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Patterns of Decline in Naming and Semantic Knowledge in Primary Progressive Aphasia

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Abstract

Background: Individuals with primary progressive aphasia (PPA) and their caregivers want to know what to expect so that they can plan support appropriately. The ability to predict decline in naming and semantic knowledge, and advise individuals with PPA and their caregivers regarding future planning, would be invaluable clinically.

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Aims: The aims of this study were to investigate patterns of decline in naming and semantic knowledge in each of the clinical variants of PPA (logopenic variant PPA, lvPPA; nonfluent agrammatic PPA, nfaPPA; and semantic variant PPA, svPPA) and to examine the effects of other variables on rate of decline. We hypothesized that speech-language rehabilitation, higher education, and higher baseline test scores would be associated with slower decline, and older age with faster decline.

Methods and Procedures: A total of ninety-four participants with PPA underwent language testing, including thirty six participants with lvPPA, thirty-one participants with nfaPPA, and twenty-seven participants with svPPA. All participant groups were similar in age and education. We focused on decline on three tests: the short form of the Boston Naming Test (BNT), the Hopkins Assessment of Naming Actions (HANA), and the short form of the Pyramids and Palm Trees Test (PPTT).

Outcome and Results: Across language tests, the most precipitous rates of decline (loss of points per month) occurred in nfaPPA, followed by svPPA, then lvPPA. Female sex, longer symptom duration, higher baseline test score, and speech-language rehabilitation were associated with slower decline.

Conclusions: PPA variants were distinguishable by rapidity of decline, with nfaPPA having the most precipitous decline. As hypothesized, higher baseline test scores and speech-language rehabilitation were associated with slower decline. Surprisingly, age and education were not important prognostically for individuals in this study. Further study of prognostically-relevant variables in PPA is indicated in this population.

Keywords

Primary progressive aphasia; nonfluent agrammatic primary progressive aphasia; semantic variant primary progressive aphasia; logopenic variant primary progressive aphasia; language symptoms

Introduction

An understanding of the natural course of a disease and predictive variables is vital for health care providers in making prognostic statements, developing treatment plans, and for advising patients and their caregivers regarding future needs. Much is known about the expected recovery from stroke and the variables that influence recovery, such as changes in blood flow in the acute post stroke period, education level, size of stroke, and initial severity (Hillis & Tippett, 2014). This knowledge enables health care providers to make recommendations, and assists patients and their caregivers in planning for anticipated needs, such as rehabilitation, personal assistance in the home setting, equipment, and modifications to the home, such as wheelchair ramps. In contrast, prediction of the clinical course of primary progressive aphasia (PPA) is relatively more complicated because of the heterogeneity of its variants and lack of data on variables that influence the course. This difficulty in prognosis can complicate planning for individuals with PPA and their families and even contribute to anxiety because of uncertainty regarding the future.

PPA is a clinical syndrome characterized by insidious onset and gradual deterioration of language manifested by deficits in word finding, word usage, word comprehension, or

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sentence construction associated with atrophy of the frontal and temporal regions of the left hemisphere (Mesulam, 2001; 2013). Language is disproportionately impaired, without impairment in other cognitive domains other than praxis (Mesulam, 1982). PPA variants are well defined and described in the literature; a classification taxonomy exists to facilitate diagnosis of PPA variant (Gorno-Tempini et al., 2011). There are three main variants, each with specific clinical features and pathophysiology: logopenic variant PPA, nonfluent agrammatic PPA, and semantic variant PPA (Gorno-Tempini et al., 2011; Josephs et al., 2008). Difficulty naming is an early and persistent impairment common to all three variants of PPA (Grossman et al., 2004; Hurley et al., 2009; Mesulam et al., 2013).

Logopenic variant (lvPPA) is distinguished by word retrieval and phrase and sentence repetition deficits. Phonological errors in naming are common. Single word comprehension is relatively spared (Gorno-Tempini et al., 2008; 2011). Generalized cognitive decline, including language abilities, attention, memory, and visuospatial skills, is manifested over time (Rohrer et al., 2013). lvPPA has been associated with left temporo-parietal atrophy (Gorno-Tempini et al., 2004a; Wilson et al., 2011) and disease progression is associated with a progression of atrophy in the left temporal, parietal, frontal and caudate areas, and in the right posterior cingulate cortex/precuneus (Rohrer et al., 2013). A subset of individuals with lvPPA has been reported to have a very slow rate of decline (Machulda et al., 2013). lvPPA is associated with Alzheimer's disease (AD) pathology (Giannini et al., 2017; Josephs et al., 2008) and frontotemporal lobar degeneration-ubiquitin positive inclusions (FTLD-U) (Mesulam et al., 2008).

Nonfluent agrammatic PPA (nfaPPA) is characterized by core features of agrammatic language production and/or apraxia of speech (Gorno-Tempini et al., 2004a; Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; Rogalski et al., 2011a). Spoken modality-specific naming impairments are reported in nfaPPA (Hillis, Tuffiash, & Caramazza, 2002) as well as naming deficits specific to impaired naming of actions rather than objects (Hillis et al., 2002; Hillis, Oh, & Ken, 2004; Hillis et al., 2006). Individuals with nfaPPA may become mute early in their disease progression (Gorno-Tempini et al., 2006) and develop clinical features of parkinsonism and related syndromes, such as corticobasal syndrome, progressive supranuclear palsy, or frontotemporal lobar degeneration-tau (FTLD-t) (Gorno-Tempini, Murray, Rankin, Weiner, & Miller, 2004b). Brain atrophy is typically present in left posterior frontal areas (Gorno-Tempini et al., 2004a; Josephs et al., 2006; Wilson et al., 2011). In some instances, atrophy is present in the insula and premotor and supplementary motor areas (Gorno-Tempini et al., 2011; Josephs et al., 2008; Wilson et al., 2011). With advancement of disease, atrophy in nfaPPA progresses into dorsolateral prefrontal cortex, inferiorly into superior temporal cortex, medially into orbital and anterior cingulate regions, and posteriorly along the Sylvian fissure into the parietal lobe (Grossman, 2010). nfaPPA is usually associated with tau-positive pathology; however, there is heterogeneity in the underlying pathology associated with this clinical syndrome. Non-tau pathology reported in nfaPPA include AD pathology (Alladi et al., 2007; Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005) and FTLD-U (Knopman et al., 2005; Mesulam et al., 2008), or more specifically, frontotemporal lobar degeneration-transactive-response DNA binding protein 43 (FTLD-TDP-43) (Josephs, Stroh, Dugger, & Dickson, 2009; Mackenzie et al., 2006; Snowden, Neary, & Mann, 2007).

