HHS Public Access

Author manuscript

Handb Clin Neurol. Author manuscript; available in PMC 2023 February 24.

Published in final edited form as:

Handb Clin Neurol. 2022 ; 185: 81–97. doi:10.1016/B978-0-12-823384-9.00016-5.

Clinical and Neuroimaging Characteristics of Primary Progressive Aphasia

Donna C. Tippett, MPH, MA, CCC-SLP [Associate Professor],
Departments of Neurology, Otolaryngology—Head and Neck Surgery, and Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

Zafer Keser, MD [Vascular Neurology Fellow]
Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

Abstract

The chapter covers the clinical syndrome of primary progressive aphasia (PPA), the demographics of this rare neurodegenerative disease, defining clinical and neuroanatomical characteristics of each PPA variant, disease progression, and behavioral features. The chapter begins with a brief introduction that includes references to seminal papers that defined this clinical syndrome and its three variants. The classic PPA subtypes discussed in the chapter are semantic variant PPA (svPPA), nonfluent/agrammatic PPA (nfaPPA), and logopenic variant PPA (lvPPA). The key language and cognitive characteristics, and language tasks that can elicit these language impairments, are detailed. Overlap in the clinical profiles of the PPA variants, which make differential diagnosis challenging, are explained. Disease progression is described, revealing that the PPA variants become more similar over time. Although PPA is a language-predominant dementia, there are behavioral manifestations, particularly in svPPA. Changes in behavior in this variant are addressed as well as behavioral changes in nfaPPA and lvPPA that are less well recognized. The patterns of atrophy in the left temporal, parietal, and/or frontal cortices unique to each PPA variant are described. The underlying neuropathologies of the PPA variants are discussed, specifically tau-opathies and non-tau-opathies associated with svPPA and nfaPPA and Alzheimer's disease pathology in lvPPA.

Keywords

primary progressive aphasia; logopenic variant primary progressive aphasia; nonfluent agrammatic primary progressive aphasia; semantic variant primary progressive aphasia; language; neurodegenerative; neuroimaging

Introduction

Primary progressive aphasia (PPA) is a neurodegenerative clinical syndrome caused by diverse underlying neuropathologies resulting in atrophy in the left temporal, parietal, and/or

Contact information: Johns Hopkins Outpatient Center, 601 N. Caroline Street, 6th floor, Baltimore, Maryland, United States, 21287-0910; Phone 410-955-7895; Fax 410-367-2364; dtippet1@jhmi.edu.

frontal cortices (Gorno-Tempini et al., 2011; Diehl-Schmid et al., 2014; Vandenberghe, 2016). Clinically, PPA is characterized by the insidious onset, gradual decline, and predominance of language impairments (with relative sparing of other cognitive abilities early in disease course, such as memory and constructional praxis), and compromised participation in activities of daily living due to these deficits (Mesulam, 2001; Mesulam et al., 2014a; Montembeault et al., 2018). The limiting effect on participation in activities of daily living has considerable individual and societal implications, despite PPA being classified as a rare disease (defined as a condition which affects fewer than 200,000 people in the United States) by the Genetic and Rare Diseases Information Center of the National Center for Advancing Translational Sciences (NCATS) (Orphanet). Mean age for disease onset is 59.6 years (SD 7.2) in semantic variant PPA (svPPA), 64.4 years (SD 7.5) in nonfluent agrammatic PPA (nfaPPA), and 63.0 years (SD 7.9) in logopenic variant PPA (lvPPA). Mean survival is 11.6 years (SD 4.3) in svPPA, 8.0 years (SD 2.5) in nfaPPA, and 11.0 years (SD 4.1) in lvPPA (Spinelli et al., 2017), thus disease is manifested in the prime of individuals' lives and requires years of supportive care and symptom management as there is no curative treatment for PPA.

Mesulam and Weintraub (1992) proposed the diagnosis "primary progressive aphasia" to describe slowly progressive aphasia without other behavioral abnormalities, which Mesulam first reported in six individuals in 1982. Identification of a progressive disorder of language associated with atrophy of the frontal and temporal regions of the left hemisphere dates to the 1890s however (Pick, 1892; Serieux, 1893), followed by descriptions of progressive language impairments in semantics and grammar. In 1975, Warrington reported selective impairment of semantic memory characterized by failure to recognize or identify common objects in three patients with diffuse cerebral lesions. Subsequently, Snowden et al. (1989) and Hodges et al. (1992) characterized the diagnostic entity of semantic dementia. In 1996, Grossman et al. reported progressive nonfluent aphasia, a syndrome distinguished by agrammatism, distinct from fluent or semantic dementia. Gorno-Tempini et al. (2004a, 2008) proposed a third entity characterized by "intermediate" fluency: logopenic variant (from Greek, meaning, "lack of words"). Gorno-Tempini et al. (2004a) argued that the fluency profile of lvPPA does not fit readily into the fluent/nonfluent classification of speech-language production applied in post-stroke aphasias. In post-stroke aphasias, nonfluent aphasias are typified by slow, effortful production, altered prosody, omission of grammatical morphemes, and motor speech impairment; fluent aphasias are characterized by the presence of phonological and lexical errors, normal speech rate, spared grammar, and intact motor speech production. In lvPPA, motor speech and grammar are preserved, but speech production is slow and halting. Those with lvPPA may be considered fluent or nonfluent depending upon the relative weight assigned to any of the multiple speech-language characteristics that comprise fluency. At present, three different PPA variants, svPPA, nfaPPA and lvPPA, are specified by international consensus criteria based on clinical presentation (language manifestations), patterns of atrophy, and/or underlying neuropathology (Gorno-Tempini et al., 2011). These guidelines are used extensively to diagnose PPA and its variants, and successfully capture the profiles of most individuals, although a subset of individuals with progressive language impairment may not correspond to one of the three clinical syndromes (Tippett, 2020).

Semantic Variant Primary Progressive Aphasia

Individuals with svPPA present with the hallmark features of anomia and single word comprehension deficits, and secondary features of impaired object knowledge, surface dyslexia, and/or surface dysgraphia. Single word repetition, speech fluency, syntax, and motor speech are not affected (Hodges et al., 1992; Gorno-Tempini et al., 2004a, 2011; Hurley et al., 2012). Although anomia and single word comprehension deficits (manifestations of language impairments) are common to both post-stroke aphasia and svPPA, the underlying cognitive processes of these overt behaviors differ. For example, in post-stroke aphasia, semantic errors in naming can arise from impairment in accessing semantics from vision, damage to the semantic system, damage to access to lexical representations for output, or damage to an output buffer (Hillis & Tippett, 2015). In svPPA, progressively degraded “object semantics” or “semantic memory” affect naming and comprehension (Sebastian & Hillis, 2015). Atrophy is seen in the anterior and inferior temporal lobes bilaterally, left greater than right, which serve amodal semantic processing (Gorno-Tempini et al., 2004a, 2011; Tsapkini et al., 2011). Approximately 30% of cases present with predominate right hemisphere atrophy (right-lateralized semantic dementia), characterized by difficulty recognizing familiar and famous faces as well as personality and behavioral manifestations, such as changes in eating habits (Snowden et al, 2004; Seeley et al., 2005; Gefen et al., 2013; Kumfor et al., 2016) (Table 1).

Demographics

Mean age of onset of symptoms of svPPA is 60 years, but can range from the early 40’s to late 60’s (Hodges et al., 2010; Spinelli et al., 2017). Mean age at diagnosis is mid-to-late 60’s (range 57 to 73 years) (Hodges et al., 2010; Coyle-Gilchrist et al., 2016; Spinelli et al., 2017), suggesting a 4-5 year lag in diagnosis. Prevalence of male sex is slightly greater than female sex (60%, Hodges et al., 2010; 52%, Coyle-Gilchrist et al., 2016; 54%, Spinelli et al., 2017). Mean survival ranges from nine to 14 years (Hodges et al., 2010; Coyle-Gilchrist et al., 2016; Spinelli et al., 2017) (Figure 1). Frontotemporal dementia (FTD) is a group of related clinical syndromes characterized by behavioral, language, and motoric impairments caused by frontotemporal-lobar degeneration (FTLD), most commonly FTLD-tau or FTLD with inclusions of transactive response DNA-binding protein (FTLD-TDP) (Olney et al., 2017). The FTD spectrum includes behavioral variant FTD (bvFTD) and the language-led dementias: svPPA and nfaPPA. Onyike and Diehl-Schmid (2013) reported that 60% of FTD cases are bvFTD, with the remaining 40% accounted for by the language variants of FTD. Distinctions between diagnostic entities can change over time; however, as individuals with svPPA develop behavioral manifestations and those with bvFTD develop language impairments (Coyle-Gilchrist et al., 2016). Coyle-Gilchrist and colleagues (2016) estimated the prevalence of FTD at 10.8/100,000, with semantic dementia accounting for approximately one-third of these cases.

Key Language and Cognitive Characteristics

The core features of svPPA are impairments in confrontation naming and single word comprehension; secondary features are impaired object knowledge, surface dyslexia, and/or

surface dysgraphia. Repetition is spared and speech production is normal (that is, without the presence of dysarthria or apraxia of speech) (Gorno-Tempini et al., 2011).

Although anomia is common to all variants of PPA, it is most profoundly impaired in svPPA compared to nfaPPA or lvPPA. In the early stages of disease progression, comprehension at the single word level is compromised for low frequency, atypical concepts, and preserved for high frequency, prototypical concepts (for example, apples and pomegranates are both fruits, but apples are more typical). With disease advancement, comprehension of even familiar words is affected (Gorno-Tempini et al., 2011). These deficits are typically attributed to loss of semantic knowledge, although anomia in svPPA can be multifactorial, especially early in disease progression (Mesulam et al., 2009a), and may vary with the robustness of semantic connections (Hodges et al., 2009). In addition to impaired performance on verbal tasks, there is impaired performance on nonverbal semantic tasks, such as color, sound, and object-use knowledge, revealing the pervasive loss of conceptual knowledge in this variant (Adlan et al, 2006; Patterson et al., 2007).

Analysis of error types on object naming reveals that individuals with svPPA tend to make circumlocutions (e.g., “you pick things up with it” for tongs), visual errors (e.g., naming an orange as a “softball”), coordinate errors (e.g., naming a horse as a “cow”), and superordinate errors (e.g., naming a dog as an “animal”). The presence of superordinate errors is consistent with the assumption of underlying degraded amodal concepts of objects (Jefferies & Lambon Ralph, 2006; Budd et al., 2010). Naming error types can change over time, with coordinate errors evident initially, progressing to superordinate errors, and then to nonresponses as semantic knowledge deteriorates further (Lambon Ralph et al., 2001; Rogers et al., 2004; Cloutman et al., 2009). Differences are seen depending on the nature of the naming task and response modality. Naming of actions is preserved despite progressive decline in object naming, and greater difficulty is evident in the written versus spoken output, although both modalities are compromised (Hillis et al., 2004). Spontaneous speech is fluent, circumlocutory, and becomes increasingly empty (i.e., verbal output without meaning) over time with the use of nonspecific words, such as “thing” and limited use of specific nouns (e.g., “room” for “office”) (Landin-Romero et al., 2016). Semantic paraphasias (e.g., “giraffe” for “elephant”), rather than phonemic paraphasias (e.g., “eletant” for “elephant”), are present in connected speech in earlier stages of disease progression, suggesting that anomia is due to degraded semantic representations or difficulty accessing the phonological representation from the semantic representation (Bettcher & Sturm, 2014; Mesulam et al., 2009a).

