Neuropsychological Findings and the Logopenic Variant of Primary Progressive Aphasia

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Abstract
Primary progressive aphasia (PPA) involves the insidious onset and gradual progression of language impairment in the context of initially preserved additional cognitive functions. PPA includes three primary variants: a nonfluent/agrammatic subtype (PPA-A) often associated with tau-positive immunoreactivity, a semantic subtype (PPA-S) frequently attributed to ubiquitin/TAR DNA-binding protein 43 pathology, and a logopenic subtype (PPA-L), which is commonly associated with Alzheimer’s disease pathology. PPA-L is characterized by speech paucity and speech hesitation with relatively preserved grammatical ability, speech articulation, single word comprehension, and semantic knowledge. Given these primary deficits, PPA-L has a relatively unique neuropsychological profile in comparison to PPA-A and PPA-S, particularly regarding expressive and receptive language. This review describes patients with PPA-L’s neuropsychological functioning across cognitive domains, including language and other cognitive abilities. In general, PPA-L is characterized by both expressive and receptive language deficits that increase in severity as demands on working memory and task complexity increase.

ABBREVIATIONS
PPA: Primary /Progressive Aphasia; PPA-A: Nonfluent/agrammatic variant of PPA; PPA-S: Semantic variant of PPA; PPA-L: Logopenic Variant of PPA; MMSE: Mini Mental State Examination; MCI: Mild Cognitive Impairment; MoCA: Montreal Cognitive Assessment; AD: Alzheimer’s disease

INTRODUCTION
Frontotemporal lobar degeneration includes two distinct but related clinical presentations. The first, a behavioral presentation, is characterized by early personality and behavioral changes including reduced social and interpersonal conduct, disinhibition, impulsivity, and apathy [1]. The second clinical presentation, Primary Progressive Aphasia (PPA), involves three phenotypes characterized by a primary language deficit at the time of symptom onset that worsens over the disease course [2]. Gorno-Tempini et al. (2011) have provided a framework for the classification of the three main variants of PPA including the nonfluent/agrammatic (PPA-A), semantic (PPA-S), and logopenic (PPA-L) subtypes [3]. Prior to diagnosis of one of the three PPA variants, a patient must meet criteria for the broad diagnosis of PPA proposed by Mesulam in the early 2000s. These criteria require generally intact premorbid language functioning followed by an insidious onset with gradual progression of language difficulties [2,4].

Three primary neuropathological changes account for the majority of pathological changes in patients with PPA: tau-positive immunoreactivity frequently associated with PPA-A, ubiquitin/TAR DNA-binding protein 43 pathology often implicated in PPA-S, and Alzheimer’s disease pathology most commonly associated with PPA-L [5-7]. PPA-A is characterized by agrammatism, apraxia of speech, and syntactic deficits in the context of preserved word comprehension [1,8]. Primary deficits associated with PPA-S include loss of word meaning and surface dyslexia with fluent, grammatically correct speech and preserved syntactical abilities [9]. In PPA-L, patients often exhibit hesitation, speech paucity, lack of specific content, and slowed speech rate (although the speech rate in PPA-A is significantly slower), false starts (i.e., partial words), and filled pauses (i.e., using words such as “uh”, “um”, “hmm”, and “ah”) in the context of generally spared articulation, syntactic construction, semantic knowledge, and single word comprehension [10]. Given preserved motor speech, patients with PPA-L are more likely to make phonemic speech errors rather than speech misarticulations suggesting the presence of phonological speech impairment [11-14].

Each of the three PPA variants displays relatively unique cognitive profiles on neuropsychological measures. Mesulam (2013) postulates that the aim of a neuropsychological evaluation when assessing patients with PPA is to illustrate a patient’s language profile to subtype and clarify the type of aphasia, as...
well as to characterize the integrity or impairment of additional aspects of cognition [15]. This brief review will focus on the neuropsychological characteristics of PPA-L. The other PPA variants will be described as needed for comparison.