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Semantic variant (svPPA) is defined by marked anomia and single-word comprehension deficits across input and output modalities (Hurley, Paller, Rogalski, & Mesulam, 2012). Individuals with svPPA may display progressively impaired object naming, with preserved naming of actions, and greater difficulty in the written versus spoken modality, although both modalities are compromised (Hillis et al., 2004; 2006). Speech fluency, syntax, and word repetition are preserved (Gorno-Tempini et al., 2004a). Individuals with svPPA also manifest behavioral symptoms as their disease progresses (Seeley et al., 2005; 2008). This variant is associated with atrophy in ventrolateral anterior temporal lobes bilaterally, usually greater atrophy on the left (Gorno-Tempini et al., 2004a; Wilson et al., 2011). The most common underlying disease pathology associated with svPPA is FTLD-U (Grossman et al., 2008; Kertesz et al., 2005; Knopman et al., 2005) and its variant FTLD-TDP-43 (Hodges et al., 2010; Snowden et al., 2007; Spinelli et al., 2017). Less commonly associated disease pathologies are AD pathology (Alladi et al., 2007) and Pick bodies (Davies et al., 2005).

The classification of PPA variants based on the taxonomy developed by Gorno-Tempini et al. (2011) can aid in anticipating the disease course. However, classification of PPA can be challenging both early and late in the disease course. In the early stages, the variants are distinct, aside from the common symptom of anomia. Later in the disease course, the variants tend to become more alike over time, making distinctions between variants less clear (Faria, Sebastian, Newhart, Mori, & Hillis, 2014; Rogalski et al., 2011b). Moreover, within variants, atypical presentations can exist, such as a slowly progressive form of lvPPA (Machulda et al., 2013).

Longitudinal imaging and assessments of cognition, language, and behavior in PPA afford insight into the expected disease course, but do not specify variables that assist in predicting future clinic course. For example, Rogalski et al. (2011b) described progressive clinical deficits and cortical atrophy in six individuals with lvPPA, three individuals with nfaPPA and four individuals with svPPA. Over a 2 year time period, the PPA variants became more alike, however, the variant-specific differential impairment of word comprehension in the svPPA group versus impairment of grammatical processing in the nfaPPA group was largely maintained. Peak atrophy sites extended beyond the initial distinctive locations that characterized each of the variants, encompassing all three major components of the language network: the inferior frontal gyrus, the temporoparietal junction, and lateral temporal cortex. Etcheverry et al. (2012) reported the results of a longitudinal assessment of three individuals with lvPPA, two over 18 months and one over 46 months. Deterioration of verbal abilities, such as picture naming, story retelling, and semantic word recall, and decrease in non-verbal skills, such as divided attention and increasing apraxia were found, although there was inter-subject variability.

Tree and Kay (2015) described their longitudinal assessment of an individuals with lvPPA revealing the key features of intact single word comprehension until later stages, and severely impaired picture naming which deteriorated further, and was underpinned by a characteristic anomic impairment (an inability to retrieve phonology from semantics). Brambati et al. (2015) investigated the patterns of longitudinal changes in cognition and anatomy in eight individuals with nonfluent variant (nfv) PPA, thirteen participants with svPPA, seven individuals with lvPPA, and 29 age-matched, neurologically healthy controls.

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All participants underwent longitudinal MRI, neuropsychological and language testing at baseline and at a 1-year follow-up. Results showed that nfvPPA patients showed gray matter atrophy progression in the left frontal and subcortical areas as well as a decline in motor speech and executive functions. The svPPA patients showed atrophy progression in the medial and lateral temporal lobe and decline in semantic memory abilities. Finally, lvPPA patients showed atrophy progression in lateral/posterior temporal and medial parietal regions with a decline in memory, sentence repetition and calculations. In addition, in all three variants, the white matter fibers underlying the atrophied cortical areas underwent significant volume contraction over a 1-year period.

Van Langenhove, Leyton, Piguet, and Hodges (2016) reported that both at baseline and after 1 year, svPPA exhibited significantly more behavioral disturbances characteristic of behavioral variant frontotemporal dementia compared with other PPA variants. At follow-up, empathy loss was significantly more pronounced in nfaPPA than lvPPA. The prevalence and course of behavioral symptoms in lvPPA was similar to that found in Alzheimer's disease. Faria et al. (2014) approached prognostication in their description of longitudinal decline in auditory comprehension and cortical atrophy in 15 individuals with PPA, relating changes in language function and individual "difference maps" in imaging, which show individual patterns of atrophy that herald future language change.

Le Rhun, Richard, and Pasquier (2005) described the natural history of PPA in a cohort of 49 individuals over a ten year period, and reported two factors predictive of future mutism and eating difficulty. Half of their cohort required assistance with toileting, personal hygiene, and dressing five years after symptom onset. Mutism, assistance with eating and walking, and need for institutionalization were observed in half of the cohort seven to eight years post symptom onset. Over half of their cohort died within seven years post symptom onset, at a median age of 71 years. The authors reported that a higher Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) score and more fluent language at baseline clinic visit reduced the relative risk of subsequent mutism, after adjusting for sex, educational level, and age at onset. Also, a higher baseline MMSE score reduced the relative risk for later eating difficulties. Age at onset, age at first clinic visit, sex, educational level, vascular risk factors, and number of clinic visits were not found to have an effect on activities of daily living.

Individuals with PPA and their caregivers most want to know what to expect so that they can plan for support appropriately. The aims of this study were to investigate longitudinal patterns of decline in naming and semantic knowledge in each of these clinical variants and to examine the effects of other variables (i.e., age, education, sex, race, symptom duration, presence or absence of speech-language rehabilitation, and baseline test score in addition to PPA variant) on the rate of decline. With regard to language testing, we specifically focused on decline in object and action naming and decline in object semantic knowledge. We hypothesized that speech-language rehabilitation, higher education, and higher baseline test scores would be associated with slower decline in naming and semantics, and older age with faster decline.

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Methods

Participants

Ninety-four patients with PPA (mean ± standard deviation age = 67.27± 8.59 years; 58 (62%) female; mean education = 16.07 ± 2.57 years) were enrolled (Table 1). These individuals were evaluated in one author's (AEH) outpatient cognitive neurology clinic and agreed to participate. Demographic (i.e., age, education, sex, race) and clinical data (i.e., symptom duration and presence or absence of speech-language rehabilitation) information were collected at baseline after enrollment. Regarding speech language rehabilitation, we asked participants whether they had received speech language rehabilitation during the course of their disease; unfortunately, we do not have information regarding the duration and nature of therapy for all patients.