Surface dyslexia, regularization of words with atypical spellings, is evident in reading. Words are read phonologically as the ability to remember spellings of atypical words is lost. For example, the word “colonel” is pronounced “kollonel;” “island” is pronounced “is-land.” Errors are present in written expression as well. Exception words are misspelled with phonetically plausible spelling errors, such as or “neesh” for “niche” (Wilson et al., 2009; Gorno-Tempini et al., 2011; Tsapkini et al., 2014).

Repetition is relatively unaffected in svPPA, giving rise to the phenomenon of word alienation in that individuals are able to repeat words, but do not appreciate word meaning

(Landin-Romero et al., 2016). They may make errors repeating long sentences (especially with low frequency words) later in the course, or fail to understand the task of sentence repetition. Grammar is typically intact, although there may be “paragrammatic” mistakes, such as errors in grammatical morphemes (e.g., “he is park,” omitting –ing) or substitutions of lexical items (Gorno-Tempini et al., 2011).

Diagnosis

Application of the international consensus criteria (Gorno-Tempini et al., 2011) facilitates classification of variant in most people with PPA, although there are some exceptions (Sajjadi et al., 2012; Harris et al., 2013; Wicklund et al., 2014). Classification can be challenging due to the commonality of language characteristics among variants (e.g., anomia), speech and language features which obscure differential diagnosis, and variability in clinical presentation, particularly in nfaPPA and lvPPA (Tippett, 2020). Diagnosis and classification are facilitated by resources that provide explicit guidance for clinicians to assess speech, language, and cognition in individuals with PPA, including predicted performance on tests by PPA variant (Henry & Grasso, 2018; Marshall et al., 2018). In contrast to the other variants, svPPA is consistently defined in the literature, and clinicians readily diagnose impairment in semantic knowledge using established measures, such as Pyramids and Palm Trees Test (Howard & Patterson, 1992).

Disease Progression

Rate of decline is variable in PPA, with both slow and rapid decliners in all variants (Sebastian et al., 2018). Severity of leukoaraiosis, however, is associated with steeper decline in naming (Odolil et al., 2020). Early in the disease progression, individuals with PPA have insight regarding their language decline and consequent impact on their personal and professional lives, and report depression that correlates with naming impairment (Medina & Weintraub, 2007; Banks & Weintraub, 2008). Individuals with svPPA develop frontotemporal lobar degeneration (FTLD)-like behavioral symptoms and social difficulties, including restlessness, personal neglect, disinhibition, eating habit changes, stereotypical behavior, and empathy loss (Van Langenhove et al., 2016; Tippett et al., 2017). Redirection to meaningful activities and provision of safe, appropriate outlets for socialization can improve overall mood and preserve some extent of autonomy (Tippett & Hillis, 2020). In contrast to behavioral decline, motoric function remains intact until the final stages of disease unless svPPA occurs in the setting of motor neuron disease (Le Ber et al., 2013).

Behavioral Characteristics

Behavioral symptoms are present relatively early in disease progression of svPPA in contrast to the other PPA variants. These manifestations are varied and include emotional distance, loss of empathy, rigidity, inflexibility, irritability, agitation, disruption of physiologic drives, presence of compulsive behaviors, apathy, and disinhibition (Seeley et al., 2005; Modirrousta et al., 2013; Gómez-Tortosa et al., 2016; Van Langenhove et al., 2016). Behaviors are in keeping with the neuropathology underlying svPPA-- frontotemporal lobar degeneration trans-activator regulatory DNA binding protein 43 (FTLD-TDP-43) pathology. In svPPA, there is greater damage to the uncinate fasciculus, a major association pathway between the anterior part of the temporal lobe, including the amygdala, and the ventral

frontal (orbitofrontal) region, compared to the other PPA variants. Damage to this neural pathway has implications for a wide range of behavioral disturbances (D'Anna et al., 2016). Although these behavioral manifestations are not central to the diagnosis of svPPA, understanding the nature of behavioral change in this variant is essential to comprehensive patient care and family/carer counseling (Macoir et al., 2017).

Neuropathology

Frontotemporal lobar degeneration trans-activator regulatory DNA binding protein 43 (FTLD-TDP-43) is the most common underlying neuropathology in svPPA (Hodges et al., 2010; Josephs et al., 2011; Rohrer et al., 2011; Mesulam et al., 2014b; Leyton et al., 2016). Less commonly, Alzheimer's disease (AD) pathology (Alladi et al., 2007; Mesulam et al., 2014b) and Pick bodies (Davies et al., 2005) are associated with svPPA.

Anatomy and Imaging

Atrophy is present in ventrolateral anterior temporal lobes bilaterally, usually left greater than right (Diehl et al., 2004; Gorno-Tempini et al., 2004a; Acosta-Cabronero et al., 2011; Wilson et al., 2011; Kumfor et al., 2016; Spinelli et al., 2017) (Figure 2). Additionally, the Papez circuit and limbic structures such as amygdala can also be affected in svPPA; but interestingly the mamillary bodies and hippocampus are typically spared, which might explain relatively intact episodic memory in this subtype of PPA (Tan et al., 2014). This imaging feature can be beneficial in differentiating svPPA from other conditions such as AD or hippocampal sclerosis (Botha et al., 2019). Hypometabolism in lateral temporoparietal and medial parietal hypometabolism is shown to be associated with svPPA (Josephs et al., 2010). In addition to cortical atrophy and hypometabolism, loss of integrity in white matter pathways such as middle longitudinal (Luo et al., 2020), uncinate and inferior longitudinal fasciculi (Tu et al., 2016) and left anterior temporal white matter pathways (Mandelli et al., 2014) are implicated in svPPA. Alterations in the functional connectivity such as disruptions in default mode connectivity and abnormally increased dorsal attention to visual association network connectivity are observed in svPPA (Popal et al., 2020).

Nonfluent Primary Progressive Aphasia

Those with nfaPPA demonstrate nonfluent, effortful speech and, in some cases, agrammatism (Gorno-Tempini et al, 2004a; Ogar et al., 2007; Rogalski et al., 2011a; Grossman, 2012; Mesulam et al., 2012). Apraxia of speech, a motor planning and programming impairment without muscular dysfunction (Duffy, 2019a), results in inconsistent speech sound errors, and contributes to slow, labored speech production and disrupted prosody (Gorno-Tempini et al., 2011). Agrammatism is manifested by short, simple phrases and omissions of grammatical morphemes. Semantic knowledge and single word comprehension are relatively spared (Gorno-Tempini et al., 2011) (Table 1).

Demographics

Compared to svPPA, the onset of symptoms is later in nfaPPA, percentage of women is greater, and survival appears to shorter although this may reflect later disease onset. Mean age of onset of symptoms of nfaPPA is 64 years, but can range from age 56 to 72 years

(Spinelli et al., 2017). Mean age at diagnosis is approximately 70 years (range 61 to 80 years) (Coyle-Gilchrist et al., 2016; Spinelli et al., 2017), suggesting a lag in diagnosis as seen in svPPA. Female sex predominates (61% versus 39%, Coyle-Gilchrist et al., 2016; 72% versus 28%, Spinelli et al., 2017). Mean survival ranges from five to eight years (Coyle-Gilchrist et al., 2016; Spinelli et al., 2017) (Figure 1). Estimated prevalence of nfaPPA due to any cause (FTLD and AD pathology) is 0.65-3.9 per 100,000, and incidence is 0.5-0.9 per 100,000 (Grossman, 2012).

Key Language and Cognitive Characteristics

Motor speech impairment and agrammatism are the hallmark speech and language features of nfaPPA (Gorno-Tempini et al., 2004a; Wilson et al, 2010; Gorno-Tempini et al., 2011). Speech production is characterized by inconsistent speech sound errors, speech sound substitutions, transpositions, insertions, and deletions, and alterations in prosody, consistent with apraxia of speech (Ogar et al., 2007; Ash et al., 2010; Utianski et al., 2018). “Primary progressive apraxia of speech” (PPAOS) is diagnosed when there is decline in motor speech deficits in isolation, without language symptoms (Utianski et al., 2018; Duffy et al., 2020). Utianski et al. (2018) further subdivided PPAOS into phonetic and prosodic classifications.

In nfaPPA, rate of speech is markedly slow compared with that of normal adults and other PPA variants. Grossman et al. (2013) reported average words per minute during a story narration tasks equaled 45 compared to 114 in healthy individuals. Wilson et al. (2010) reported average words per minute was 51 in nfaPPA, 83 in lvPPA, 115 in svPPA, and 149 in normal controls. Dysarthria, a neurologic speech disorder due to abnormalities in strength, speed, range, steadiness, tone, or accuracy of movement (Duffy, 2019b), can co-occur with apraxia of speech in nfaPPA. In Ogar et al. (2007), 11 of 18 individuals had dysarthria concomitant with apraxia of speech. Dysarthria type was hypokinetic (perceptual deviations include reduced vocal loudness, breathiness, monotone pitch, imprecise articulation, variable speaking rate) and mixed hypokinetic/spastic (perceptual deviations include hypokinetic features plus strained, harsh voice quality, slow rate, pitch breaks). Even early in disease progression, those with nfaPPA may become mute (Gorno-Tempini et al., 2006; Croot et al., 2012), and then rely on spelling when they can no longer communicate orally. This compensatory strategy can work well since surface dysgraphia, usually found in svPPA and lvPPA, occurs rarely in nfaPPA (Gorno-Tempini et al., 2011; Sepelyak et al., 2011).

When considering word class deficits in PPA, greater verb naming deficits have been found in nfaPPA (Cotelli et al., 2006; Hillis et al., 2002, 2004, 2006; Silveri & Ciccarelli, 2007; Thompson et al., 2012), whereas greater noun naming deficits have been reported in svPPA and lvPPA (Bak & Hodges, 2003; Hillis et al., 2004, 2006; Silveri & Ciccarelli, 2007; Thompson et al., 2012). There are, however, conflicting findings regarding this difference in naming performance (Cotelli et al., 2006; Marcotte et al., 2014; Riello et al., 2018), and grammatical ability, rather than PPA variant, predicts relative action naming impairment (Meyer et al., 2020).

Oral and written expression are characterized by reduced mean length of utterance, incorrect word order, and simplified grammar (Wilson et al., 2010). In contrast to svPPA, phonemic paraphasic errors, rather than semantic errors, are likely to occur in nfaPPA (Ash et

al., 2010, 2013), suggesting that the anomic deficit is at the level of the phonological representation itself. Individuals with nfaPPA produce fewer verbs than nouns and fewer function words (e.g., articles, conjunction, prepositions, pronouns) than content words (Wilson et al., 2010; Thompson et al., 2012). In addition to impaired grammar in expression, impaired comprehension of complex syntax is a distinctive feature of nfaPPA (Thompson & Mack, 2014). For example, individuals with nfaPPA evidence difficulty understanding complex syntax, such as embedded sentences in which there is a subordinate clause in the middle of the sentence (e.g., my car, which is very old, has a flat tire). Grossman (2012), however, notes that performance on tasks of grammatical processing can be confounded be deficits in executive resources and working memory in nfaPPA. In a meta-analysis of memory deficits in PPA, all PPA variants performed more poorly on working memory tasks than healthy controls; lvPPA performed more poorly than nfaPPA and nfaPPA performed more poorly than svPPA (Eikelboom et al., 2018). Comprehension at the single word level and simple sentence level as well as semantic knowledge are spared (Gorno-Tempini et al., 2011). Spelling is generally preserved, except for spelling of nonwords (Shim et al., 2012). Episodic memory and visuospatial abilities also remain generally intact, except in cases of corticobasal syndrome (CBS) (Mesulam, 2007).

