INTERNATIONAL RECOMMENDATIONS FOR THE DIAGNOSIS OF PRIMARY PROGRESSIVE APHASIA AND ITS VARIANTS

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ABSTRACT

This paper provides diagnostic recommendations for three variants of primary progressive aphasia (PPA) to improve the uniformity of case reporting and reliability of research results. Criteria for the three variants of PPA – nonfluent, semantic, and logopenic – were developed by an international group of PPA investigators who convened on three occasions to operationalize earlier published clinical descriptions for PPA subtypes. Patients are first diagnosed with PPA and are then divided into clinical variants based on specific speech and language features characteristic of each subtype. Diagnoses can then be further specified as "imaging-supported" if the expected pattern of atrophy is found and "with definite specified pathology" if pathological or genetic data are available. The working recommendations are presented in lists of features, and suggested assessment tasks are also provided. These recommendations have been widely agreed upon by a large group of experts and should be used to ensure consistency of PPA classification in future studies. Future collaborations will collect prospective data to identify relations between each of these syndromes and specific biomarkers for a more detailed understanding of clinico-pathological correlations.

BACKGROUND

A progressive disorder of language associated with atrophy of the frontal and temporal regions of the left hemisphere was first described in the 1890's by Pick [1] and Serieux [2]. In the modern literature, Mesulam [3] described a series of cases with "slowly progressive aphasia," subsequently renamed "primary progressive aphasia" (PPA) [4]. Warrington [5] described a progressive disorder of semantic memory in 1975. The condition was also described by Snowden as "semantic dementia" (SD) [6]. In the early 1990s, Hodges and colleagues provided

a comprehensive characterization of semantic dementia [7]. Subsequently, Grossman described a different form of progressive language disorder, termed progressive nonfluent aphasia [8]. A consensus meeting attempted to develop criteria for these conditions in relation to frontotemporal lobar degeneration [9].

For about two decades, cases of PPA were generally categorized as semantic dementia or progressive nonfluent aphasia, or in some studies as "fluent" versus "nonfluent". However, there were a number of PPA cases who did not seem to fit a binary classification [10], and a third clinical variant was empirically described and termed logopenic progressive aphasia by Gorno-Tempini and colleagues [11]. At a meeting of the World Federation of Neurology Research Group on Aphasia and Cognitive Disorders in Buenos Aires in March of 2006, a large number of investigators of PPA reviewed videotapes of patients with PPA, to determine the degree of agreement on these classifications and on the terms "fluent" versus "nonfluent". It became apparent that there were some patients categorized as nonfluent by some investigators and as fluent by others. Some considered PPA a spectrum disorder and emphasized the changing language pattern during the course of the disease [12].

Identifying speech and language criteria for each of the PPA variants is important for scientific exchange across laboratories studying the cognitive, neuroanatomic, and molecular basis for the observed difficulties in these patients. The collection of data on the presence or absence of each criterion, along with autopsy and genetic data, will allow determination of the value of these criteria, potentially supplemented by other biomarkers, for predicting pathology. Widely accepted clinical criteria will become essential in the coming years as a new generation of disease-modifying treatment options emerge.

Development of "Criteria" for PPA Variants

A group of experienced clinicians met at the University of California San Francisco in 2006 to discuss a potential classification system for PPA. The group reviewed video presentations of PPA cases and scored salient speech and language features using a checklist. An analysis of the observed features revealed a high level of agreement. There were 17 clinical features in which experts agreed over 80% of the time. Using these features, we developed initial PPA variant criteria.

Group members tested these criteria within their own research programs and then reconvened in 2009 at the American Academy of Neurology meeting in Seattle to discuss their findings. The majority of members believed the criteria were useful for classifying PPA into three variants. Further refinements of the criteria took place by email. It was widely agreed that the criteria should be used to classify PPA patients for research studies and to provide a checklist for future studies to evaluate the usefulness of each criterion for predicting pathology and/or genetics.