Participants were diagnosed with PPA on the basis of presenting with a predominant and progressive deterioration in language abilities in the absence of major change in personality, behavior, or cognition other than praxis (Mesulam, 1982). PPA variant was identified on the basis of history, comprehensive neurological examination, imaging, and a battery of language and cognitive tests at the initial clinic visit. Testing was completed based on participant tolerance and included the following: Word Reading Test; Semantic Word-Picture Matching Test (Rogalsky, Love, Driscoll, Anderson, & Hickok, 2011c); Semantic Associates Test; JHU Anagram Test; Sentence Repetition Test; Noun and Verb Naming Tests; Sentence Reading Test; Boston Naming Test, short form (BNT; Kaplan, Goodglass, & Weintraub, 2001; Mack, Freed, Williams, & Henderson, 1992); Hopkins Assessment of Naming Actions (HANA; Breining et al., 2015b), short form of the Pyramids and Palm Trees Test (PPTT; Breining et al., 2015a; Howard & Patterson, 1992); Benson Figure Copy and Recall; Forward and Backward Digit Span; Verbal Fluency Task including both letter (FAS) (Loonstra, Tarlow, & Sellers, 2001) and action (verb) (Woods et al., 2005) word fluency; Spelling to Dictation Test; a Picture Word Verification Test (Caramazza & Hillis, 1990); and Kissing and Dancing Test (Bak & Hodges, 2003). This battery (including unpublished subtests) is an expansion of the National Alzheimer's Coordinating Center's Frontotemporal Dementia Battery, from the National Institute on Aging (NIA, a US Government Health Institute). Some patients were also administered the Apraxia Battery for Adults (Dabul, 2000); in others assessment of speech and limb praxis was done as a part of the comprehensive neurological examination.

Patients were classified using consensus criteria for each variant (Gorno-Tempini et al., 2011). Ten individuals who did not meet the criteria for any variant were judged to be unclassifiable, and were not included in this study. Thirty-six patients with lvPPA (mean age = 69.28 ± 8.01 years; mean education = 16.56 ± 2.90 years), 31patients with nfaPPA (mean age = 67.68 ± 9.61 years; mean education = 15.77 ± 2.58 years), and 27 patients with svPPA (mean age = 64.11 ± 7.39 years; mean education = 15.78 ± 2.01years) were included. All participants provided written informed consent under the Human Subjects Protocol approved by the Institutional Review Board for the Johns Hopkins University School of Medicine.

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Procedure

This study focused on three tests to investigate longitudinal decline in PPA. We focused on two language components that are commonly impaired in PPA: naming and semantic knowledge. The three tests included: Boston Naming Test, short form (BNT; Kaplan, Goodglass, & Weintraub, 2001; Mack et al., 1992); Hopkins Assessment of Naming Actions (HANA; Breining et al., 2015b), and the short form of the Pyramids and Palm Trees Test (PPTT; Breining et al., 2015a; Howard & Patterson, 1992). Up to three assessment of each test per participant were available and were used in the analyses. The mean interval between administrations of the BNT time point 1 and 2 was 10.04 ± 4.30 months and time point 2 and 3 was 18.22 ± 5.03 months; the mean interval between administrations of the HANA time point 1 and 2 was 10.14 ± 4.74 months and time point 2 and 3 was 21.29 ± 8.13 months; the mean interval between administrations of the PPTT time point 1 and 2 was 10.32 ± 4.67 months and between time point 2 and 3 was 18.89 ± 7.14 months. There was attrition in the participant groups over time. Please see Table 2 for details of participants tested at each time point. Reasons for attrition included participants not returning for follow up, not being able to complete tasks, or participants not wanting to undergo language assessment. Individuals with all variants of PPA were tested at each of the time points, and there were no significant differences in the percentages of individuals with each of the PPA variants tested at each of the time points.

Participants were asked to name 30 line drawings of objects orally on the short form of the BNT (score range 0 – 30). Objects ranged from high familiarity items, such as “bed,” to low frequency items, such as “sphinx.” If a participant experienced difficulty naming a pictured object, a phonemic cue was provided, however, these responses were not included in the total correct.

Participants were instructed to name 35 line drawings of actions on the HANA (e.g., run, spill, whisper) (score range 0 – 35), which are matched in frequency to the items on the BNT. If participants named an object in the test picture, they were re-instructed to name actions.

Participants were asked to identify a line drawing of an object semantically related to 14 target pictured objects on the PPTT (score range 0 – 14). Target pictures were presented along with two additional pictures. Participants were asked to point to the picture related to the target. For example, the target picture of eye glasses (spectacles) was presented along with pictures depicting an eye and an ear. Participants were asked to decide which picture is more related in meaning to the target picture (eye glasses).

Data Analysis

A general linear mixed-effects model analysis with repeated measurements was performed which took into account the varying number of measurements between subjects. Factors in the analysis included: age (>60 years), education years, sex (female), race (nonwhite), symptom duration (defined as the number of months between participants and/or their caregivers first noticing symptoms and their baseline assessment), PPA variant, and presence or absence of speech-language rehabilitation. Two-factor interactions were also included for

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testing interval, with sex, PPA variant, presence or absence of speech-language rehabilitation, and baseline test score. Three-factor interactions were included for testing interval by PPA variant with sex and baseline test score to allow rates of outcome decline to be different according to combinations of demographic and clinical characteristics.

Results

Table 1 describes the age, education, sex, race, and symptom duration of the groups. The groups were not significantly different on these characteristics. There was attrition in the participant groups over time. Table 2 shows the number and percentages of participants tested at Time Points 1, 2 and 3 by PPA variants. With regard to the presence or absence of therapy, fifty-two of the 94 (55%) participants reported that they received therapy [(23 lvPPA (64%); 17 nfaPPA (55%); 12 svPPA 44%)]. Individual variation in decline in test performance was evident on the spaghetti plots for all three PPA variants (Figures 1–3). Relatively more stable performance over time was observed on the PPTT.