When compared to svPPA, there is variability in the clinical presentation in those with nfaPPA and lvPPA (Sajjadi et al, 2012; Wicklund et al., 2014). Hoffman et al. (2017) used k-means clustering to group individuals with PPA based on similar linguistic and neuropsychological profiles. They described three PPA clusters. One cluster closely corresponded to svPPA with bilateral anterior temporal lobe (ATL) atrophy (left greater than right), consistent with the clearly defined diagnostic entity of this variant. Another cluster included features of both nfaPPA and lvPPA. A third cluster was a mixed PPA group characterized by weak semantic abilities and severe impairments in speech production, repetition, and syntax (not attributable to more advanced disease). Patterns of atrophy were distributed widely in the non-svPPA clusters. More controversially, deviation from classic clinical presentation nfaPPA is described with a subset of those in this mixed variant exhibiting single word comprehension and semantic knowledge deficits in addition to the typical apraxia of speech and/or agrammatism. Schaeverbeke et al. (2018) found that seven out of 12 individuals with a priori diagnosis of nfaPPA demonstrated single word comprehension deficits, consistent with a mixed variant PPA, and found that those with this mixed presentation had deficits in object knowledge and object recognition relative to healthy controls, but to a lesser degree than those with svPPA. Variability within nfaPPA, or a fourth variant not recognized in current international consensus guidelines for diagnostic classification, are possible explanations for these clinical presentations (Mesulam et al., 2009b; Mesulam et al., 2012; Mesulam et al., 2014b). Alternatively, individuals may have a more typical presentation of nfaPPA at onset, but are not seen by a neurologist until they later develop additional deficits in comprehension and object recognition. Unfortunately, if individuals with PPA of any variant live long enough, they eventually develop a more generalized dementia, corresponding to diffuse cortical atrophy,

Diagnosis

Apraxia of speech in nfaPPA can be identified through verbal agility tasks, such as sequential motion tasks (i.e., repetition of the syllable series “puh-tuh-kuh”) and repetition of multisyllabic words requiring rapid sequencing of various articulatory positions (e.g., repetitions of “caterpillar,” “Methodist Episcopal”) and repetition of words of increasing length (e.g., thick, thicken, thickening) (Ogar et al., 2007).

Language testing that taps comprehension and production of syntactically complex sentences, such as embedded and object-relative clauses are particularly challenging for those with nfaPPA, revealing characteristic agrammatism (Thompson & Mack, 2014). Grammatical ability can also be assessed by evaluating spontaneous oral and written language samples. “Agrammatic PPA” (AgPPA) is applied when grammatical deficits are the prominent deficit (Mesulam et al., 2009b). Analysis of acoustic and linguistic speech features using machine learning has potential to enable diagnosis of PPA variant. Themistocleous et al. (2021) showed that a machine learning model based on deep neural networks correctly identified 90% of individuals with nfaPPA (95% lvPPA, 65% svPPA). The morphosyntactic generation (MorGen) test can also be useful for identifying deficits in morphosyntactic production (Stockbridge et al., 2021).

Disease Progression

Sebastian et al. (2018) investigated longitudinal patterns of decline in naming and semantic knowledge in individuals with PPA who had similar symptom duration at baseline testing and found that nfaPPA had the most precipitous rates of decline in oral naming of objects and actions, followed by svPPA, then lvPPA. This decline was in part due to presence of apraxia of speech in nfaPPA. In contrast, individuals with nfaPPA demonstrated more stable performance over time on a test of semantic associations, indicating that semantic knowledge was relatively spared compared to naming. These patients may also develop motor and cognitive symptoms consistent with parkinsonism and related syndromes, such as CBS, progressive supranuclear palsy (PSP), or behavioral variant frontotemporal dementia (due to frontotemporal lobar degeneration-tau; FTLD-t) (Kertesz et al., 2000; Deramecourt et al., 2010; Gorno-Tempini et al., 2004b). Eventually, most of those with nfaPPA will satisfy the diagnostic criteria for progressive CBS or PSP (Kertesz et al., 2000; Deramecourt et al., 2010). Designation of primary progressive apraxia of speech as a separate entity is debated by some and instead considered an early presentation of an nfaPPA spectrum. Longitudinal case series of patients with primary progressive apraxia of speech show that these patients develop aphasia (Santos-Santos et al., 2016) and pathological studies show that FTLD-tau underlies a majority of both nfaPPA and primary progressive apraxia (Josephs et al., 2006; Santos-Santos et al., 2016; Spinelli et al., 2017). Executive dysfunction, including difficulty planning, organizing and problem solving, is manifested with progression of disease (Bettcher & Sturm, 2014; Butts et al., 2015; Grossman, 2012).

Behavioral Characteristics

Behavioral changes are not typically seen in the early stages of nfaPPA (Neary et al., 1998; Modirrousta et al., 2013). For example, when compared to svPPA and lvPPA with symptom duration of approximately 4 years, those with nfaPPA demonstrated only mildly

low scores on cognitive flexibility and processing speed tasks consistent with left frontal lobe compromise (Butts et al., 2015). Longitudinal imaging studies reveal that, while cortical atrophy remains primarily left hemisphere lateralized, there is progression into the right hemisphere and worsening of clinical deficits over time (Rogalski et al., 2011b; Rohrer et al., 2013). Rogalski et al. (2011b) found peak atrophy in nfaPPA over a two-year period extended from initial locations of inferior frontal gyrus (IFG), dorsal lateral prefrontal cortex, and temporoparietal cortex of the left hemisphere, including the dorsal and ventral prefrontal cortex, a greater portion of temporoparietal cortex, and the anterior temporal lobe of the left hemisphere. Peak atrophy sites in the right hemisphere also spread involve the IFG, temporoparietal regions, and a larger region of dorsal prefrontal cortex. Apathy, agitation, loss of empathy, depression, and limited self-awareness of comportment changes emerge with disease progression (Eslinger et al., 2005; Rohrer & Warren, 2010).

Neuropathology

Tau-positive pathology is the underlying pathology in 70% of those with nfaPPA (Irwin et al., 2013). More recently, Spinelli et al. (2017) reported that 88% of autopsied cases of nfaPPA had FTLD-tau. At autopsy, the tau pathology is often diagnosed as Progressive Supranuclear Palsy or Corticobasal Degeneration. Non-tau pathologies have been reported as well, including include AD pathology (Kertesz et al., 2005; Alladi et al., 2007; Grossman et al., 2008), FTLD-U (Knopman et al., 2005; Mesulam et al., 2008), or more specifically, FTLD-TDP-43) (Mackenzie et al., 2006; Snowden et al., 2007; Josephs et al, 2009).

Anatomy and Imaging

Neuroimaging shows abnormalities of the left posterior and inferior frontal regions (Gorno-Tempini et al., 2004a; Josephs et al., 2006; Wilson et al., 2011, Botha et al., 2018) as well as atrophy in the insula, premotor, and supplementary motor areas (Josephs et al., 2008; Gorno-Tempini et al., 2011; Wilson et al., 2011) in nfaPPA. To a lesser extent, there is atrophy in the posterior temporal regions (Nestor et al., 2003; Gorno-Tempini et al, 2004a; Mandelli et al, 2016 a, b; Sajjadi et al., 2013) (Figure 2). When nfaPPA is accompanied by apraxia of speech, atrophy in dorsolateral premotor cortex and primary motor cortex can also be seen (Botha et al., 2019). Selective left frontal lobe hypometabolism is observed in this variant of PPA (Rabinovici et al., 2008). Degeneration in white matter pathways such as left intrafrontal, frontal aslant and frontostriatal pathways are observed in contrast to svPPA and lvPPA and premotor-SMA pathway is shown to be associated with speech fluency (Mandelli et al, 2014, Mandelli et al., 2016a). Another study showed frontal aslant pathway is associated with verbal fluency across all types of PPA (Catani et al., 2013).

Logopenic Variant Primary Progressive Aphasia

Individuals with lvPPA present with impaired single word retrieval in confrontation naming and in spontaneous speech, and impaired repetition of phrases and sentences (Gorno-Tempini et al., 2004a, 2008; Grossman, 2010). Auditory-verbal short-term memory impairments are manifested by impaired sentence repetition and phonological errors in naming (Gorno-Tempini et al., 2008; Grossman, 2010). Grammar, single word comprehension, object knowledge, and motor speech are preserved. Over time, there is

generalized cognitive decline, affecting memory and visuospatial skills (Grossman, 2010; Josephs et al., 2008; Rohrer et al., 2013) (Table 1).

Demographics

Mean age of onset of symptoms of lvPPA is 63.0 ± 7.9 years and mean age at diagnosis is 66.8 ± 8.6 years (Spinelli et al., 2017), suggesting a lag in diagnosis as seen in svPPA and nfaPPA. Female sex is slightly predominate (55% versus 45%, Spinelli et al., 2017). Mean survival is 11.0 ± 4.1years (Spinelli et al., 2017) (Figure 1). Gorno-Tempini et al. (2008) reported that lvPPA represented 30% of their PPA cases. Similarly, Teichmann et al. (2013) reported that 31% of their cohort of patients with PPA over a two-year interval were diagnosed with lvPPA (39% with svPPA, 18% with nfaPPA, 12% with unclassifiable PPA).

Key Language and Cognitive Characteristics

Gorno-Tempini et al. (2004a) described a subset of patients with PPA who did not meet the criteria for svPPA or nfaPPA and labelled this group “logopenic.” These patients presented with slow rate of speech, word finding difficulty, impaired sentence repetition, impaired syntactic comprehension (differently from nfaPPA with impairment of constructions such as simple passives; e.g., the dress is sewed by the father). Maximum speech rate (which may be more useful that rate of speech that can be affected by linguistic and nonlinguistic factors) is reduced for lvPPA and nfaPPA relative to svPPA and healthy controls (161 in lvPPA, 98 in nfaPPA, 255 in svPPA and healthy controls) (Wilson et al., 2010). There was no evidence of agrammatism, single word comprehension impairment, semantic association impairment, or speech articulation deficit. A short-term phonological memory deficit was proposed as the underlying mechanism of this language profile. Imaging supported this hypothesis. Voxel based morphometry showed that left posterior temporal and parietal lobules were the areas most atrophied in the logopenic subset. The inferior parietal lobule is considered the site for the phonological store portion of the phonological loop. The phonological loop, which is a component of working memory, is comprised of a phonological store and articulatory rehearsal mechanisms (Baddeley, 1988; Vallar et al., 1997). Subsequently, Gorno-Tempini et al. (2008) established the logopenic diagnosis as a distinct entity from svPPA and nfaPPA based on the performance of six individuals on an experimental phonological loop battery. In their patients with lvPPA, sentence repetition was severely compromised; yet single word repetition was spared. Digit span was markedly reduced, but single digit repetition was normal, indicating that the deficit cannot be attributed to defective speech perception. Performance was not affected by the mode of presentation or facilitated by pointing. Letter span was severely reduced as well, and phonologically dissimilar letters did not facilitate performance, suggesting that the store component of the phonological loop is not intact. Finally, word span was limited to a few short words, and only one long word. Gorno-Tempini et al. (2008) likened the language attributes of lvPPA to vascular conduction aphasia (Caramazza et al., 1981) and progressive conduction aphasia (Hillis et al., 1999).

