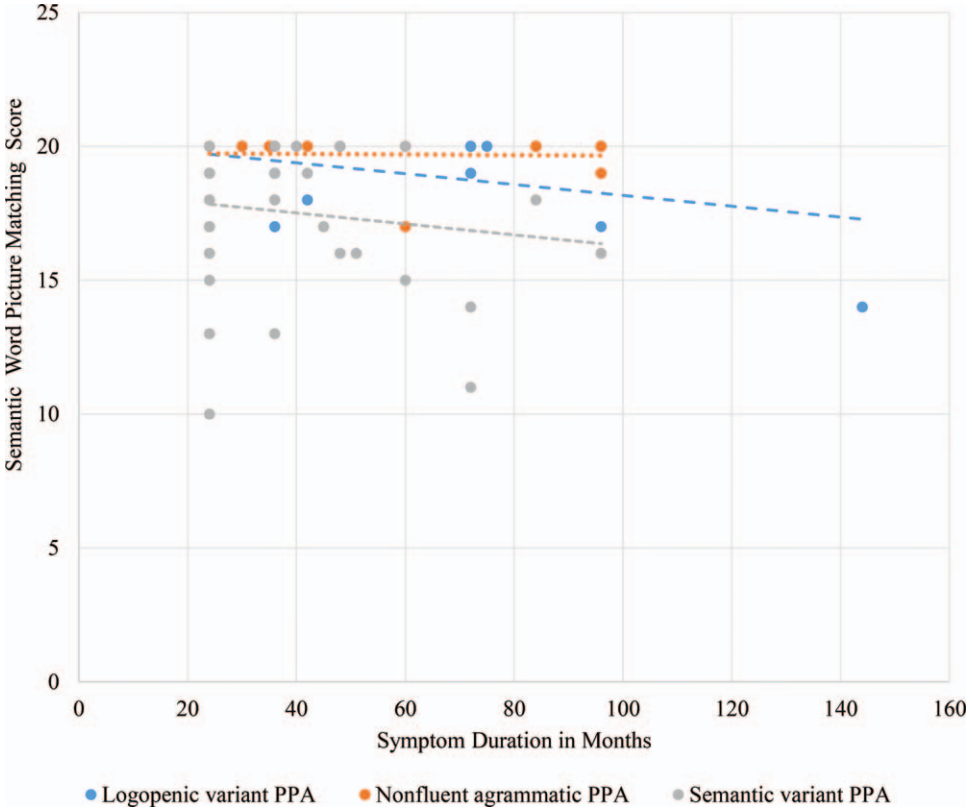

Figure 1. PPA, Primary progressive aphasia.

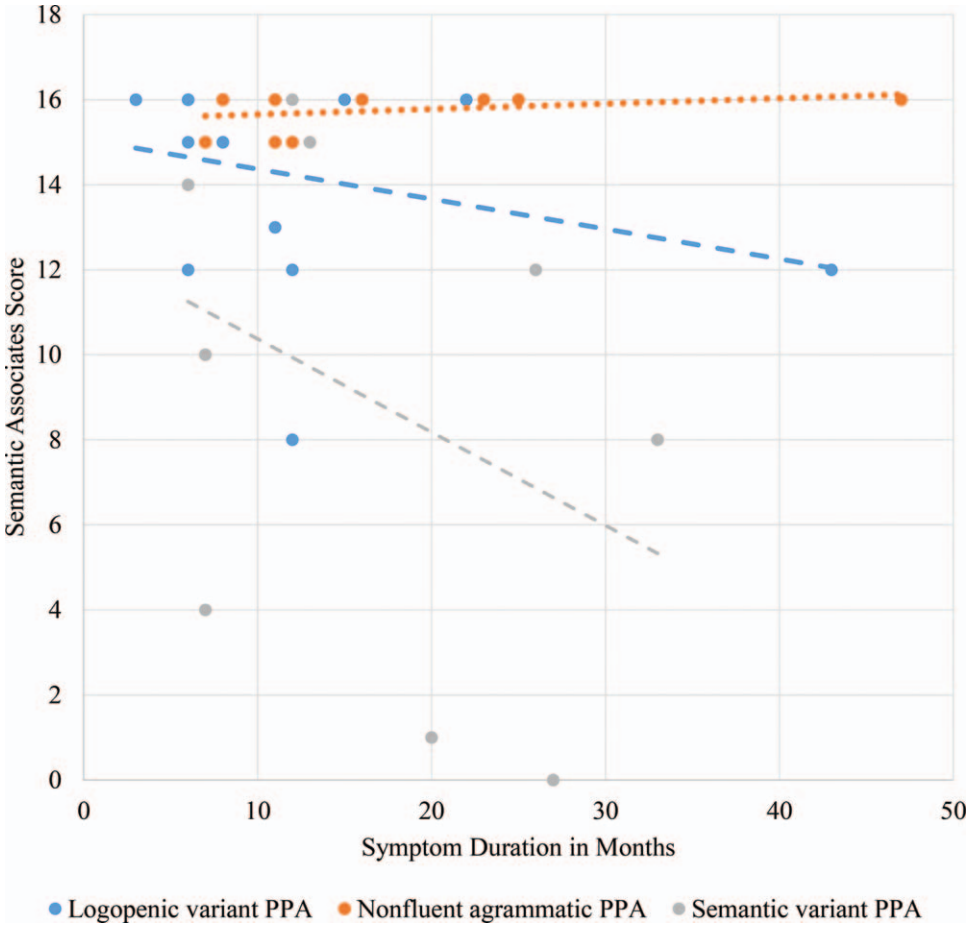

Figure 2. PPA, Primary progressive aphasia.