The proposed guidelines are meant to capture patients with the most common presentations of PPA, and are intended to be most applicable in patients at the relatively early stages of the disease, at about two years after onset of symptoms. It was also recognized that some patients may have isolated language symptoms (such as anomia or dyslexia), without reaching all criteria for a particular variant, or may have features characteristic of more than one PPA variant. Although these patients will remain "unclassifiable" at present, their clinical syndrome may become clearer as disease progresses, and their data will nevertheless be useful in future studies that refine correlations of behavioral criteria with pathology and genetics.

Relationship between Behaviorally-Defined PPA Variants and Biomarkers

Considerable advances have been made in characterizing neuroimaging and biological features of PPA and it was collectively decided to incorporate these findings into the classification system. These correlations, though included in the criteria, still require additional empirical testing.

Brain atrophy in PPA was initially thought to encompass widespread perisylvian regions within the left hemisphere [3]. Later studies reported associations between PPA variants and particular patterns of neuroanatomical damage. Specifically affected are the left posterior frontal region in nonfluent progressive aphasia [13; 8; 14], the anterior temporal region in semantic dementia [7; 15], and left temporo-parietal regions in the logopenic variant.

PPA is a clinical syndrome with heterogeneous pathological causes. At autopsy, most patients with PPA have been found to have tau-positive pathology, ubiquitin/TDP-43–positive, tau-negative frontotemporal lobar degeneration (FTLD) pathology [16; 17; 14], or Alzheimer's disease (AD) pathology [18; 19]. Progressive nonfluent aphasia is most often caused by tau-positive pathology, particularly corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP) [14; 20]. Semantic dementia has often been associated with ubiquitin-positive, TDP-43–positive pathology [16; 21; 22; 23]. The logopenic variant has mostly been associated with AD pathology and with in-vivo biomarkers suggestive of AD, such as PET-PIB positivity, apoEe4 genotype, and decreased $A\beta_{42}$ and increased tau in the CSF [14; 24; 25]. Currently, clinical-pathological correlations reflect group-wide probabilities; more studies, with consistent clinical descriptions and larger numbers of patients, must determine if there are reliable associations between clinical symptoms and histopathology.

PPA can be inherited in an autosomal-dominant manner; the majority of these patients have mutations in the progranulin (*GRN*) gene [26; 27; 28]. The PPA phenotype associated with a *GRN* mutation has not been studied in detail. Initial reports indicated prominent anomia without development of motor speech impairment and relatively early single word comprehension impairment [29; 26; 27; 30; 31]. Other genes related to FTLD, such as the microtubule-associated protein tau *(MAPT)* gene, may be associated with PPA as well [26 28]. It is not yet clear how the guidelines reported here will apply to genetic cases.

Terminology

The terms used to label the three variants were a matter of extensive discussion. It was recognized that many previous reports likely included logopenic patients within the category of progressive nonfluent aphasia (or less often, semantic dementia), and that "nonfluent" is a term that depends on weighing multiple dimensions of spoken output (melody, prosody, grammatical structure, speech rate, articulatory agility, and so on). It was agreed that agrammatism is a salient feature of the nonfluent variant. "Logopenic" was also a controversial term, meaning a paucity of words. All variants can literally be logopenic, so the term required consideration in the context of minimally impaired articulation, grammar, and semantics. The term "semantic dementia" was also controversial, because "dementia" typically refers to progressive impairment in multiple domains of cognition. The terminology proposed here represents a compromise between the existing literature and current understanding of the phenomenology. Abbreviations were selected to parallel the abbreviation of behavioral variant FTD (bvFTD) but complete was not reached on this topic. It is advisable to include the older terms in the keywords of new articles, to improve

homogeneity when using literature search engines. Furthermore, these guidelines can be referred to even when using the older terminology.