Further support of the concept that impaired phonological processing underlies lvPPA comes from studies investigating language disabilities in childhood and lvPPA in adulthood. In multiple studies, an association is reported between learning disabilities, such as dyslexia, and lvPPA, indicating that developmental weakness of phonologic processing within the left

temporoparietal junction might be related to neurodegeneration of the left temporoparietal region later in life (Rogalski et al., 2008; Miller et al., 2013).

Naming errors are typically phonemic paraphasic errors instead of semantic paraphasias in lvPPA (Gorno-Tempini et al., 2008; Henry & Gorno-Tempini, 2010). Verbal output is characterized by islands of fluent output with pauses, false starts, and hesitations. Verbal output is not effortful as seen in nfaPPA, and fluency (as measured by words per minute, although the multidimensionality of this construct is acknowledged) is intermediate (Wilson et al., 2010). Difficulty comprehending complex syntax is seen, but reflects impairment of short-term memory rather than impairment of grammatical processing (Gorno-Tempini et al., 2008). Phonological processing difficulties are also manifested in reading and spelling. Individuals with lvPPA demonstrate greater difficulty reading and spelling pseudo words (nonwords that conform to English spelling) than real words (e.g., “nold” versus “gold”) (Faria et al., 2013; Henry et al., 2015). Those with lvPPA also have greater difficulty spelling irregular than regular words (e.g., bowl, calf, cough) (Sepelyak et al., 2011; Faria et al. 2013). Single word comprehension, object knowledge, motor speech, and grammar are typically spared. (Gorno-Tempini et al., 2008, 2011).

Like nfaPPA, there is variability within the clinical presentation of lvPPA. Sajjadi et al. (2014) reported left temporoparietal atrophy in 14 individuals whose language profiles did not meet the criteria for any of the three PPA variants. This pattern of atrophy is comparable to that typically seen in lvPPA. Although the authors did not have confirmation of underlying pathology, they proposed that Alzheimer’s pathology, the foremost underlying etiology of lvPPA, could result in a heterogeneous language profile in a PPA subtype that is neither svPPA nor nfaPPA, but instead reflects a more diverse form of AD-related PPA. Preiß et al. (2019) described diffuse cortical thickness reductions in the left hemisphere language network in AD-related PPA, including regions characteristically associated with nfaPPA and svPPA. This finding may account for the more extensive language deficit in AD-PPA than captured by the consensus guidelines for diagnosing lvPPA. Giannini et al. (2017) advanced the concept of a logopenic spectrum that encompasses lvPPA (as defined by consensus guidelines), lvPPA+, and lvPPA− (defined as clinical phenotypes that are partially consistent with consensus criteria).

Although PPA is characterized by predominance of language deficits, generalized cognitive decline, including attention, memory, and visuospatial skills, is manifested over time (Rohrer et al., 2013). Individuals with lvPPA often develop symptoms, such as impaired episodic memory, of the most common underlying disease—AD (Josephs et al., 2008). Individuals with lvPPA perform similarly to individuals with AD on complex figure copy and recall tasks (Foxe et al., 2013, 2016). Comparisons of visuospatial abilities in the different variants of PPA on figure copy tasks and delayed figure copy tasks reveal that those with lvPPA and svPPA score significantly lower than those with nfaPPA (Kramer et al., 2003; Possin et al., 2011; Tippett et al., 2019). Butts et al. (2015) found group differences in visual learning and memory, as well as in executive and visuospatial function, with the lvPPA group performing more poorly than either the svPPA or nfaPPA groups on multiple measures. Watson et al. (2018) investigated visuospatial cognition across several tasks in 156 individuals with PPA. They adjusted for differences in age, education, and dementia severity,

and found that those with lvPPA had significantly lower scores on a visuospatial factor and the most impaired composite scores. Those with lvPPA may have difficulty on visuospatial tasks because of disruption of the dorsal stream of vision processing, involving the parietal lobe. Poor figure copying is correlated with right parietal atrophy in AD, which is the most common underlying neuropathology of lvPPA (Possin et al., 2011). Other features are dyscalculia and ideomotor apraxia (Rohrer et al., 2010; Teichmann et al., 2013).

Diagnosis

Repetition impairment can be manifested on sentence repetition tasks, especially for lengthy sentences containing low frequency vocabulary. Repetition impairment can be seen in lvPPA and nfaPPA, albeit for different underlying reasons. Impaired repetition may be secondary to impaired working memory in lvPPA and to apraxia of speech in nfaPPA, thereby obscuring the distinction between lvPPA versus nfaPPA superficially. The nature of repetition errors, however, aids diagnosis, as those with lvPPA do not demonstrate effortful, groping speech production with inconsistent articulatory errors as seen in apraxia of speech. A comparison of repetition to oral reading of the same set of sentences can distinguish errors in repetition due to impaired phonological memory in lvPPA (with relatively intact oral reading), to errors in repetition due to apraxia of speech in nfaPPA (with similar errors in sentence repetition and reading) or impaired comprehension (sometimes with fewer errors in repetition, especially of irregular words. For example, Ruch, Stockbridge, Walker, and Hillis [unpublished data] studied 210 participants with PPA (84 lvPPA, 66 svPPA, and 60 nfaPPA) on two sentence reading and repetition tasks, including one from the National Alzheimer's Coordinating Center's (NACC) FTLD Neuropsychological Battery (www.naccdata.org) with sentences of 5-10 words each and a new task with longer sentences (10-16 words each) including longer words with lower frequency (e.g., Japanese, intimidated). Only the lvPPA patients made significantly more total errors on the new repetition than the new reading task ($p<0.00001$ vs. $p>0.1$ for the other variants. For those with lvPPA, the ratio of reading errors: repetition errors was 0.11. Performance on visuospatial memory tasks may facilitate diagnosis of lvPPA versus nfaPPA with relatively spared delayed figure copying helping to identify those with nfaPPA (Tippett et al., 2019). Individuals with lvPPA have greater difficulty spelling pseudo words than those with nfaPPA (Henry et al., 2015).

Disease Progression

As previously noted, there is variability in rates of decline in PPA. Machulda et al. (2013) reported that some individuals with lvPPA present with mild aphasia despite long disease duration (i.e., equal to or greater than 4 years). Atrophy was limited to posterior regions of the left lateral temporal lobe in this group. Machulda et al. (2013) speculated that this subset of lvPPA might have better prognosis, and potentially greater stimulability to language therapy, than other PPA groups. In general, those with lvPPA develop global aphasia, episodic memory impairment, executive dysfunction, and visuospatial deficits over time (Gorno-Tempini et al., 2008; Rohrer et al., 2013; Watson et al., 2018).

Behavioral Characteristics

Neuropsychiatric symptoms are infrequent in the early stages of lvPPA; however, with disease progression, apathy, anxiety, irritability, and agitation with a maintenance of self-

awareness emerge (Rosen et al., 2006; Rohrer & Warren, 2010; Van Langenhove, et al., 2016). Frank disinhibition and lack of empathy are rare (Rohrer & Warren, 2010). In a comparison of PPA variants, more severe personal neglect was demonstrated in svPPA and nfaPPA groups than lvPPA, and more severe judgment impairments distinguished nfaPPA from the lvPPA group (Tippett et al., 2017). Language (repetition, semantic knowledge, action naming) and behavioral disturbances have been found to be negatively correlated in lvPPA (but not other PPA subtypes), suggesting that negative behaviors do not develop until language deficits are severe in this variant (Keator et al, 2019).

Neuropathology

Alzheimer's disease (AD) pathology is commonly associated with lvPPA (Josephs et al., 2008; Modirrousta et al., 2013; Leyton et al., 2016). In a minority of cases, there is FTLD pathology (Mesulam et al., 2014b).

Anatomy and Imaging

Atrophy in the left temporoparietal junction, left posterior perisylvian and parietal regions are typically observed (Gorno-Tempini et al., 2004a; Wilson et al., 2010; Spinelli et al., 2017). Hypometabolism and diminished structural white matter connectivity in the left temporoparietal region are also shown (Rabinovici et al. 2008; Magnin et al. 2012) (See Figure 2). Reduction of the functional connectivity in the left temporal language and working memory networks is revealed, and this pattern is associated with aphasia severity (Whitwell et al., 2015).

References

Acosta-Cabronero J, Patterson K, Fryer TD, et al. (2011). Atrophy, hypometabolism and white matter abnormalities in semantic dementia tell a coherent story. Brain 134: 2025–2035. doi: 10.1093/brain/awr119 [PubMed: 21646331]

Adlan AL, Patterson K, Rogers TT, et al. (2006). Semantic dementia and fluent primary progressive aphasia: two sides of the same coin? Brain 129: 3066–3080. doi: 10.1093/brain/awl285 [PubMed: 17071925]

Alladi S, Xuereb J, Bak,T, et al. (2007). Focal cortical presentations of Alzheimer's disease. Brain 130: 2636–2645. doi:10.1093/brain/awm213 [PubMed: 17898010]

Ash S, Evans E, O'Shea J, et al. (2013). Differentiating primary progressive aphasias in a brief sample of connected speech. Neurology 81: 329–336. doi: 10.1212/WNL.0b013e31829c5d0e [PubMed: 23794681]

Ash S, McMillan C, Gunawardena D, et al. (2010). Speech errors in progressive non-fluent aphasia. Brain Lang 113: 13–20. doi: 10.1016/j.bandl.2009.12.001 [PubMed: 20074786]

Baddeley A (1988). Cognitive psychology and human memory. Trends Neurosci 11: 176–181. doi: 10.1016/0166-2236(88)90145-2 [PubMed: 2469187]

Bak TH, Hodges JR (2003). Kissing and dancing—a test to distinguish the lexical and conceptual contributions to noun/verb and action/object dissociation. Preliminary results in patients with frontotemporal dementia. J Neuroling 16: 169–181. doi:10.1016/S0911-6044(02)00011-8

Banks SJ, Weintraub S (2008). Cognitive deficits and reduced insight in primary progressive aphasia. Am J Alzheimers Dis Other Demen 23: 363–371 doi:10.1177/1533317508320351 [PubMed: 18836134]

Bettcher BM, Sturm VE (2014). Neuropsychological assessment of primary progressive aphasia. Perspect Neurophysiol Neurogenic Speech Lang Disord 24: 128–136. doi:10.1044/nnsld24.4.128

Botha H, Josephs KA. (2019). Primary progressive aphasias and apraxia of speech. Continuum (Minneap Minn) 25: 101–127. doi: 10.1212/CON.0000000000000699. [PubMed: 30707189]

Budd MA, Kortte K, Cloutman L, et al. (2010). The nature of naming errors in primary progressive aphasia versus acute post-stroke aphasia. Neuropsychology 24: 581–589. doi:10.1037/a0020287 [PubMed: 20804246]

Butts AM, Machulda MM, Duffy JR, et al. (2015). Neuropsychological profiles differ among the three variants of primary progressive aphasia. J Int Neuropsychol Soc 21: 429–35. doi: 10.1017/S1355617715000399 [PubMed: 26067425]

Caramazza A, Berndt RS, Basili AG, Koller JJ (1981). Syntactic processing deficits in aphasia. Cortex 17: 333–48. doi: 10.1016/s0010-9452(81)80021-4 [PubMed: 7333108]