Overview of Test Results

Across language tests, the most precipitous rates of decline (loss of points per month) overall occurred in nfaPPA (BNT: 0.91, 95% CI: 0.74 – 1.07, $p < 0.001$; HANA: 0.76, 95% CI: 0.60 – 0.92, $p < 0.001$; PPTT: 0.35, 95% CI: 0.26 – 0.44, $p < 0.001$). Compared to the nfaPPA subtype, decline on all three test scores in the svPPA subtype was significantly slower. Decline of BNT scores in the svPPA subtype was 0.35 points slower per month (95% CI: 0.20 – 0.50, $p < 0.001$); decline of HANA scores was 0.23 points slower per month (95% CI: 0.12 – 0.33, $p < 0.001$); decline of PPTT scores was 0.05 points per month (95% CI: 0.02 – 0.07, $p = 0.001$). Compared to the nfaPPA subtype, decline of BNT test scores in the lvPPA subtype was 0.24 points slower per month (95% CI: 0.09 – 0.39, $p = 0.002$). Decline on HANA and PPTT test scores per month in the lvPPA subtype were slower than the nfaPPA subtype, however the differences were not significantly different (HANA: 0.10 points slower per month, 95% CI: −0.005 – 0.21, $p = 0.06$; PPTT: 0.01 points slower per month, 95% CI: −0.005 – 0.04, $p = 0.14$) (Table 3). However, modeling results exploring for two-way and three-way interactions among factors suggest some significantly different rates of declines in the three test outcomes across different demographic and clinical subgroups.

Below we describe in detail the results for each language test. From the multivariable mixed-effects linear model, we first report the effect of the factors (age, education, sex, race, symptom duration, PPA variant, and presence or absence of speech-language rehabilitation) on the three language tests at the initial (baseline) assessment. Next, we report the model-based association of the factors on the three language tests over time (longitudinal change/decline). We report factors and interactions that are significant in the text, and significant and nonsignificant results in Tables 4–9.

Boston Naming Test

Baseline Assessment: Results for the baseline (initial visit) analysis showed a significant effect for sex, symptom duration and PPA variant (Table 4).

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Sex: After accounting for other variables in the statistical model, female participants, on average, scored 3.69 (95% CI: 0.45 – 6.92) points lower on the BNT than males at initial testing (p = 0.03).

Symptom Duration: After accounting for other variables in the statistical model, participants with longer symptom duration before baseline, on average, scored 0.18 (95% CI: 0.05 – 0.31) points higher on the BNT at initial testing (p = 0.008).

PPA Variant: After accounting for other variables in the statistical model, participants with svPPA, on average, scored 10.31 (95% CI: 4.39 – 16.22) points lower in BNT than those with nfaPPA at initial testing (p = 0.001.

Longitudinal Change: Results for the longitudinal analysis showed a significant effect for two and three factor interactions (Table 5).

Two factor Interactions: Two factor interactions were significant for BNT change over time and sex, and BNT change over time and symptom duration. Results for the interaction of BNT change over time and sex indicated that male participants in the nfaPPA group had 0.19 points faster decline per month than females (95% CI: 0.06 – 0.31, p = 0.004). Results for the interaction of testing interval and symptom duration indicated that participants who reported longer symptom duration at their initial BNT testing had significantly slower progression, on average 0.002 points slower per month for every additional month of self-reported symptom duration before initial BNT testing (95% CI: 0.0007 – 0.003, p = 0.002) across all PPA variants

Three factor interactions: Three factor interactions were significant for BNT change over time, PPA variant, and sex; and for BNT change over time, PPA variant, and BNT baseline test score. The results of the interaction of BNT change over time, PPA variant, and sex indicated that female participants had slower decline than male participants, but the sex differences varied by PPA variants (p = 0.016 for sex x PPA variants interaction on rate of BNT decline over time), with nfaPPA showing the greatest sex difference (0.19 points faster decline per month in men, 95% CI: 0.06 – 0.31, p = 0.004). The results of the interaction of BNT change over time, PPA variant, and BNT baseline test score indicated that rates of decline by PPA variant were modified by BNT scores at the initial testing, where nfaPPA participants who had high BNT scores (25 points or more out of 30) at initial testing had significantly slower decline in BNT scores over time. Every 10-points higher in BNT score at initial testing in the nfaPPA subtype was associated with 0.26 points slower decline per month on the BNT compared with lvPPA and svPPA subtypes (95% CI: 0.20 – 0.31, p < 0.001). Participants with lvPPA had the smallest difference in rate of decline across the levels of BNT score at initial testing (p = 0.001 for initial BNT score x PPA subtypes interaction on rate of BNT decline over time.

Hopkins Assessment of Naming Actions

Baseline Assessment: Results for the baseline (initial visit) analyses showed a significant effect for sex and PPA variant (Table 6).

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Sex: After accounting for other variables in the statistical model, female participants, on average, scored 6.06 (95% CI: 1.91 – 10.21) points lower on the HANA than males at initial testing (p = 0.005).

PPA Variant: After accounting for other variables in the statistical model, participants with lvPPA, on average, scored 6.70 (95% CI: 2.00 – 11.40) points lower on the HANA than those with nfaPPA (p = 0.006) at initial testing. Participants with svPPA, on average, scored 12.31 (95% CI: 7.63 – 16.98) points lower in HANA than those with nfaPPA (p < 0.001) at initial testing.

Longitudinal Change: Results for the longitudinal analyses showed a significant effect for two and three factor interactions (Table 7).

Two factor Interactions.—Two factor interactions were significant for HANA change over time and sex, and HANA change over time and symptom duration. Results for the interaction of HANA change over time and sex indicated that female participants had slower decline than male participants (on average 0.16 points per month, 95% CI: 0.07 – 0.24, p < 0.001). Results for the interaction of HANA change over time and symptom duration indicated that participants who reported longer PPA duration at initial HANA testing had significantly slower progression, on average 0.002 (95% CI: 0.0009 – 0.003) points slower per month for every additional month of self-reported symptom duration across all PPA variants (p < 0.001).

Three factor interactions: Results were significant for HANA change over time, PPA variant, and HANA baseline test score, and for HANA change over time, HANA baseline score, and speech and language rehabilitation. Results for the interaction of HANA change over time, PPA variant, and HANA baseline score indicated that participants with nfaPPA who had high HANA scores (31 or more points out of 35) at initial testing had slower decline in HANA scores over time, with every 10-points higher in HANA score at initial testing associated with 0.18 points slower in HANA decline per month during follow up (95% CI: 0.14 – 0.21, p < 0.001). Results indicated that speech and language rehabilitation seemed to help slow decline in HANA scores over time, especially among those with higher HANA scores (31 or more points out of 35) at initial testing (95% CI: 0.001 – 0.09, p = 0.008.

Pyramids and Palm Trees

Baseline Assessment: Results for the baseline (initial visit) analyses showed a significant effect for race, symptom duration and PPA variant (Table 8).

Race: After accounting for other variables in the statistical model, nonwhite participants, on average, scored 0.60 (95% CI: 0.02 – 1.19) points higher on the PPTT than white participants at initial testing (p = 0.04).