WORKING RESEARCH CRITERIA

Diagnostic Process and the PPA Classification

Establishing a classification or "diagnosis" involves a two-step process. Patients should first meet basic PPA criteria, based on Mesulam's initial guidelines [32; 33] (see Table 1). A PPA diagnosis requires a prominent, isolated language deficit during the first two years of the disease. There is an insidious onset and gradual progressive impairment of language production, object naming, syntax or word comprehension that is apparent during conversation or through speech and language assessments. Activities of daily living are maintained except those related to language (i.e., using the telephone). Other cognitive functions may be affected after the first two years of illness, but language remains the most impaired domain throughout the course of the illness [33; 34].

Exclusionary criteria include prominent episodic and nonverbal memory loss and visuospatial impairment during the initial two years of illness. Specific causes of aphasia, such as stroke or tumor, are absent, as ascertained by neuroimaging. Behavioral disturbances can be early features in PPA (especially in the nonfluent and semantic variants), but they should not be the main complaint or the main cause of functional impairment. Effortful speech and motor speech (articulation) errors can, in some cases, be the earliest signs of PPA. However, cases with severe, isolated spastic dysphonia or repetitive language behaviors, such as palilalia or echolalia, should be excluded from the PPA syndrome because their deficit is non-linguistic in nature.

Classification into PPA variants

Once a PPA diagnosis is established, the presence or absence of salient and prominent speech and language features should be considered to diagnose one of the main PPA variants. Clinical criteria for nonfluent, semantic, and logopenic variants are detailed in Tables 2 through 4. Suggested tasks for assessing speech and language functions are presented in Table 5.

The classification of PPA into one of the variants may occur at one of three levels: clinical, imaging-supported, or definite pathological diagnosis. Clinical diagnosis occurs when a case presents with speech and language features that are characteristic of a specific variant. At least one of the "core features" should be present for the nonfluent variant, while both must be present for semantic and logopenic variants. At least three of the other features should be present in order to make a clinical diagnosis of a specific syndrome. Future studies will determine if there is a more useful combination of features. Some authors argued for a simpler approach to PPA subtyping (into PPA-agrammatic, logopenic and semantic) based on tasks of word comprehension and sentence construction [35], but there was general agreement that a more extended approach might be better suited for a multi-centric approach, since different language measures might be implemented at each site.

For an "imaging-supported" diagnosis, the next level of classification, a case should meet clinical diagnosis but should also show the distribution of neuroimaging changes (structural or functional imaging) previously associated with each variant. Since there is a direct, although still relatively imprecise, correspondence between language symptoms and site of anatomical damage, a consistent pattern of imaging change can support the clinical diagnosis.

The third level, a "definite pathology" diagnosis, refers to cases that present with typical clinical characteristics (with or without neuroimaging evidence) of each variant and pathologic or genetic mutations associated with "definite" or known frontotemporal lobar degeneration (FTLD) spectrum (tau– or TDP-43–positive FTLD) pathology, AD pathology, or other specific etiology. The presence of "definite pathology" does not imply that the clinical syndrome is better defined clinically, but only that it has been associated with a known biological feature.

Nonfluent Variant PPA (NFV-PPA; also known as progressive nonfluent aphasia or PNFA, and as PPA agrammatic or PPA-G)

The criteria for NFV-PPA are summarized in Table 2. Agrammatism and effortful speech are the core criteria for NFV-PPA, and at least one should be present. Agrammatism typically consists of short, simple phrases (reduced mean length of utterance) and omissions of grammatical morphemes (e.g., function words, inflections). Agrammatism can often be mild in PPA when compared to vascular aphasia, especially in the early stages of the disease. Therefore, constrained-syntax sentence production tests might be needed (see Table 5) [36]. Effortful speech is the second core criterion for this variant. This refers to labored speech production. An articulation planning deficit, i.e., apraxia of speech, is the most common disturbance, and can be the initial feature [11; 14]. Irrespective of the cause (motor planning or linguistic), patients with NFV-PPA typically make inconsistent speech sound errors, consisting of distortions, deletions, substitutions, insertions, and/or transpositions of speech sounds, of which they are aware. Prosody is disrupted, and rate of speech is markedly reduced [11; 37]. Although isolated motor speech deficits, such as prominent, isolated dysarthria

or palilalia, are excluded by a core PPA clinical syndrome, it should be noted that effortful speech and production errors can often be the first symptoms of this variant, even before clear apraxia of speech or agrammatic errors occur. In these cases, a written production test (such as a written description of a picture) or syntax comprehension tasks can often reveal grammatical errors.