Catani M, Mesulam MM, Jakobsen E, et al. (2013). A novel frontal pathway underlies verbal fluency in primary progressive aphasia. Brain 136: 2619–28. doi: 10.1093/brain/awt163. [PubMed: 23820597]

Cloutman L, Gottesman R, Chaudhry P, et al. (2009). Where (in the brain) do semantic errors come from? Cortex 45: 641–649. doi: 10.1016/j.cortex.2008.05.013 [PubMed: 19084219]

Cotelli M, Borroni B, Manenti R, et al. (2006). Action and object naming in frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration. Neuropsychology 20: 558–65. doi: 10.1037/0894-4105.20.5.558 [PubMed: 16938018]

Coyle-Gilchrist ITS, Dick KM, Patterson K, et al. (2016). Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. Neurology 86: 1736–1743. doi: 10.1212/WNL.0000000000002638 [PubMed: 27037234]

Croot K, Ballard K, Leyton CE, et al. (2012). Apraxia of speech and phonological errors in the diagnosis of nonfluent/agrammatic and logopenic variants of primary progressive aphasia. J Speech Lang Hear Res 55: S1562–72. doi: 10.1044/1092-4388(2012/11-0323) [PubMed: 23033449]

D'Anna L, Mesulam MM, Thiebaut de Schotten M, et al. (2016). Frontotemporal networks and behavioral symptoms in primary progressive aphasia. Neurology 86: 1393–1399. doi:10.1212/WNL.0000000000002579 [PubMed: 26992858]

Davies RR, Hodges JR, Kril JJ et al. (2005). The pathological basis of semantic dementia. Brain 128: 1984–1995. doi:10.1093/brain/awh582 [PubMed: 16000337]

Deramecourt V, Lebert F, Debachy B, et al. (2010). Prediction of pathology in primary progressive language and speech disorders. Neurology 74: 42–49. doi: 10.1212/WNL.0b013e3181c7198e [PubMed: 19940270]

Diehl J, Grimmer T, Drzezga A, et al. (2004). Cerebral metabolic patterns at early stages of frontotemporal dementia and semantic dementia. A PET study. Neurobiol Aging 25: 1051–1056. doi:10.1016/j.neurobiolaging.2003.10.007 [PubMed: 15212830]

Diehl-Schmid J, Onur OA, Kuhn J, et al. (2014). Imaging frontotemporal lobar degeneration. Curr Neurol Neurosci Rep 14: 489. doi:10.1007/s11910-014-0489-x [PubMed: 25171901]

Duffy J (2019a). Apraxia. In: Motor speech disorders: substrates, differential diagnosis, and management. Elsevier, New York, pp. 257–279.

Duffy J (2019b). Defining, understanding, and categorizing motor speech disorders. In: Motor speech disorders: substrates, differential diagnosis, and management. Elsevier, New York, pp. 2–12.

Duffy JR, Utianski RL, Josephs KA. (2020). Primary progressive apraxia of speech: from recognition to diagnosis and care. Aphasiology 35: 560–591. doi:10.1080/02687038.2020.1787732 [PubMed: 34219857]

Eikelboom WS, Janssen N, Jiskoot LC, et al. (2018). Episodic and working memory function in primary progressive aphasia: A meta-analysis. Neurosci Biobehav Rev 92:243–254. doi: 10.1016/j.neubiorev.2018.06.015. [PubMed: 29928907]

Eslinger PJ, Dennis K, Moore P, et al. (2005). Metacognitive deficits in frontotemporal dementia. J Neurol Neurosurg Psychiatry 76:1630–1635. doi:10.1136/jnnp.2004.053157 [PubMed: 16291884]

Faria AV, Crinion J, Tsapkini K, et al. (2013). Patterns of dysgraphia in primary progressive aphasia compared to post-stroke aphasia. Behav Neurol 26: 21–34. doi: 10.3233/BEN-2012-110237 [PubMed: 22713396]

Foxe DG, Irish M, Hodges JR, et al. (2013). Verbal and visuospatial span in logopenic progressive aphasia and Alzheimer's disease. J Int Neuropsychol Soc 19: 247–253. doi.10.1017/S1355617712001269 [PubMed: 23298815]

Foxe D, Leyton CE, Hodges JR, et al. (2016). The neural correlates of auditory and visuospatial span in logopenic progressive aphasia and Alzheimer's disease. Cortex 83: 39–50. doi.10.1016/j.cortex.2016.07.003 [PubMed: 27474916]

Gefen T, Wieneke C, Martersteck A, et al. (2013). Naming vs knowing faces in primary progressive aphasia: a tale of 2 hemispheres. Neurology 81: 658–664. doi:10.1212/WNL.0b013e3182a08f83 [PubMed: 23940020]

Giannini LAA, Irwin DJ, McMillan CT, et al. (2017). Clinical marker for Alzheimer disease pathology in logopenic primary progressive aphasia. Neurology 88: 2276–2284. doi: 10.1212/WNL.0000000000004034 [PubMed: 28515265]

Gómez-Tortosa E, Rigual R, Prieto-Jurczynska C, et al. (2016). Behavioral evolution of progressive semantic aphasia in comparison with nonfluent aphasia. Dement Geriatr Cogn Disord 41: 1–8. doi: 10.1159/000439521 [PubMed: 26426392]

Gorno-Tempini ML, Brambati SM, Ginex V, et al. (2008). The logopenic/phonological variant of primary progressive aphasia. Neurology 71: 1227–1234. doi:10.1212/01.wnl.0000320506.79811.da [PubMed: 18633132]

Gorno-Tempini ML, Dronkers NF, Rankin KP, et al. (2004a). Cognition and anatomy in three variants of primary progressive aphasia. Ann Neurol 55: 335–346. doi:10.1002/ana.10825 [PubMed: 14991811]

Gorno-Tempini ML, Hillis AE, Weintraub S, et al. (2011). Classification of primary progressive aphasia and its variants. Neurology 76: 1006–1014. doi:10.1212/WNL.0b013e31821103e6 [PubMed: 21325651]

Gorno-Tempini ML, Murray RC, Rankin KP, et al. (2004b). Clinical, cognitive and anatomical evolution from nonfluent progressive aphasia to corticobasal syndrome: A case report. Neurocase 10: 426–436. doi:10.1080/13554790490894011 [PubMed: 15788282]

Gorno-Tempini ML, Ogar JM, Brambati SM, et al. (2006). Anatomical correlates of early mutism in progressive nonfluent aphasia. Neurology 67: 1849–1851. doi:10.1212/01.wnl.0000237038.55627.5b [PubMed: 16931509]

Grossman M (2010). Primary progressive aphasia: Clinicopathological correlations. Nat Rev Neurol 6:88–97. doi:10.1038/nrneurol.2009.216 [PubMed: 20139998]

Grossman M (2012). The non-fluent/agrammatic variant of primary progressive aphasia. Lancet Neurol 11:545–55. doi:10.1016/S1474-4422(12)70099-6 [PubMed: 22608668]

Grossman M, Mickanin J, Onishi K, et al. (1996). Progressive non-fluent aphasia: language, cognitive and PET measures contrasted with probable Alzheimer's disease. J Cogn Neurosci 8: 135–154. doi:10.1162/jocn.1996.8.2.135 [PubMed: 23971420]

Grossman M, Powers J, Ash S, et al. (2013). Disruption of large-scale neural networks in non-fluent/agrammatic variant primary progressive aphasia associated with frontotemporal degeneration pathology. Brain Lang 127: 106–120. doi: 10.1016/j.bandl.2012.10.005. [PubMed: 23218686]

Grossman M, Xie SX, Libon DJ, et al. (2008). Longitudinal decline in autopsy-defined frontotemporal lobar degeneration. Neurology 70: 2036–2045. doi: 10.1212/01.wnl.0000303816.25065.bc [PubMed: 18420483]

Harris JM, Gall C, Thompson JC, et al. (2013). Classification and pathology of primary progressive aphasia. Neurology 81: 1832–9. doi:10.1212/01.wnl.0000436070.28137.7b [PubMed: 24142474]

Henry ML, Gorno-Tempini ML (2010). The logopenic variant of primary progressive aphasia. Curr Opin Neurol 23: 633–637. doi: 10.1097/WCO.0b013e32833fb93e [PubMed: 20852419]

Henry ML, Grasso SM (2018). Assessment of individuals with primary progressive aphasia. Semin Speech Lang 39: 231–241. doi:10.1055/s-0038-1660782 [PubMed: 29933490]

Henry ML, Wilson SM, Babiak MC, et al. (2015). Phonological processing in primary progressive aphasia. J Cogn Neurosci 28: 210–222. doi:10.1162/jocn_a_00901 [PubMed: 26544920]

Hillis AE, Heidler-Gary J, Newhart M, et al. (2006). Naming and comprehension in primary progressive aphasia: the influence of grammatical word class. Aphasiology 20: 246–256. doi: 10.1080/02687030500473262

Hillis AE, Oh S, Ken L (2004). Deterioration of naming nouns versus verbs in primary progressive aphasia. Ann Neurol 55: 268–75. doi: 10.1002/ana.10812 [PubMed: 14755731]

Hillis AE, Selnes OA, Gordon B (1999). Primary progressive conduction aphasia: a cognitive analysis of two cases. Brain Lang 69: 478–481.

Hillis AE, Tuffiash E, Caramazza A (2002). Modality-specific deterioration in naming verbs in nonfluent primary progressive aphasia. J Cogn Neurosci 14: 1099–1108. doi: 10.1162/089892902320474544 [PubMed: 12419132]

Hodges JR, Davies RR, & Patterson K (2009). Semantic dementia. In: Miller BL, Boeve BF (Eds.), The behavioral neurology of dementia. Cambridge University Press, New York. pp 264–278.

Hodges JR, Mitchell J, Dawson K, et al. (2010). Semantic dementia: demography, familial factors and survival in a consecutive series of 100 cases. Brain: 133: 300–306. doi:10.1093/brain/awp248 [PubMed: 19805492]

Hodges JR, Patterson K, Oxbury S, et al. (1992). Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. Brain 115: 1783–1806. doi:10.1093/brain/115.6.178 [PubMed: 1486461]

Hoffman P, Sajjadi SA, Patterson K, et al. (2017).Data-driven classification of patients with primary progressive aphasia. Brain Lang 174: 86–93. doi:10.1016/j.bandl.2017.08.001 [PubMed: 28803212]

Howard D, Patterson K (1992). The pyramids and palm trees test: A test of semantic access from words and pictures. Pearson, Cambridge, UK.