SCREENING MEASURES OF COGNITION

Studies utilizing brief measures of general cognitive functioning have found scores consistent with mild cognitive impairment in individuals with PPA-L at the time of clinical diagnosis. For example, Teichmann et al. (2013) and Leyton et al. (2013) found average scores on the Mini Mental State Examination (MMSE) in patients with PPA-L indicative of Mild Cognitive Impairment (MCI; <24) [16-18]. Gorno-Tempini et al., (2008) also found patients with PPA-L exhibited abnormal scores on the MMSE, while Rohrer et al. (2009) found the mean score of PPA-L patients on the MMSE to be as low as 16 out of 30 [19,20]. Research utilizing other screening measures of cognition, including the Montreal Cognitive Assessment (MoCA) [21], Clinical Dementia Rating Scale [22], and Dementia Rating Scale-2 [23] revealed PPA-L performance well below the range of what is considered “normal” [16,19,20,24]. In fact, patients diagnosed with PPA-L scored an average of only 15/30 on the MoCA, which is considered in the range of dementia [24]. Normative data suggest that the average score for individuals with PPA-L is 22/30 and for that with mild Alzheimer’s disease (AD) is 16/30 [21]. Thus, patients with PPA-L perform in the range of AD patients on the MoCA, but more consistently in the range of MCI on the MMSE. This may suggest that the MoCA is a more sensitive screening measure of global cognitive impairment in patients with PPA-L, is more language dependent than the MMSE, or simply reflects a difference in sample characteristics (e.g., disease duration).

Language Assessment

Given that primary language deficits are integral to PPA, and that language presentations vary between the three main PPA variants, assessment of these functions during a neuropsychological evaluation is of primary importance to aid in differential diagnosis.

Expressive Language

Although impaired object naming (i.e., confrontation naming) is a primary deficit in patients with PPA-S, multiple studies have also found impaired object naming in patients with PPA-L [13,16,17,20,24-28]. While naming in PPA-L is reduced compared to patients with PPA-A, patients with PPA-L perform better on these tasks than those with PPA-S [17,24,28,29]. Similarly, others have found confrontation naming abilities to be relatively preserved or only mildly impaired in PPA-L patients [19,30]. Furthermore, errors in these patients commonly are non-answers or phonological paraphasias [16,19,20,30,31]. Thus, word-finding hesitations may cause PPA-L patients to present as though they have more severe naming deficits than truly exists [14,30]. Speech conduction difficulties and impaired retrieval of speech also manifest on tasks of verbal fluency, when patients are required to rapidly retrieve words either to a semantic category or target letter (i.e., semantic and phonemic fluency) [16,24,28,29,32].

Repetition of digits, short-words, phrases or sentences has also been evaluated extensively in patients with PPA-L. Repetition of digits, especially when requiring working memory (i.e., actively holding and mentally manipulating information) is a hallmark deficit in these patients [19,33]. For example, the ability to repeat strings of digits in the forward order is increasingly impaired as the sequences exceed three digits [19,28]. In addition, marked deficits have also been found when patients are required to repeat digits in a backward format [16,19,28,29,34,35]. Similar findings have been observed on a letter span task, with patients performing in the impaired range on more complex tasks (i.e., when presented with more than three letters) [19]. This suggests that the deficit involves working memory rather than simple repetition. Word and sentence repetition abilities are also more severely impaired when tasks involve a greater working memory demand. Although, single word repetition was found to be below expectation in patients with PPA-L [17,29,36], word length has also been found to affect repetition. Specifically, intact repetition was found for three short words, but an inability to accurately repeat one long word [19]. Interestingly, patients were twice as likely to exhibit phonological errors on a word repetition task as in an interview [12], and thus, repetition errors may not be readily evident in casual conversation.

Although not unique to PPA-L, sentence and phrase repetition deficits, due to the tendency to frequently omit words or substitute similar words, are also present in most PPA-L patients [14,16,19,25,28,33].

Patients with PPA-L exhibit moderate difficulty on tasks requiring the oral production of sentences, also known as syntactic construction, although at a lower frequency than patients with PPA-A [30]. The errors in syntactic construction also seem to be distinct relative to errors made by individuals with PPA-A and tend to be paragrammatic (i.e., poorly constructed sentences with errors in grammatical morphemes) rather than agrammatic (i.e., omission of function words and telegraphic speech) [11,16]. Mesulam et al. (2014) found the majority of PPA-L patients exhibited spared grammar and the absence of telegraphic speech in early disease stage, providing support for the differentiation in syntactic error production between PPA-A and PPA-L patients [26].

Receptive Language

Although multiple studies have found spared single word comprehension, at least in the initial disease stages [14,19,25,27,35,36], other studies have found that 20% to 50% of patients with PPA-L are impaired on single word comprehension [16,29]. In contrast, patients with PPA-L almost universally exhibit deficits with complex tasks of comprehension, such as those requiring multiple steps or the comprehension of sentences [13,16,19,24,25].