At least two of the other three features of NFV-PPA should be present. Sentence comprehension is impaired for the most difficult syntactic constructions, such as negative passives and object relative clauses (e.g., "The picture was not given by a girl") [8; 38; 9; 11; 39]. While sentence comprehension can also be impaired in logopenic and semantic variants, in NFV-PPA the impairment is clearly influenced by the grammatical complexity of the sentence. Single-word comprehension and object knowledge are usually spared in the NFV-PPA until late in the disease course, and this sparing is usually helpful in early differential diagnosis.

Imaging abnormalities in the left posterior fronto-insular region, i.e. inferior frontal gyrus, insula, premotor and supplementary motor areas, are necessary to make a diagnosis of "imaging-supported" NFV-PPA.

Cases will be defined as NFV-PPA with definite pathology when patients present with the clinical features of NFV-PPA, imaging-supported or not, and a known histopathological picture. In the case of NFV-PPA, patients will most often show FTLD-tau or FTLD-U type pathological changes.

Semantic Variant PPA (SV-PPA; also known as semantic dementia or SD, and as semantic PPA or PPA-S)

The semantic variant is probably the most consistently defined PPA clinical syndrome. The criteria are summarized in Table 3. In the current guidelines, anomia and single word comprehension deficits are considered the core features, both essential for a semantic variant diagnosis. Although naming problems are present in other variants of PPA and in other neurodegenerative conditions, in SV-PPA the disturbance is very severe, particularly when compared to relative sparing of other language domains. Single-word comprehension is also severely impaired, especially for low familiarity items (e.g., 'zebra' versus the more familiar/frequent 'cat'). Low familiarity words can be the only impaired items at the earliest stages. There may be a dissociation between repeating (preserved) and defining the meaning (impaired) of low frequency, words such as hippopotamus [40]. Poor comprehension of single words is usually the earliest and most obvious manifestation of a widespread semantic memory deficit that causes impairments in object and people recognition, also when presented from other modalities of input such as visual (pictorial representations and real objects), tactile, olfactory, and gustatory [6; 7; 41; 42; 43]. Semantic deficits in other modalities of input are therefore included among the other diagnostic features of SV-PPA, three of which must be present for clinical diagnosis. Multimodal semantic deficits are usually present for most categories, although rarer cases have been described with greater, or even selective, deficits for people and animals [44; 45]. Others describe worse performance with concrete object concepts than abstract concepts [5; 46]. These cases are usually associated with greater right temporal atrophy (see below) and early behavioral changes, such as loss of empathy and compulsions [47].

Surface dyslexia and dysgraphia are also features of SV-PPA and refer to an impairment in reading and writing words with irregular spellings [48]. Patients typically "regularize" irregularly spelled words, so that "colonel" is read as /kolonel/ and "tomb" is written as "t-o-o-m". Surface errors have recently been conceptualized as another symptom of general semantic memory impairment [49].

Sparing of repetition and motor speech, even when semantic deficits are prominent, are the other two features. Although language production sounds grammatically accurate, it can at times contain some "paragrammatic" errors, such as substituting less appropriate closed class words or inflections [50].

Anatomically, the SV-PPA has very consistently been associated with atrophy in the ventral and lateral portions of the anterior temporal lobes bilaterally, although damage is usually greater on the left [15; 51; 52; 11]. Neuroanatomical involvement is usually relatively focal and quite prominent, making it a very useful feature in the diagnostic process.