Hurley RS, Paller KA, Rogalski EJ, et al. (2012). Neural mechanisms of object naming and word comprehension in primary progressive aphasia. J Neurosci 32: 4848–55. doi:10.1523/JNEUROSCI.5984-11.2012 [PubMed: 22492040]

Irwin DJ, Trojanowski JQ, Grossman M (2013). Cerebrospinal fluid biomarkers for differentiation of frontotemporal lobar degeneration from Alzheimer's disease. Front Aging Neurosci 5: 6. doi:10.3389/fnagi.2013.00006 [PubMed: 23440936]

Jefferies E, Lambon Ralph MA (2006). Semantic impairment in stroke aphasia versus semantic dementia: a case-series comparison. Brain 129: 2132–2147. doi: 10.1093/brain/awl153 [PubMed: 16815878]

Josephs KA, Duffy JR, Fossett TR, et al. (2010). Fluorodeoxyglucose F18 positron emission tomography in progressive apraxia of speech and primary progressive aphasia variants. Arch Neurol 67: 596–605. doi: 10.1001/archneurol.2010.78. [PubMed: 20457960]

Josephs KA, Duffy JR, Strand EA, et al. (2006). Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain 129: 1385–1398. doi:10.1093/brain/awl078 [PubMed: 16613895]

Josephs KA, Hodges JR, Snowden JS, et al. (2011). Neuropathological background of phenotypical variability in frontotemporal dementia. Acta Neuropathol 122: 137–153. doi: 10.1007/s00401-011-0839-6 [PubMed: 21614463]

Josephs KA, Stroh A, Dugger B, et al. (2009). Evaluation of subcortical pathology and clinical correlations in FTLD-U subtypes. Acta Neuropathol 118: 349–358. doi:10.1007/s00401-009-0547-7 [PubMed: 19455346]

Josephs KA, Whitwell JL, Duffy JR, et al. (2008). Progressive aphasia secondary to Alzheimer disease vs FTLD pathology. Neurology 70: 25–34. doi:10.1212/01.wnl.0000287073.12737.35 [PubMed: 18166704]

Keator LM, Wright AE, Saxena S, et al. (2019). Distinguishing logopenic from semantic and nonfluent variant primary progressive aphasia: patterns of linguistic and behavioral correlations. Neurocase 25:98–105. doi: 10.1080/13554794.2019.1625929 [PubMed: 31164050]

Kertesz A, Martinez-Lage P, Davidson W, et al. (2000). The corticobasal degeneration syndrome overlaps progressive aphasia and frontotemporal dementia. Neurology 55: 1368–1375. doi: 10.1212/wnl.55.9.1368 [PubMed: 11087783]

Kertesz A, McMonagle P, Blair M, et al. (2005). The evolution and pathology of frontotemporal dementia. Brain 128: 1996–2005. doi:10.1093/brain/awh598 [PubMed: 16033782]

Knopman DS, Boeve BF, Parisi JE, et al. (2005). Antemortem diagnosis of frontotemporal lobar degeneration. Annals of Neurology 57: 480–488. doi:10.1002/ana.20425 [PubMed: 15786453]

Kramer JH, Jurik J, Sha SJ, et al. (2003). Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. Cogn Behav Neurol 16: 211–218. doi: 10.1097/00146965-200312000-00002 [PubMed: 14665820]

Kumfor F, Landin-Romero R, Devenney E, et al. (2016). On the right side? A longitudinal study of left- versus right-lateralized semantic dementia. Brain 139: 986–998. doi: 10.1093/brain/awv387 [PubMed: 26811253]

Lambon Ralph MA, McClelland JL, Patterson K, et al. (2001). No right to speak? The relationship between object naming and semantic impairment: neuropsychological evidence and a computational model. J Cogn Neurosci 13: 341–56. doi: 10.1162/08989290151137395 [PubMed: 11371312]

Landin-Romero R, Tan R, Hodges JR, et al. (2016). An update on semantic dementia: genetics, imaging, and pathology. Alzheimers Res Ther 8: 52. doi:10.1186/s13195-016-0219-5 [PubMed: 27915998]

Le Ber I, Camuzat A, Guillot-Noel L, et al. (2013). C9ORF72 repeat expansions in the frontotemporal dementias spectrum of diseases: a flow-chart for genetic testing. J Alzheimers Dis 34: 485–99. doi: 10.3233/JAD-121456 [PubMed: 23254636]

Leyton CE, Britton AK, Hodges JR, et al. (2016). Distinctive pathological mechanisms involved in primary progressive aphasias. Neurobiol Aging 38: 82–92. doi: 10.1016/j.neurobiolaging.2015.10.017 [PubMed: 26827646]

Luo C, Makaretz S, Stepanovic M, et al. (2020). Middle longitudinal fascicle is associated with semantic processing deficits in primary progressive aphasia. Neuroimage Clin 25: 102115. doi: 10.1016/j.nicl.2019.102115. [PubMed: 31865024]

Machulda MM, Whitwell JL, Duffy JR, et al. (2013). Identification of an atypical variant of logopenic progressive aphasia. Brain Lang 127: 139–44. doi: 10.1016/j.bandl.2013.02.007 [PubMed: 23566690]

Mackenzie IR, Baborie A, Pickering-Brown S, et al. (2006). Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: Classification and relation to clinical phenotype. Acta Neuropathol 112: 539–549. doi:10.1007/s00401-006-0138-9 [PubMed: 17021754]

Macoir J, Lavoie M, Laforce R, et al. (2017) Dysexecutive symptoms in primary progressive aphasia: beyond diagnostic criteria. J Geriatr Psychiatry Neurol 30: 151–161. doi:10.1177/0891988717700507 [PubMed: 28355946]

Magnin E, Cattin F, Vandel P, et al. (2012). Fractional anisotropy in three variants of primary progressive aphasia. Eur Neurol 68: 229–233. doi: 10.1159/000339947. [PubMed: 22964895]

Mandelli ML, Caverzasi E, Binney RJ, et al. (2014). Frontal white matter tracts sustaining speech production in primary progressive aphasia. J Neurosci 16: 9754–9767. doi:10.1523/JNEUROSCI.3464-13.2014

Mandelli ML, Vilaplana E, Brown JA, et al. (2016a). Healthy brain connectivity predicts atrophy progression in non-fluent variant of primary progressive aphasia. Brain 139: 2778–2791. doi:10.1093/brain/aww195 [PubMed: 27497488]

Mandelli ML, Vitali P, Santos M, et al. (2016b). Two insular regions are differentially involved in behavioral variant FTD and nonfluent/agrammatic variant PPA. Cortex 74: 149–157. doi:10.1016/j.cortex.2015.10.012 [PubMed: 26673947]

Marcotte K, Graham NL, Black SE, et al. (2014). Verb production in the nonfluent and semantic variants of primary progressive aphasia: the influence of lexical and semantic factors. Cogn Neuropsychol 31: 565–583. doi: 10.1080/02643294.2014.970154 [PubMed: 25358022]

Marshall CR, Hardy CJD, Volkmer A, et al. (2018). Primary progressive aphasia: a clinical approach. J Neurol 265: 1474–1490. doi:10.1007/s00415-018-8762-6 [PubMed: 29392464]

Medina J, Weintraub S (2007). Depression in primary progressive aphasia. J Geriatr Psychiatry Neurol 20: 153–160. doi:10.1177/0891988707303603 [PubMed: 17712098]

Mesulam MM (1982). Slowly progressive aphasia without generalized dementia. Ann Neurol 11: 592–598. doi:10.1002/ana.410110607 [PubMed: 7114808]

Mesulam MM (2001). Primary progressive aphasia. Ann Neurol 49: 425–432. doi:10.1002/ana.91 [PubMed: 11310619]

Mesulam MM (2007). Primary progressive aphasia: a 25-year retrospective. Alzheimer Dis Assoc Disord 21: S8–S11. doi: 10.1097/WAD.0b013e31815bf7e1 [PubMed: 18090430]

Mesulam MM, Rogalski E, Wieneke C, et al. (2009a). Neurology of anomia in the semantic variant of primary progressive aphasia. Brain 132: 2553–2565. doi:10.1093/brain/awp138 [PubMed: 19506067]

Mesulam MM, Rogalski EJ, Wieneke C, et al. (2014a). Primary progressive aphasia and the evolving neurology of the language network. Nat Rev Neurol 10: 554–569. doi: 10.1038/nrneurol.2014.159 [PubMed: 25179257]

Mesulam MM, Weintraub S (1992). Spectrum of primary progressive aphasia. Baillieres Clin Neurol 1: 583–609. [PubMed: 1344204]

Mesulam MM, Weintraub S, Rogalski EJ, et al. (2014b). Asymmetry and heterogeneity of Alzheimer's and frontotemporal pathology in primary progressive aphasia. Brain 137: 1176–1192. doi:10.1093/brain/awu024 [PubMed: 24574501]

Mesulam M, Wicklund A, Johnson N, et al. (2008). Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. Ann Neurol 63: 709–719. doi:10.1002/ana.21388 [PubMed: 18412267]

Mesulam MM, Wieneke C, Thompson C, et al. (2012). Quantitative classification of primary progressive aphasia at early and mild impairment stages. Brain 135:1537–1553. doi:10.1093/brain/aws080 [PubMed: 22525158]

Mesulam M, Wieneke C, Rogalski E, et al. (2009b). Quantitative template for subtyping primary progressive aphasia. Arch Neurol 66: 1545–51. doi:10.1001/archneurol.2009.288 [PubMed: 20008661]

Meyer AM, Snider SF, McGowan SA, et al. (2020). Grammatical ability predicts relative action naming impairment in primary progressive aphasia. Aphasiology 34: 664–674. doi:10.1080/02687038.2020.1734527 [PubMed: 33716376]

Miller ZA, Mandelli ML, Rankin KP, et al. (2013). Handedness and language learning disability differentially distribute in progressive aphasia variants. Brain 136: 3461–3473. doi:10.1093/brain/awt242 [PubMed: 24056533]

Modirrousta M, Price BH, Dickerson BC (2013). Neuropsychiatric symptoms in primary progressive aphasia: phenomenology, pathophysiology, and approach to assessment and treatment. Neurodegener Dis Manag 3:133–146. doi:10.2217/nmt.13.6 [PubMed: 23997827]

Montembeault M, Brambati SM, Gorno-Tempini ML, et al. (2018). Clinical, anatomical, and pathological features in the three variants of primary progressive aphasia: a review. Front Neurol 9: 692. doi:10.3389/fneur.2018.00692 [PubMed: 30186225]

Neary D, Snowden JS, & Gustafson L, et al. (1998). Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. Neurology 51: 1546–1554. doi:10.1212/wnl.51.6.1546 [PubMed: 9855500]

Nestor PJ, Graham NL, Fryer TD, et al. (2003). Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. Brain 126:2406–2418. doi:10.1093/brain/awg240 [PubMed: 12902311]

Odolil A, Wright AE, Keator LM, et al. (2019). Leukoaraiosis severity predicts rate of decline in primary progressive aphasia. Aphasiology 34: 365–375. doi:10.1080/02687038.2019.1594152 [PubMed: 32377026]

Ogar JM, Dronkers NF, Brambati SM, et al. (2007). Progressive nonfluent aphasia and its characteristic motor speech deficits. Alzheimer Dis Assoc Disord 21: S23–S30. doi: 10.1097/WAD.0b013e31815d19fe [PubMed: 18090419]

Olney NT, Spina S, Miller BL. (2017). Frontotemporal dementia. Neurol Clin 35: 339–374. doi:10.1016/j.ncl.2017.01.008 [PubMed: 28410663]

Onyike CU, Diehl-Schmid J. (2013). The epidemiology of frontotemporal dementia. Int Rev Psychiatry 25: 130–137. doi:10.3109/09540261.2013.776523 [PubMed: 23611343]

Orphanet. Primary progressive aphasia. Available at: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=95432. Accessed 05/02/2021.

Patterson K, Nestor PJ, Rogers TT (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. Nat Rev Neurosci 8: 976–987. doi: 10.1038/nrn2277 [PubMed: 18026167]

Pick A (1892). Uber die Beziehungen der senilen Hirnatrophie zur Aphasie. Pragen Medizinischen Wochenschrift 17: 165–167.