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Symptom Duration: After accounting for other variables in the statistical model, participants with longer self-reported symptom duration, on average, scored 0.06 (95% CI: 0.02 – 0.10) points higher on the PPTT at initial testing ($p = 0.003$).

PPA Variant: After accounting for other variables in the statistical model, participants with svPPA, on average, scored 2.65 (95% CI: 1.41 – 3.89) points lower on the PPTT than those with nfaPPA ($p < 0.001$) at initial testing.

Longitudinal Change: Results for the longitudinal analyses showed a significant effect for two and three factor interactions (Table 9).

Two factor Interactions: Results were significant for PPTT change over time and speech and language rehabilitation. The results for the interaction of PPTT change over time and speech and language rehabilitation indicates that participants who received speech and language rehabilitation showed slower decline in PPTT scores over time (95% CI: −0.35 - −0.09, $p = 0.001$).

Three factor interactions: Results were significant for PPTT change over time, PPA variant, and PPTT baseline score, and for PPTT change over time, PPTT baseline score, and speech and language rehabilitation. Results for the interaction of PPTT change over time x PPA variant x PPTT baseline score indicated that participants with nfaPPA who had high PPTT scores (14 out of 14 points) at initial testing had significantly slower decline in PPTT scores over time. Every 10-points higher in PPTT score at initial testing in the nfaPPA subtype was associated with 0.21 points slower decline per month on the PPTT compared with lvPPA and svPPA subtypes (95% CI: 0.14 – 0.28, $p < 0.001$). Results for the interaction of PPTT change over time, PPTT baseline score, and speech and language rehabilitation and indicated that speech and language rehabilitation seemed to help slow decline in PPTT scores over time, especially among those with high PPTT scores (14 out of 14 points) at initial testing (95% CI: 0.06 – 0.24, $p = 0.002$).

Discussion

As expected, there was decline in performance in naming and semantic knowledge in all variants of PPA. PPA variants were distinguishable by rapidity of decline, although there were individual differences within each group (Figures 1–3). Across language tests, the most precipitous rates of decline occurred in nfaPPA, followed by svPPA, then lvPPA. We can speculate that this steep downward trajectory may be due in part to apraxia of speech in many nfaPPA participants. Many nfaPPA patients become mute early in their disease progression (Croot, Ballard, Leyton, & Hodges, 2012; Gorno-Tempini et al., 2006), thereby compromising performance on confrontation naming tests. In our nfaPPA group, 14 individuals demonstrated apraxia of speech as evidenced by variable articulation of words of increasing length (e.g., thick, thicken, thickening) and one individual was nearly mute (spoken output was limited to “yes” and “no”). Individuals with nfaPPA demonstrated more stable performance over time on the PPTT than the BNT and HANA indicating that semantic knowledge was relatively spared compared to object and action naming. This result is in line with the findings of Botha et al. (2015), who found that individuals with semantic

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dementia performed significantly more poorly on the PPTT than those with progressive apraxia of speech and progressive agrammatic aphasia.

Individuals with svPPA performed significantly more poorly on the BNT, HANA, and PPTT than individuals with lvPPA. Semantic knowledge was mostly intact for the logopenic variants, at least until late in the course of the disorder with less than one point decline per month. Corbett, Jefferies, Ehsan and Lambon Ralph (2009) reported that individuals with svPPA were able to complete straightforward item matching tasks, such as word-picture matching, but performed more poorly on associative picture-matching tasks like the PPTT.

Individuals with nfaPPA showed more precipitous decline on the HANA than individuals with lvPPA and svPPA (see Figure 2). This finding is in line with studies examining word class deficits in PPA, which have found greater verb-naming deficits in nfvPPA and greater noun-naming deficits in lvPPA and svPPA (e.g., Bak & Hodges, 2003; Hillis et al., 2004).

Female sex, longer symptom duration, higher baseline test score, and having at least some speech-language rehabilitation were associated with slower decline. Although female participants demonstrated significantly lower scores on the BNT and HANA than male participants at the initial (baseline) assessment, they experienced slower decline on test scores than male participants. One consideration was whether lower test scores among female participants reflected delays in seeking health care by women compared to men. For example, in a study of self-reported delays in health care, midlife women with diabetes or cardiovascular conditions were more likely to report delays in care than men, even after adjusting for insurance coverage (Ng et al., 2010). In our study, duration from symptom onset at initial presentation was slightly longer in women, although not significantly so (mean = 38.16$\pm$26.09 months) than men (mean = 37.25$\pm$24.11 months). Slower decline in female than male participants may be influenced by a number of factors not captured in this study (e.g., other health comorbidities, availability of support from family and friends). Although study findings are inconsistent, many lend support to the hypothesis that healthy women not only have a higher level of functional impairment than men but also experience a faster decline in general functional status after age 50 (Liang et al., 2008), a contrast to our more specific cognitive/language finding. Studies have not examined sex disparities in decline in PPA. However, gender differences in brain structure in healthy individuals have been reported, supporting the concept of sexual dimorphism in brain structures that may underlie gender differences in behavioral and cognitive functioning and the need to delineate pathophysiological mechanisms underlying sex differences in neuropsychiatric disorders (Sun et al, 2015).

Longer symptom duration was associated with higher test scores on the BNT and PPTT at initial testing, and longer symptom duration was associated with slower decline. These findings indicate that people with PPA who have slower rate of progression may wait longer to seek medical care for their problems. They still have milder symptoms (higher naming scores) than those with precipitous decline when they do present to the neurologist, and continue to have a slower decline.

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Also, as expected, having some speech-language rehabilitation was associated with slower decline on HANA and PPTT scores, especially for those with higher test scores. Word retrieval is an easily identifiable therapy target, and positive treatment effects have been reported in several studies in this population (e.g., Beeson et al., 2011; Henry et al., 2013; Jokel, Rochon, & Anderson, 2010; Jokel, Rochon, & Leonard, 2006; Meyer, Getz, Brennan, Hu, & Friedman, 2016; Meyer, Snider, Eckmann, & Friedman, 2015; Newhart et al., 2009). Results of this study suggest that therapy targets may differ depending upon the PPA variant. Therapy may focus upon naming of actions in lvPPA and naming of both objects and actions may be important in svPPA. Access to semantic knowledge may be a strength in nfaPPA, and a cueing hierarchy may be developed to access this relatively preserved ability. These findings also support referral for speech-language pathology intervention for those with PPA, a practice which may not be routine in the setting of neurodegenerative disease.

Surprisingly, age and education were not important prognostically for individuals in this study. These variables, however, are typically considered in estimating recovery from stroke (e.g., Suneja, Gonzalez-Fernandez, & Hillis, 2014).