Cases will be defined as SV-PPA with definite pathology when patients present with the clinical features of SV-PPA, imaging-supported or not, and a known histopathological picture. In the case of SV-PPA, FTLD-U type pathological changes will be the most common finding.

Logopenic Variant PPA (LV-PPA; also known as logopenic progressive aphasia or LPA, and as logopenic PPA or PPA-L)

LV-PPA is the most recently described variant of PPA [11; 53]. The criteria are summarized in Table 4. Word retrieval (in spontaneous speech and confrontation naming) and sentence repetition deficits are the core features of LV-PPA. Spontaneous speech is characterized by slow rate, with frequent pauses due to significant word finding problems, but there is no

agrammatism, no distortions (a sign of articulation deficits) and no prosodic deficits. The language production deficit is therefore distinct from that of patients with the NFV-PPA, who also speak in a slow and halting manner, but with output that is dysprosodic, and marked by motor speech errors and agrammatism [8; 53; 54]. The confrontation naming impairment in LV-PPA is usually less severe than in SV-PPA [11]. LV-PPA is easily differentiated from SV-PPA because single-word comprehension is characteristically spared early in the disease.

Consistent with the hypothesis that a phonological short-term memory deficit is a key cognitive mechanism underlying most language deficits in LV-PPA variant [53], sentence and phrase repetition is characteristically impaired, while reproduction of short, single words can be spared. This same mechanism can cause impairment in sentence comprehension in LV-PPA, which is influenced more by length and frequency of a sentence than its grammatical complexity.

Other diagnostic features include phonological paraphasias in spontaneous speech and naming. The sound substitutions that cause phonological paraphasia in LV-PPA can be difficult to distinguish from motor speech errors typical of the NFV-PPA. To be noted is that sound errors in LV-PPA are usually well articulated, without distortion. Sparing of single word comprehension and general semantics differentiate LV-PPA from SV-PPA, while absence of agrammatism and motor speech errors (no distortions) distinguish it from NFV-PPA. In particular, patients with LV-PPA do not produce the telegraphic speech with missing function words and morphemes, which is characteristic of Broca's aphasia and of some patients with NFV-PPA.

Imaging abnormalities in the left temporo-parietal junction area, i.e., posterior superior and middle temporal gyri and supramarginal and angular gyri, are necessary to make a diagnosis of "imaging-supported" LV-PPA [11].

Cases will be defined as LV-PPA with definite pathology when they present with the clinical features of LV-PPA, imaging-supported or not, and a known histopathological picture. In the case of LV-PPA, recent evidence shows that AD might be the most common underlying pathology.

Conclusion

We have delineated a list of working criteria or guidelines that can be used to classify PPA variants for clinical and research purposes. Uniformity in diagnosis for research is essential for ensuring reliable results in future studies that may seek to define the underlying biology of disease in specific PPA variants. Ultimately, accurate classification is essential for studies that group patients for treatment purposes (e.g., tau-related disorders must be identified for trials of medications targeting tau). Improved clinico-pathological correlations will be helped by the development of better biomarkers (e.g., molecular PET imaging or CSF markers) that will allow underlying, tau, TDP-43 or AD pathology to be diagnosed in life. For this purpose, we encourage investigators to collect biofluid and pathological and genetic data along with a checklist of all criteria that were observed in the patient (1) at presentation, and (2) before death, for future large-scale collaborative investigations.