Popal H, Quimby M, Hochberg D, et al. (2020). Altered functional connectivity of cortical networks in semantic variant primary progressive aphasia. Neuroimage Clin 28: 102494. doi: 10.1016/j.nicl.2020.102494 [PubMed: 33395985]

Possin KL, Laluz VR, Alcantar OZ, et al. (2011). Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia. Neuropsychologia 49: 43–48. doi: 10.1016/j.neuropsychologia.2010.10.026 [PubMed: 21029744]

Preiß D, Billette OV, Schneider A, et al. (2019). The atrophy pattern in Alzheimer-related PPA is more widespread than that of the frontotemporal lobar degeneration associated variants. Neuroimage Clin 24: 101994. doi: 10.1016/j.nicl.2019.101994 [PubMed: 31505368]

Rabinovici GD, Jagust WJ, Furst AJ, et al. (2008). Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia. Ann Neurol 64: 388–401. doi: 10.1002/ana.21451 [PubMed: 18991338]

Riello M, Faria AV, Ficek B, et al. (2018). The role of language severity and education in explaining performance on object and action naming in primary progressive aphasia. Front Aging Neurosci 10: 346. doi: 10.3389/fnagi.2018.00346 [PubMed: 30425638]

Rogalski E, Cobia D, Harrison TM, et al. (2011a). Anatomy of language impairments in primary progressive Aphasia. J. Neurosci 31: 3344–3350. doi:10.1523/JNEUROSCI.5544-10.2011 [PubMed: 21368046]

Rogalski E, Cobia D, Harrison TM, et al. (2011b). Progression of language decline and cortical atrophy in subtypes of primary progressive aphasia. Neurology 76: 1804–1810. doi: 10.1212/WNL.0b013e31821ccd3c [PubMed: 21606451]

Rogalski E, Johnson N, Weintraub S, et al. (2008). Increased frequency of learning disability in patients with primary progressive aphasia and their first-degree relatives. Arch Neurol 65: 244–248. doi: 10.1001/archneurol.2007.34 [PubMed: 18268195]

Rogers TT, Lambon Ralph MA, Garrard P, et al. (2004). Structure and deterioration of semantic memory: a neuropsychological and computational investigation. Psychol Rev 111: 205–35. doi: 10.1037/0033-295X.111.1.205 [PubMed: 14756594]

Rohrer JD, Caso F, Mahoney C, et al. (2013). Patterns of longitudinal brain atrophy in the logopenic variant of primary progressive aphasia. Brain Lang 127: 121–126. doi:10.1016/j.bandl.2012.12.008 [PubMed: 23395096]

Rohrer JD, Lashley T, Schott JM, et al. (2011). Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. Brain 134: 2565–2581. doi: 10.1093/brain/awr198 [PubMed: 21908872]

Rohrer JD, Ridgway GR, Crutch SJ, et al. (2010). Progressive logopenic/phonological aphasia: erosion of the language network. Neuroimage 49: 984–93. doi: 10.1016/j.neuroimage.2009.08.002 [PubMed: 19679189]

Rohrer JD, Warren JD (2010). Phenomenology and anatomy of abnormal behaviours in primary progressive aphasia. J Neurol Sci 293: 35–38. doi:10.1016/j.jns.2010.03.012 [PubMed: 20400120]

Rosen HJ, Allison SC, Ogar JM, et al. (2006). Behavioral features in semantic dementia vs other forms of progressive aphasias. Neurology 67: 1752–1756. doi:10.1212/01.wnl.0000247630.29222.34 [PubMed: 17130406]

Sajjadi SA, Acosta-Cabronero J, Patterson K, et al. (2013). Diffusion tensor magnetic resonance imaging for single subject diagnosis in neurodegenerative diseases. Brain 136:2253–2261. doi:10.1093/brain/awt118 [PubMed: 23729473]

Sajjadi SA, Patterson K, Arnold RJ, et al. (2012). Primary progressive aphasia: a tale of two syndromes and the rest. Neurology 78: 1670–1677. doi:10.1212/WNL.0b013e3182574f79 [PubMed: 22573633]

Sajjadi SA, Patterson K, Nestor PJ (2014). Logopenic, mixed, or Alzheimer-related aphasia? Neurology 82: 1127–1131. doi: 10.1212/WNL.0000000000000271 [PubMed: 24574548]

Santos-Santos MA, Mandelli ML, Binney RJ, et al. (2016). Features of patients with nonfluent/agrammatic primary progressive aphasia with underlying progressive supranuclear palsy pathology or corticobasal degeneration. JAMA Neurol 73: 733–42. doi: 10.1001/jamaneurol.2016.041 [PubMed: 27111692]

Schaeverbeke J, Gabel S, Meersmans K, et al. (2018). Single-word comprehension deficits in the nonfluent variant of primary progressive aphasia. Alzheimers Res Ther 10: 68. 10.1186/s13195-018-0393-8 [PubMed: 30021613]

Sebastian R, Hillis AE (2015). Neural substrates of semantics. In: Hillis AS (Ed.), The handbook of adult language disorders. Psychology Press, New York. pp 212–230.

Sebastian R, Thompson CB, Wang NY, et al. (2018). Patterns of decline in naming and semantic knowledge in primary progressive aphasia. Aphasiology 32: 1010–1030. doi:10.1080/02687038.2018.1490388 [PubMed: 30613121]

Seeley WW, Bauer AM, Miller BL, et al. (2005). The natural history of temporal variant frontotemporal dementia. Neurology 64: 1384–1390. doi:10.1212/01.WNL.0000158425.46019.5C [PubMed: 15851728]

Sepelyak K, Crinion J, Molitoris J, et al. (2011). Patterns of breakdown in spelling in primary progressive aphasia. Cortex 47: 342–52. doi: 10.1016/j.cortex.2009.12.001 [PubMed: 20060967]

Serieux P (1893). Sur un cas de surdite verbale pure. Rev Med 13: 733–750.

Shim H, Hurley RS, Rogalski E, et al. (2012). Anatomic, clinical, and neuropsychological correlates of spelling errors in primary progressive aphasia. Neuropsychologia 50: 1929–1935. doi:10.1016/j.neuropsychologia.2012.04.017 [PubMed: 22579708]

Silveri MC, Ciccarelli N (2007). Naming of grammatical classes in frontotemporal dementias: linguistic and non linguistic factors contribute to noun-verb dissociation. Behav Neurol 18: 197–206. doi: 10.1155/2007/428191 [PubMed: 18430977]

Snowden JS, Goulding PJ, Neary D. (1989) Semantic dementia: a form of circumscribed cerebral atrophy. Behav Neurol 2: 167–182. doi.org/10.1155/1989/124043

Snowden J, Neary D, Mann D (2007). Frontotemporal lobar degeneration: Clinical and pathological relationships. Acta Neuropathologica 114: 31–38. doi:10.1007/s00401-007-0236-3 [PubMed: 17569065]

Snowden JS, Thompson JC, Neary D (2004). Knowledge of famous faces and names in semantic dementia. Brain 127: 860–872. doi:10.1093/brain/awh099 [PubMed: 14985259]

Spinelli EG, Mandelli ML, Miller ZA, et al. (2017). Typical and atypical pathology in primary progressive aphasia variants. Ann Neurol 81: 430–443. doi:10.1002/ana.24885 [PubMed: 28133816]

Stockbridge MD, Walker A, Matchin W, et al. (2021). A double dissociation between plural and possessive "s": Evidence from the morphosyntactic generation test. Cogn Neuropsychol 38: 116–123. doi: 10.1080/02643294.2020.1833851 [PubMed: 33096962]

Tan RH, Wong S, Kril JJ, et al. (2014). Beyond the temporal pole: limbic memory circuit in the semantic variant of primary progressive aphasia. Brain 137: 2065–2076. doi: 10.1093/brain/awu118. [PubMed: 24844729]

Teichmann M, Kas A, Boutet C, et al. (2013). Deciphering logopenic primary progressive aphasia: a clinical, imaging and biomarker investigation. Brain 136: 3474–3488. doi: 10.1093/brain/awt266 [PubMed: 24108322]

Themistocleous C, Ficek B, Webster K, (2021). Automatic subtyping of individuals with primary progressive aphasia. J Alzheimers Dis 79: 1185–1194. doi: 10.3233/JAD-201101 [PubMed: 33427742]

Thompson CK, Lukic S, King MC, et al. (2012). Verb and noun deficits in stroke-induced and primary progressive aphasia: The Northwestern Naming Battery. Aphasiology 26: 632–655. doi: 10.1080/02687038.2012.676852 [PubMed: 23188949]

Thompson CK, Mack JE (2014). Grammatical impairments in PPA. Aphasiology 28: 1018–1037. doi: 10.1080/02687038.2014.912744 [PubMed: 25642014]

Tippett DC (2020). Classification of primary progressive aphasia: challenges and complexities. F1000Res. 9: F1000 Faculty Rev–64. doi:10.12688/f1000research.21184.1

Tippett DC, Breining B, Goldberg E, et al. (2019). Visuomotor figure construction and visual figure delayed recall and recognition in primary progressive aphasia. Aphasiology 34:1456–1470. doi:10.1080/02687038.2019.1670330 [PubMed: 33281269]

Tippett DC, Hillis AE (2015). The cognitive processes underlying naming. In: Hillis AS (Ed.), The handbook of adult language disorders. Psychology Press, New York. pp 141–160.

Tippett DC, Hillis AE (2020). Ethical and practical challenges of the communication and behavioral manifestations of primary progressive aphasia. Semin Speech Lang 41: 249–256. doi: 10.1055/s-0040-1710062 [PubMed: 32585709]

Tippett DC, Thompson CB, Demsky C, et al. (2017). Differentiating between subtypes of primary progressive aphasia and mild cognitive impairment on a modified version of the frontal behavioral inventory. PloS One 12: e0183212. doi:10.1371/journal.pone.0183212 [PubMed: 28813486]

Tsapkini K, Frangakis C, Gomez Y et al. (2014). Augmentation of spelling therapy with transcranial direct current stimulation in primary progressive aphasia: preliminary results and challenges. Aphasiology 28: 1112–1130. doi:10.1080/02687038.2014.930410 [PubMed: 26097278]

Tsapkini K, Frangakis CE, Hillis AE. (2011). The function of the left anterior temporal pole: evidence from acute stroke and infarct volume. Brain 134: 3094–3105. doi:10.1093/brain/awr050 [PubMed: 21685458]

Tu S, Leyton CE, Hodges JR, et al. (2016). Divergent longitudinal propagation of white matter degradation in logopenic and semantic variants of primary progressive aphasia. J Alzheimers Dis 49: 853–861. doi: 10.3233/JAD-150626 [PubMed: 26484929]

Utianski RL, Duffy JR, Clark HM, et al. (2018). Prosodic and phonetic subtypes of primary progressive apraxia of speech. Brain Lang 184: 54–65. doi: 10.1016/j.bandl.2018.06.004 [PubMed: 29980072]

Vallar G, Di Betta AM, Silveri MC (1997). The phonological short-term store-rehearsal system: patterns of impairment and neural correlates. Neuropsychologia 35: 795–812. doi: 10.1016/s0028-3932(96)00127-3 [PubMed: 9204486]

Vandenberghe R (2016). Classification of the primary progressive aphasias: principles and review of progress since 2011. Alzheimers Res Ther 8: 16. doi:10.1186/s13195-016-0185-y [PubMed: 27097664]