Limitations of this study include that not all tests were given to all participants at all three time points; however all tests were administered to participants in each of the PPA variants. It should be noted that participants were initially tested when they first presented to clinic, which represents a variable time from disease onset in our statistical analysis. Another limitation was that this paper did not study decline focusing on all language tasks. Therefore, it is possible that other components of language (e.g., auditory comprehension) might have a different trajectory of decline in the three variants. A third limitation was that we did not investigate functional communication. The relationship between severity of language impairment and functional communication is complex. Fridriksson, Nettles, Davis, Morrow, and Montgomery (2006) reported that language impairment correlated with functional communication ability in individuals with aphasia as measured on the Communication Independence scale ($r(25) = .52$, $p = .004$) and the Qualitative Dimensions scale ($r(25) = .49$, $p = .006$) of the American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults (Frattali, Thompson, Holland, Wohl, & Ferketic, 1995). For the majority of individuals, language impairment was associated with decreased functional communication ability, although there were two exceptions in which language impairment did not correlate with real life communication ability. Finally, we did not include imaging data to study longitudinal decline. Future studies should include measures of language impairment, functional communication, and imaging data to clarify further the language and functional decline and anatomical progression of the disease in the three clinical variants of the disease.

In summary, patterns of decline in naming and semantic knowledge in the variants of PPA were investigated, and the effects of other variables (i.e., age, sex, race, symptom duration, speech-language rehabilitation, education, baseline test score, and PPA variant) on rate of decline were examined. A main strength of this study was that our data analysis accounted for variables thought to influence participants' change in performance over time. PPA variants were distinguishable by rapidity of decline, with nfaPPA having the most precipitous decline (unless they had high scores at baseline, in which case they had the

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slowest decline). These results indicate within the variant of nfaPPA there are both slow decliners and rapid decliners. As hypothesized, higher baseline test scores and speech-language rehabilitation were associated with slower decline. Our hypotheses regarding age and education were not supported. Further study of prognostically relevant variables is indicated in this population. The ability to predict decline in language and functional communication abilities, and thus advise individuals with PPA and their caregivers regarding future planning, would be invaluable clinically.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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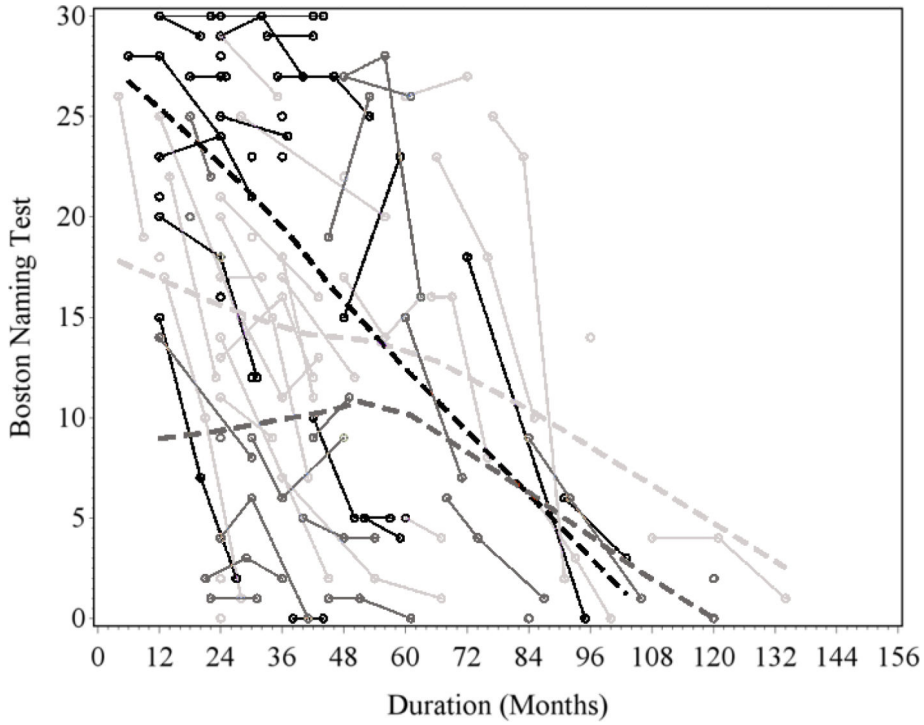

Figure 1:

Decline in Scores on the Boston Naming Test over Time in PPA Variants

lvPPA, logopenic primary progressive aphasia (light gray); nfaPPA, nonfluent agrammatic primary progressive aphasia (black); svPPA semantic variant primary progressive aphasia (medium gray); duration: symptom duration. The solid lines represent data points for each participants and the dashed lines represent the average decline for each variant.

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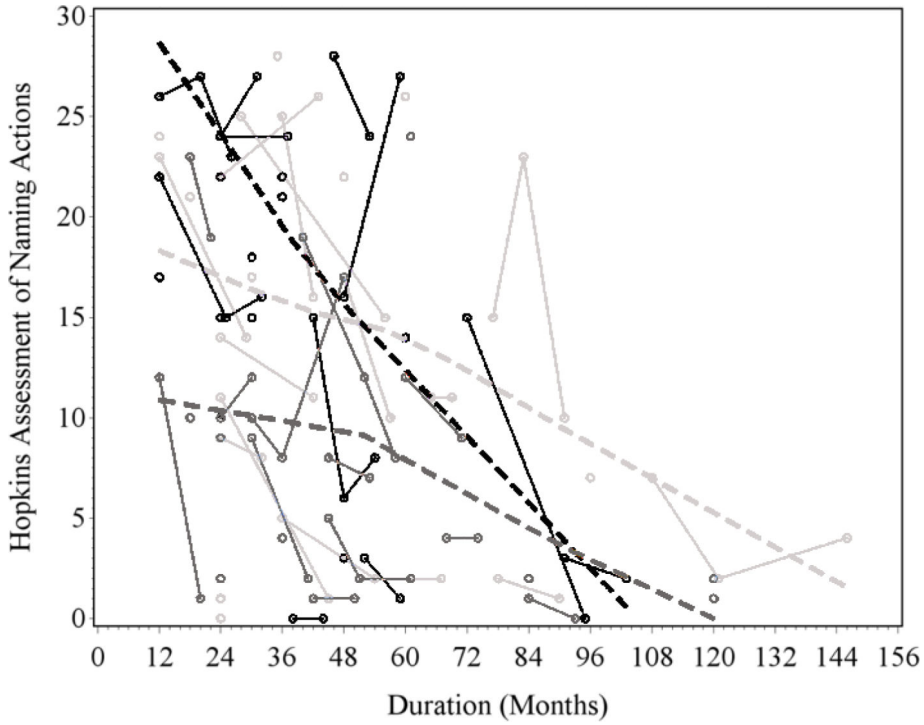

Figure 2:

Decline in Scores on the Hopkins Assessment of Naming Actions over Time in PPA Variants lvPPA, logopenic primary progressive aphasia (light gray); nfaPPA, nonfluent agrammatic primary progressive aphasia (black); svPPA semantic variant primary progressive aphasia (medium gray); duration: symptom duration. The solid lines represent data points for each participants and the dashed lines represent the average decline for each variant.