There are a number of outstanding challenges in the field of PPA research. Determining the primary cognitive deficit in the NFV-PPA is a matter of much debate. Agrammatism and motor speech errors characteristic of NFV-PPA may be quite subtle initially and difficult to

detect with clinical measures. Also, some patients may present with predominant apraxia of speech, which has led many to question whether the introduction of a separate syndrome of "progressive apraxia of speech" may be more appropriate for these cases [14], although all such cases do appear to eventually develop an aphasia as the disease progresses. Developing reliable and objective measures that capture patients early in the disease process is very important. Toward this end, more longitudinal studies of PPA are required, particularly for LV-PPA, which is the least consistently defined presentation. In addition, the features of genetic forms of PPA need to be studied in more detail, to identify whether the phenotypes fit into one of the three variants or present as a separate or mixed PPA phenotype. Finally, SV-PPA is a relatively homogeneous syndrome typically associated with TDP-43 pathology, but larger pathological series are needed to determine how such cases can be distinguished in vivo from rarer cases with dementia with Pick bodies or AD.

Despite these outstanding challenges, these guidelines are an attempt to provide a common approach to PPA patient classification across centers. Future studies aimed at identifying associations between subtypes and specific imaging, genetic, or pathological findings will be more interpretable if these guidelines are utilized across centers.

Table 1. Inclusion and Exclusion Criteria for the Diagnosis of Primary Progressive Aphasia (modified from Mesulam, 2003)

INCLUSION: Criteria 1 through 3 must be answered positively
1. Most prominent clinical feature is difficulty with language (word-finding deficits, paraphasias, effortful speech, grammatical and/or comprehension deficits) 2. These deficits are the principal cause of impaired daily living activities (e.g., problems with communication activity related to speech and language, such as using the telephone) 3. Aphasia should be the most prominent deficit for approximately two years since symptom onset.
EXCLUSION: Criteria 1 through 4 must be answered negatively for a PPA diagnosis
1. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders (e.g., neoplasm, cerebrovascular disease, hypothyroidism, etc.) 2. Cognitive disturbance is better accounted for by a psychiatric diagnosis (e.g., depression, bipolar disorder, schizophrenia, pre-existing personality disorder) 3. Prominent initial episodic memory, visual memory and visuo-perceptual impairments (e.g., inability to copy simple line drawings) 4. Prominent initial behavioral disturbance (e.g., marked disinhibition, emotional detachment, hyperorality or repetitive/compulsive behaviors)

Table 2. Diagnostic features for the nonfluent variant PPA (NFV-PPA; also known as progressive nonfluent aphasia or PNFA, and as agrammatic PPA or PPA-G**)** .

I. Clinical Diagnosis of NFV-PPA
At least one of the following **core features** must be present: 1. Grammatical errors and simplification in language production 2. Effortful, halting speech with inconsistent distortions, deletions, substitutions, insertions, or transpositions of speech sounds, particularly in polysyllabic words (often considered to reflect "apraxia of speech") At least two of three of the following **other** features must be present: 1. Impaired comprehension of syntactically complex sentences, with relatively spared comprehension of syntactically simpler sentences 2. Spared content, single word comprehension 3. Spared object knowledge
II. Imaging-Supported NFV-PPA Diagnosis
Both of the following criteria must be present: 1. Clinical diagnosis of NFV-PPA 2. Imaging must show one or more of the following results: a. Predominant left posterior fronto-insular atrophy on MRI b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET

III. NFV-PPA with Definite Pathology:
Clinical diagnosis (Criteria 1 below) and either Criterion 2 or 3 must be present:
1. Clinical diagnosis of NFV-PPA
2. Histopathological evidence of a specific pathology (e.g., FTLD-tau, FTLD-TDP) on biopsy or at post-mortem
3. Presence of a known pathogenic mutation

Table 3. Diagnostic Criteria for the Semantic Variant PPA (SV-PPA; also known as Semantic Dementia or PPA-S)

I. Clinical Diagnosis of SV-PPA:
Both of the following **core features** must be present: 1. Poor confrontation naming (of pictures or objects), particularly for low familiarity or low frequency items 2. Impaired single-word comprehension At least three of the following **other** diagnostic features must be present: 1. Poor object and/or person knowledge, particularly for low frequency or low familiarity items 2. Surface dyslexia and/or dysgraphia 3. Spared repetition 4. Spared motor speech
II. Imaging-Supported SV-PPA Diagnosis
Both of the following criteria must be present: 1. Clinical diagnosis of SV-PPA 2. Imaging must show one or more of the following results: a. predominant anterior temporal lobe atrophy b. predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