previously found that semantic knowledge remained intact until late in disease course of lvPPA, with <1-point decline per month on the PPTT.[43] In addition, in a study of language abilities and behavioral presentations in PPA, we found significant negative correlations between behavioral ratings and language repetition, semantic knowledge, and action naming in lvPPA, but no correlations in other PPA variants.[44] We interpreted these results as evidence that those with lvPPA do not develop negative behaviors until their language deficits are severe, consistent with the underlying pathology of AD. Those with nfaPPA and svPPA, however, develop negative behaviors and disinhibition behaviors, even when their language deficits are mild. This is consistent with the underlying cause of these variants: frontotemporal lobar degeneration trans-activator regulatory DNA binding protein 43 (FTLD-TDP43), frontotemporal lobar degeneration-tau (FTLD-t), or related tau-opathies.[45–49] Funayama et al[50] also found that semantic memory deficits, as well as

Table 10

Mean rates of decline on single word picture matching and semantic associates for ppa variants and for participants overall.

Variant	Single word picture matching, M (SD)	Semantic associates, M (SD)
lvPPA (n = 15)	−0.25 (0.57)	−0.84 (1.30)
nfaPPA (n = 11)	−0.05 (0.11)	−0.18 (0.32)
svPPA (n = 9)	−1.64 (0.95)	−1.61 (3.81)
Overall (n = 35)	−0.54 (0.89)	−0.83 (2.11)
$F_{2,32}$	19.84	1.15
P^*	<.001	.33
Tukey HSD	lvPPA vs nfaPPA .66 lvPPA vs svPPA <.001 nfaPPA vs svPPA <.001	

HSD = honestly significant difference, lvPPA = logopenic primary progressive aphasia, M = mean, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, SD = standard deviation, svPPA = semantic variant primary progressive aphasia.
* *P* values were calculated using 1-way analysis of variance.

Table 11

Number (percent) of scores in trichotomized mean rates of decline on single word picture matching for PPA variants and for participants overall.

Variant	≤−1.44	−1.43 to 0	>0
lvPPA (n = 15)	0	13 (87)	2 (13)
nfaPPA (n = 11)	0	11 (100)	0
svPPA (n = 9)	5 (56)	4 (44)	0
Overall (n = 35)	5 (14)	28 (80)	2 (6)
P^*	<.001		

lvPPA = logopenic primary progressive aphasia, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, svPPA = semantic variant primary progressive aphasia.
* *P* value was calculated using Fisher exact test.

Table 12

Number (percent) of scores in trichotomized mean rates of decline on semantic associates for PPA variants and for participants overall.

Variant	≤−2.07	−2.06 to 0	>0
lvPPA (n=15)	3 (20)	11 (73)	1 (7)
nfaPPA (n=11)	0	11 (100)	0
svPPA (n=9)	3 (33)	4 (44)	2 (22)
Overall (n=35)	6 (17)	26 (74)	3 (9)
P^*	.05		

lvPPA = logopenic primary progressive aphasia, nfaPPA = nonfluent agrammatic primary progressive aphasia, PPA = primary progressive aphasia, svPPA = semantic variant primary progressive aphasia.
* *P* value was calculated using Fisher exact test.

apraxia, developed in 3 individuals with lvPPA as they progressed to the advanced stages of their disease.

The entity of mixed PPA, although controversial, and progression of language deficits over time render differential diagnosis a challenge. It is relatively easier to distinguish svPPA from nfaPPA and lvPPA (non-svPPA), but the distinctions between lvPPA and nfaPPA are less clear.[5] In a previous study, we found that performance on visuospatial memory might facilitate appropriate diagnosis of lvPPA versus nfaPPA with relatively spared delayed figure copying helping to identify those with nfaPPA.[51]

Appropriate classification of PPA is important in clinical practice as each of the variants presents with different trajectories and manifestations, although these distinctions may become less apparent over time. Individuals and their caregivers need to have accurate information about disease progression for future planning. Also, as our knowledge about PPA evolves, correct phenotypic diagnosis has implications for treatment as some variants may respond differently to intervention than other PPA subtypes.[52,53]

Limitations of this study included lack of follow-up data for all participants. We used word–picture matching and picture–picture matching to assess word comprehension (lexical semantics) and object knowledge, respectively. Impaired visual association abilities affecting picture recognition or impaired comprehension of the task could potentially confound performance on these tasks. We did not assess this potential confound by assessing word–word association. However, there was a strong positive correlation between scores on the PPTT and SA tests for all subjects ($r[93]=0.776$, $P<.001$). In addition, we focused on two language tests in this study, capturing limited aspects of the complex constructs of spoken word recognition and object knowledge. Further investigation of the receptive language deficits in PPA is warranted to identify speech and language impairments where therapy may be indicated, enhance differential diagnosis of PPA that has implications for patient/family education and counseling, and investigate the evolution of the PPA variants over time.

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