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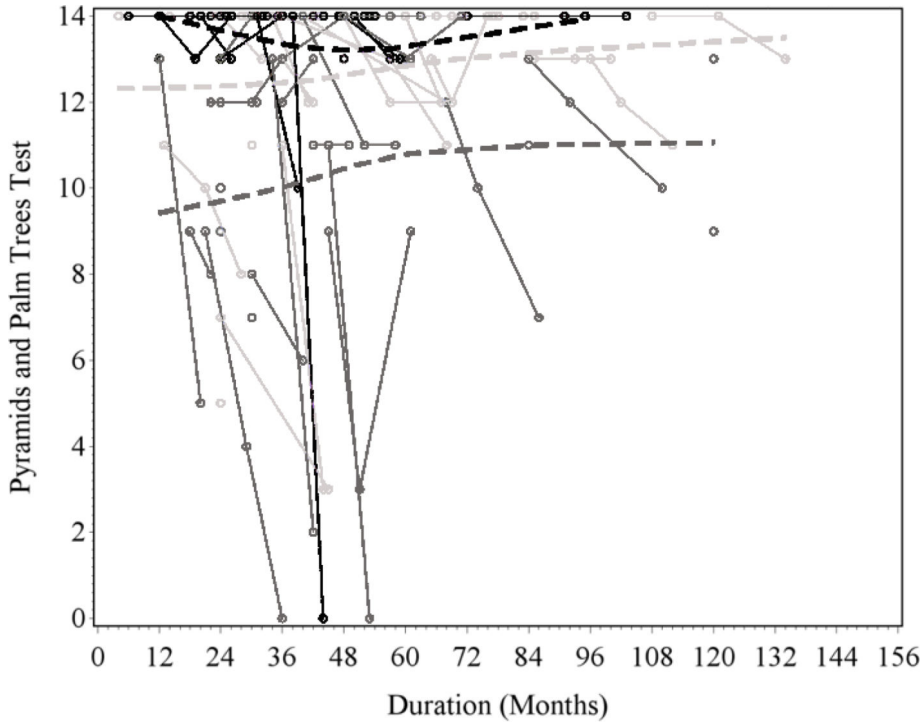

Figure 3:

Decline in Scores on the Pyramids and Palm Trees Test over Time in PPA Variants lvPPA, logopenic primary progressive aphasia (light gray); nfaPPA, nonfluent agrammatic primary progressive aphasia (black); svPPA semantic variant primary progressive aphasia (medium gray); duration: symptom duration. The solid lines represent data points for each participants and the dashed lines represent the average decline for each variant.

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Table 1:

Age, Education, Sex, Race and Symptom Duration for PPA Variants, and for Participants Overall

Variant	Age (yrs) (mean, SD)	Education (yrs)(mean, SD)	Sex (F) N (%)	Race (Nonwhite)N (%)	Symptom Duration (months)(mean, SD)
lvPPA(n=36)	69.28 (8.01)	16.56 (2.90)	24 (67)	3 (8)	39.44 (25.98)
nfaPPA(n=31)	67.68 (9.61)	15.77 (2.58)	20 (65)	5 (16)	30.55 (19.45)
svPPA(n=27)	64.11 (7.39)	15.78 (2.01)	14 (52)	3 (11)	43.96 (28.72)
Overall(n=94)	67.27 (8.59)	16.07 (2.57)	58 (62)	11 (12)	37.81 (25.22)
P values	0.057	0.361	0.479	0.609	0.114

F, female; SD, standard deviation; yrs, years; mos, months; lvPPA, logopenic variant primary progressive aphasia; nfaPPA, nonfluent agrammatic primary progressive aphasia; svPPA semantic variant primary progressive aphasia

*p values were calculated using one-way ANOVA for age, education, and symptom duration and using chi square for sex and race

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Table 2:

Number and Percentages of Individuals Tested at Time Points 1, 2 and 3 by PPA Variants

	BNT			HANA			PPTT		
Variant	**Time 1 Number (%)**	**Time 2 Number (%)**	**Time 3 Number (%)**	**Time 1 Number (%)**	**Time 2 Number (%)**	**Time 3 Number (%)**	**Time 1 Number (%)**	**Time 2 Number (%)**	**Time 3 Number (%)**
lvPPA(n=36)	32 (89)	24 (67)	12 (33)	23 (64)	14 (39)	5 (14)	36 (100)	28 (78)	15 (42)
nfaPPA(n=31)	29 (94)	18 (58)	8 (26)	28 (90)	16 (52)	6 (19)	30 (97)	20 (65)	7 (23)
svPPA(n=27)	24 (89)	16 (59)	7 (26)	21 (78)	13 (48)	3 (11)	27 (100)	18 (67)	7 (26)
P values	0.839			0.826			0.312		

lvPPA, logopenic variant primary progressive aphasia; nfaPPA, nonfluent agrammatic primary progressive aphasia; svPPA semantic variant primary progressive aphasia; BNT, Boston Naming Test; HANA, Hopkins Assessment of Naming Actions; PPTT, Pyramids and Palm Trees Test

*p values were calculated using chi square

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Table 3:

Comparison of Overall Differences in Rates of Decline per Month with Nonfluent Primary Progressive Aphasia by Test

	BNT			HANA			PPTT		
	Rate	**95% CI**	**P value**	**Rate**	**95% CI**	**P value**	**Rate**	**95% CI**	**P value**
lvPPA(n=36)	0.24	0.09–0.39	0.002	0.10	−0.005– 0.21	0.06	0.01	−0.005– 0.04	0.14
svPPA(n=27)	0.35	0.20–0.50	<0.001	0.23	0.12– 0.33	<0.001	0.05	0.02–0.07	0.001

BNT, Boston Naming Test; HANA, Hopkins Action Naming Assessment; PPTT, Pyramids and Palm Trees Test; CI, confidence interval; lvPPA, logopenic variant primary progressive aphasia; svPPA, semantic variant primary progressive aphasia

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Table 4:

Model-Based Estimates of Boston Naming Test Scores at Baseline Associated with Demographic and Clinical Characteristics