III. SV-PPA with Definite Pathology
Clinical diagnosis (Criteria 1 below) and either Criterion 2 or 3 must be present: 1. Clinical diagnosis of SV-PPA 2. Histopathological evidence of a specific pathology (e.g., FTLD-tau, FTLD-TDP) on biopsy or at post-mortem 3. Presence of a known pathogenic mutation

Table 4. Diagnostic criteria for Logopenic Variant PPA (LV-PPA; also known as Logopenic Progressive Aphasia or LPA, and as logopenic PPA or PPA-L)

I. Clinical Diagnosis of LV-PPA:
Both of the following **core features** must be present: 1. Impaired single-word retrieval in spontaneous speech (speech fluency interrupted by word finding pauses) and confrontational naming 2. Impaired repetition of sentences and phrases At least three of the following **other** features must be present: 1. Speech sound (phonological) errors in spontaneous speech and naming 2. Spared single word comprehension and object knowledge 3. Spared motor speech (no distortions) 4. Absence of frank agrammatism
II. Imaging-Supported LV-PPA Diagnosis:
Both criteria must be present: 1. Clinical diagnosis of LV-PPA 2. Imaging must show at least one of the following results: a. predominant left posterior perisylvian or parietal atrophy on MRI b. predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET

III. LV-PPA with Definite Pathology:
Clinical diagnosis **(**Criterion 1 below) and either Criterion 2 or 3 must be present: 1. Clinical diagnosis of LV-PPA 2. Histopathological evidence of a specific pathology (usually AD in this case) on biopsy or at post-mortem 3. Presence of a known pathogenic mutation.

Table 5. Tasks that may be used to assess speech and language functions in PPA.

SPEECH/LANGUAGE FUNCTION	**TASK**	**OBSERVABLE BEHAVIORAL MEASURES**
Grammatical language production	Picture description task Story re-telling (e.g., picture aided) Constrained-syntax sentence production task	Grammatical structure; mean length of utterance; speech rate; word-finding; accuracy of content; melody; prosody; specific error types in word selection; articulation
Motor speech/articulation	Motor speech evaluation, including multiple repetitions of multisyllabic words; diadochokinesis of speech articulators; spontaneous speech	Effortfulness; hesitations; presence of apraxia of speech or dysarthria; specific types of speech sound errors; factors that affect articulation (e.g., word length in syllables)
Confrontation naming	Single-word retrieval in response to pictures, sounds, foods, and odors	Error rate; delay in naming; factors that affect naming accuracy (e.g., familiar vs. unfamiliar items, nouns vs. verbs, semantic category); error types (e.g., semantic errors, phonemic errors)
Repetition	Oral repetition of words, pseudowords, phrases and sentences	Factors that affect repetition accuracy (e.g., predictability of the phrase, sentence length, grammatical complexity); error types
Sentence Comprehension	Matching orally presented	Factors that affect comprehension

	sentences to pictures; Answering yes/no questions; Following directions	(e.g., grammatical complexity; reversibility of the sentence e.g., The boy was kicked by the girl vs. The ball was kicked by the girl)
Word Knowledge	Picture-to-picture matching; Word-to-definition matching; Synonym matching	Factors that affect comprehension (e.g., familiarity; frequency; grammatical word class)
Object Knowledge	Word-to-picture matching; picture-picture matching; odd-one-out; semantic associations; gesture-object matching	Factors that affect object knowledge (e.g., familiarity, semantic category)
Reading /Spelling	Regular and irregular word lists, from various word classes and word lengths, matched for other factors; pseudowords matched in length to words	Factors that affect reading/spelling accuracy (e.g., regularity, frequency, word class); error types (e.g., semantic, phonologically plausible errors; articulatory distortions)

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