Van Langenhove T, Leyton CE, Piguet O, et al. (2016). Comparing longitudinal behavior changes in the primary progressive aphasias. J Alzheimers Dis 53: 1033–1042. doi:10.3233/JAD-160010 [PubMed: 27340847]

Warrington EK (1975). The selective impairment of semantic memory. Q J Exp Psychol 27: 635–657. doi:10.1080/14640747508400525 [PubMed: 1197619]

Watson CL, Possin K, Allen IE, et al. (2018). Visuospatial functioning in the primary progressive aphasias. J Int Neuropsychol Soc 24: 259–268. doi:10.1017/S1355617717000984 [PubMed: 29039275]

Whitwell JL, Jones DT, Duffy JR, et al. (2015). Working memory and language network dysfunctions in logopenic aphasia: a task-free fMRI comparison with Alzheimer's dementia. Neurobiol Aging 36: 1245–1252. doi:10.1016/j.neurobiolaging.2014.12.013 [PubMed: 25592958]

Wicklund MR, Duffy JR, Strand EA, et al. (2014). Quantitative application of the primary progressive aphasia consensus criteria. Neurology 82: 1119–1126. doi: 10.1212/WNL.0000000000000261 [PubMed: 24598709]

Wilson SM, Brambati SM, Henry RG, et al. (2009). The neural basis of surface dyslexia in semantic dementia. Brain 132: 71–86. doi:10.1093/brain/awn300 [PubMed: 19022856]

Wilson SM, Galantucci S, Tartaglia MC, et al. (2011). Syntactic processing depends on dorsal language tracts. Neuron 72: 397–403. doi:10.1016/j.neuron.2011.09.014 [PubMed: 22017996]

Wilson SM, Henry ML, Besbris M, et al. (2010). Connected speech production in three variants of primary progressive aphasia. Brain 133:2069–2088. doi:10.1093/brain/awq129 [PubMed: 20542982]

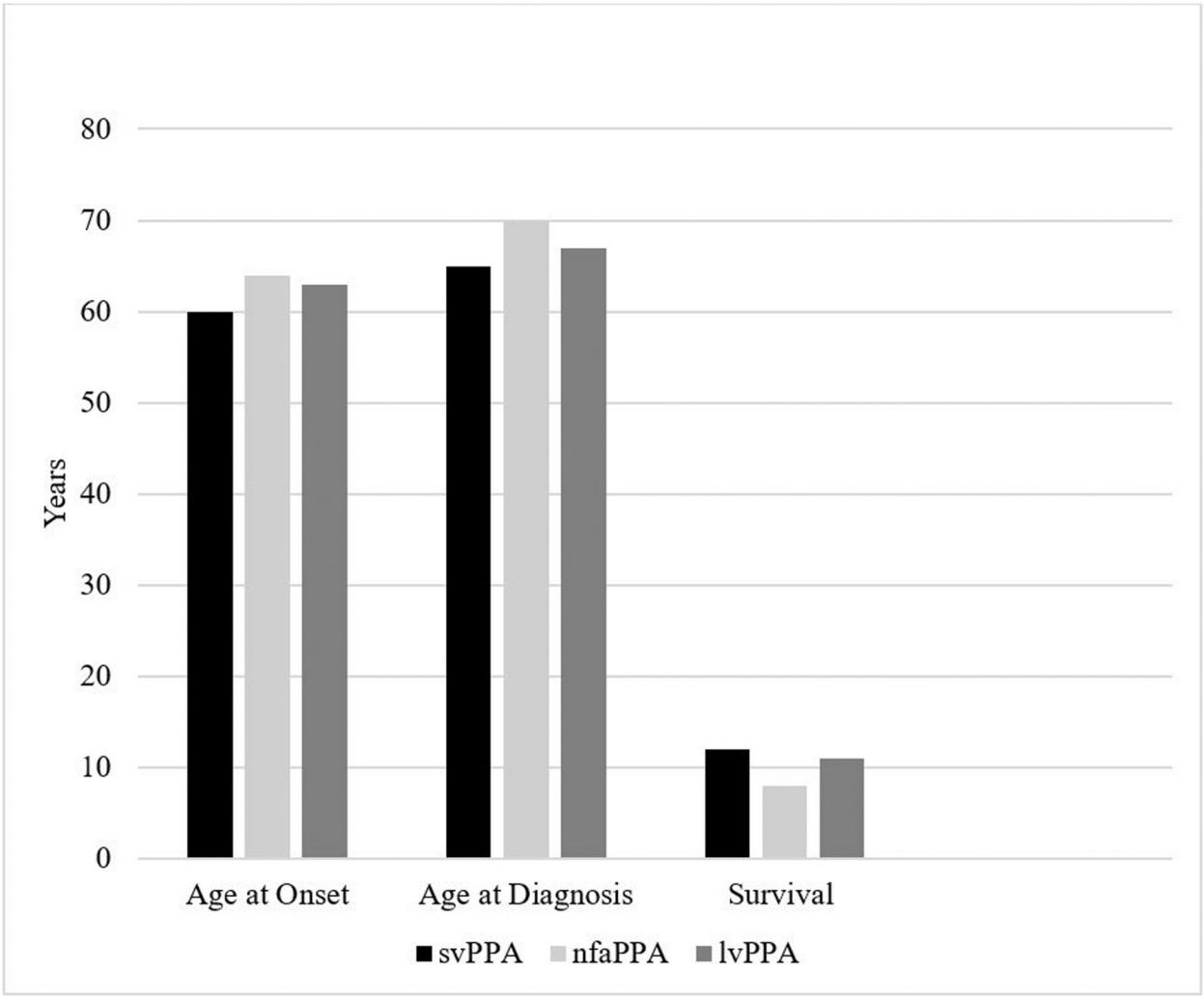

Figure 1:

Demographic Summary of Age at Onset, Age at Diagnosis and Survival in Years for Variants of Primary Progressive Aphasia

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

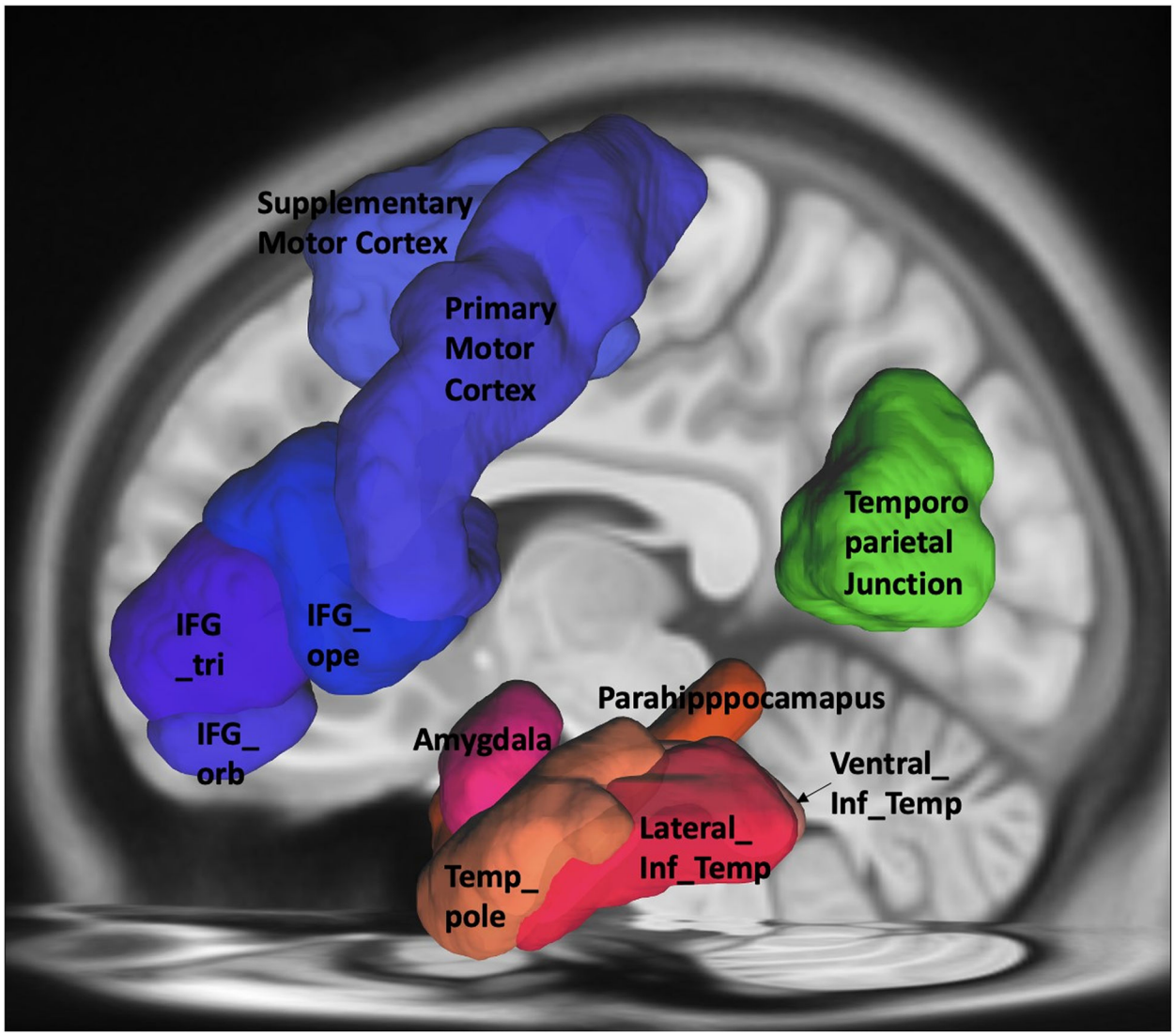

Figure 2:

Illustration of major cortical regions that are affected in semantic variant primary progressive aphasia (svPPA) (represented in red toned colors), nonfluent agrammatic PPA (nfaPPA) (represented in blue toned colors), and logopenic variant PPA (lvPPA) (represented in green). Please note that temporal and limbic structures are affected in svPPA, frontal regions in nfaPPA and temporoparietal junction in lvPPA. For the illustration purposes, only main regions were included.

IFG: Inferior frontal gyrus, Inf=inferior, ope=opercularis, orb=orbitalis, Temp=Temporal, tri=triangularis.

Table 1:

Summary of Presenting Clinical Characteristics in the Variants of Primary Progressive Aphasia

PPA Variant	Word Retrieval	Naming Error Types	Fluency	Words per Minute	Repetition	Grammar	Semantic Knowledge	Auditory Comprehension	Reading and Spelling	Motor Speech
svPPA	−	Circumlocutions Visual errors Coordinate errors Superordinate errors Semantic paraphasias Noun naming deficit > verb naming deficit	+ Circumlocutory	115	+	+/− Paragrammatic	−	− Impaired at single word level	Surface dyslexia/ dysgraphia	+
nfaPPA	−	Phonemic paraphasias Verb naming deficit > noun naming deficit	−	45-51	+/−	− Agrammatic	+	−/+ Intact at single word and simple sentence level Impaired for complex syntax	+	Apraxia of speech Hypokinetic Hypokinetic/ spastic
lvPPA	−	Phonemic paraphasias	+/−	83	− Impaired repetition of phrases and sentences	+	+	Intact at single word level Impaired for some complex constructions	+/− Difficulty reading and spelling pseudo words and irregular words	+

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