Characteristic	Comparison	Estimate	95% CI	P value
Age	Per Year Increase	−0.06	−0.21 – 0.09	0.42
Education	Per Year Increase	0.15	−0.15 – 0.45	0.33
Sex	Female vs Male	−3.69	−6.92 – −0.45	0.03
Race	Nonwhite vs White	−1.52	−4.69 – 1.66	0.34
Symptom Duration	Per Month Increase	0.18	0.05 – 0.31	0.008
PPA Variant	lvPPA vs nfaPPA	−2.57	−7.90 – 2.76	0.34
	svPPA vs nfaPPA	−10.31	−16.22 – −4.39	0.001
Therapy	With vs Without Therapy	−1.45	−5.64 – 2.75	0.49

CI, confidence interval; lvPPA, logopenic variant primary progressive aphasia; nfaPPA, nonfluent agrammatic primary progressive aphasia; svPPA, semantic variant primary progressive aphasia

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Table 5:

Model-based Estimates of Changes in Boston Naming Test Scores over Time (Points per Month) Associated with Demographic and Clinical Characteristics

Characteristic	Comparison	Estimate	95% CI	P value
Sex	Female vs Male	0.19	0.06 – 0.31	0.004
Symptom Duration	Per Month Increase	0.002	0.0007 – 0.003	0.002
PPA Variant	nfaPPA	−0.91	−1.07 – −0.74	<0.001
	lvPPA vs nfaPPA	0.24	0.09 – 0.39	0.002
	svPPA vs nfaPPA	0.35	0.20 – 0.50	<0.001
Therapy	With vs Without Therapy	0.03	−0.07 – 0.14	0.53
PPA Variant by Baseline Test Score, per 10 Point Increase	nfaPPA	0.26	0.20 – 0.31	<0.001
	lvPPA vs nfaPPA	−0.13	−0.20 – −0.06	<0.001
	svPPA vs nfaPPA	−0.08	−0.15 – −0.02	0.02

CI, confidence interval; BNT, Boston Naming Test; lvPPA, logopenic variant primary progressive aphasia; nfaPPA, nonfluent agrammatic primary progressive aphasia; svPPA, semantic variant primary progressive aphasia

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Table 6:

Model-Based Estimates of Hopkins Assessment of Naming Actions Scores at Baseline Associated with Demographic and Clinical Characteristics

Characteristic	Comparison			
		Estimate	95% CI	P value
Age	Years	−0.08	−0.19 – 0.03	0.16
Education	Years	−0.09	−0.47 – 0.30	0.66
Sex	Female vs Male	−6.06	−10.21 – −1.91	0.005
Race	Nonwhite vs White	−1.03	−3.89 – 1.84	0.48
Symptom Duration	Months	0.11	−0.04 – 0.26	0.14
PPA Variant	lvPPA vs nfaPPA	−6.70	−11.40 – −2.00	0.006
	svPPA vs nfaPPA	−12.31	−16.98 – −7.63	<0.001
Therapy	With vs Without Therapy	0.14	−3.91 – 4.19	0.95

CI, confidence interval; lvPPA, logopenic variant primary progressive aphasia; nfaPPA, nonfluent agrammatic primary progressive aphasia; svPPA, semantic variant primary progressive aphasia

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Table 7:

Model-Based Estimates of Changes in Hopkins Assessment of Naming Actions Test Scores over Time (Points per Month) Associated with Demographic and Clinical Characteristics

Characteristic	Comparison	Estimate	95% CI	P value
Sex	Female vs Male	0.16	0.07 – 0.24	<0.001
Symptom Duration	Months	0.002	0.0009 – 0.003	<0.001
PPA Variant	nfaPPA	−0.76	−0.92 – −0.60	<0.001
	lvPPA vs nfaPPA	0.10	−0.005 – 0.21	0.06
	svPPA vs nfaPPA	0.23	0.12 – 0.33	<0.001
Therapy	With vs Without Therapy	−0.05	−0.12 – 0.01	0.10
PPA Variant by Baseline Test Score, per 10 Point Increase	nfaPPA	0.18	0.14 – 0.21	<0.001
	lvPPA vs nfaPPA	−0.01	−0.05 – 0.03	0.65
	svPPA vs nfaPPA	−0.03	−0.07 – 0.01	0.13

CI, confidence interval; lvPPA, logopenic variant primary progressive aphasia; nfaPPA, nonfluent agrammatic primary progressive aphasia; svPPA, semantic variant primary progressive aphasia

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Table 8:

Model-Based Estimates of Pyramids and Palm Trees Scores at Baseline Associated with Demographic and Clinical Characteristics

Characteristic	Comparison	Estimate	95% CI	P value
Age	Years	0.005	−0.03 – 0.04	0.77
Education	Years	−0.06	−0.20 – 0.08	0.43
Sex	Female vs Male	−0.77	−1.80 – 0.26	0.14
Race	Nonwhite vs White	0.60	0.02 – 1.19	0.04
Symptom Duration	Months	0.06	0.02 – 0.10	0.003
PPA Variant	lvPPA vs nfaPPA	−0.45	−1.35 – 0.45	0.32
	svPPA vs nfaPPA	−2.65	−3.89 – −1.41	<0.001
Therapy	With vs Without Therapy	0.62	−0.34 – 1.57	0.20

CI, confidence interval; lvPPA, logopenic variant primary progressive aphasia; nfaPPA, nonfluent agrammatic primary progressive aphasia; svPPA, semantic variant primary progressive aphasia

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Table 9:

Model-Based Estimates of Changes in Pyramids and Palm Trees Test Scores over Time (Points per Month) Associated with Demographic and Clinical Characteristics

Characteristic	Comparison	Estimate	95% CI	P value
Sex	Female vs Male	0.02	−0.01 – 0.04	0.22
Symptom Duration	Months	0.00004	−0.0003 – 0.0004	0.82
PPA Variant	nfaPPA	−0.35	−0.44 – −0.26	< 0.001
	lvPPA vs nfaPPA	0.01	−0.005 – 0.04	0.14
	svPPA vs nfaPPA	0.05	0.02 – 0.07	0.001
Therapy	With vs Without Therapy	−0.22	−0.35 – 0.09	0.001
Baseline Test Score, per 10 Point Increase	With Therapy	0.21	0.14 – 0.27	< 0.001
	With vs Without Therapy	0.15	0.06 – 0.24	0.002

CI, confidence interval; lvPPA, logopenic variant primary progressive aphasia; nfaPPA, nonfluent agrammatic primary progressive aphasia; svPPA, semantic variant primary progressive aphasia