Semantic Associations

Patients with PPA-L’s capacity to identify if objects are semantically related (i.e., semantic association abilities) has been assessed to determine their ability to create meaningful semantic relationships, understand words and their meanings, and retrieve semantic information. Findings are variable. Although a subset of studies found intact performance on verbal and
visual semantic abilities [19,25,29], Wicklund et al. (2014) found impaired semantic association abilities in patients with PPA-L. Of note, although this deficit was present in those diagnosed with PPA-L, patients with PPA-S had more severe semantic association deficits [24].

**Reading**

Errors in reading are often characterized through the assessment of the ability to read regular, irregular (i.e., words with atypical spelling to sound correspondence), or pseudowords. Phonological dyslexia is typically identified when patients are required to read pseudo-words and are unable to utilize phonetic skills to sound them out. While some studies found deficits in single word reading regardless of word type (i.e., both regular and irregular) in PPA-L patients [25], Brambati et al (2009) did not find evidence of either regular or irregular single word reading deficits. They found phonological dyslexia exhibited by reduced accuracy to read pseudo-words compared to controls and other individuals with dementia [28]. Additional research also suggests that patients with PPA-L perform poorly on irregular word reading tasks and pseudo-word reading tasks [20].

**Additional Cognitive Abilities**

Assessment of non-language abilities is also important in understanding cognition in PPA-L. Although these tasks do not primarily assess language functions, to suggest that they are purely nonverbal is somewhat misleading as instruction modality, comprehension of instructions, and task responses are often provided in a verbal format. Thus, performance on tasks of non-verbal functioning may be erroneously reduced and falsely indicate impairment [15].

**Visuospatial Functions**

Visuospatial perceptual abilities, or the ability to integrate and organize visual information, are generally preserved in PPA-L patients [13,19,24,35]. However, performance on tasks of visuospatial construction (e.g., identifying parts of a picture/object and constructing or assembling a replica) are variable, with some studies illustrating intact functioning, and others displaying impairment [19,24,28,29].

**Memory**

Measures of verbal short-term memory have revealed poor encoding abilities [28,32], as well as immediate/short-term memory impairment [19,24,25,28], which may be confounded by impaired repetition of words, phrases, and sentences. The presence of long-term memory deficits is varied, as some studies displayed intact long-term memory even in the context of short-term memory impairment, while others have found long-term memory deficits to be present on various verbal memory tasks [13,25]. Although Wicklund et al. (2014) and Rohrer et al. (2009) observed visual recall and recognition memory to be deficient, the majority of studies assessing visual recognition memory have found generally intact visual memory [20,24,25,28,35]. Patients with PPA-L often also exhibit stronger spatial memory than verbal and working memory [19,34].

**Attention and Executive Functioning**

Performance on tasks of visuomotor scanning and sequencing, tapping aspects of attention, processing speed, and executive functioning (i.e., cognitive set shifting), are generally impaired in patients with PPA-L [20,24,28,29]. Executive dysfunction on tasks of problem solving and inhibition is also prominent [24,35]. Furthermore, dyscalculia is evident in patients with PPA-L on various calculation tasks [20,32,35].

**Neuropathological Correlates**

Language impairment characteristic of PPA-L is associated with the posterior language network [20]. Impaired sentence and multword repetition, poor comprehension, deficient verbal span, poor encoding and short term memory are attributable to working memory deficits and impairment in the phonological loop [25]. Imaging studies have found phonological processing deficits, reduction in auditory short term/working memory, and repetition impairment to be associated with atrophy in the left posterior superior temporal and inferior parietal cortices [13,19,25,27]. Damage likely initially affects the tempoparietal junction and then progresses to involve the dorsal language network, including the inferior parietal and posterior frontal lobe. This subsequently affects the repetition of speech due to an impaired sensorimotor ability to link acoustic speech sounds/phonetics in the superior temporal lobe with articulatory codes in the posterior inferior frontal gyrus [37-39]. Atrophy in the dominant parietal cortex can also account for symptoms associated with Gerstmann’s syndrome [40], such as dyscalculia and phonological dyslexia [20].

**CONCLUSION**

PPA-L is characterized by expressive and receptive language deficits that increase in severity as demands on working memory and complexity increase. For example, receptive language impairment is especially evident on tasks requiring multiple steps or sentence comprehension [13,16,19,24,25]. Deficits in expressive language are most obvious on speech repetition and syntactic production, as tasks progress from the use of single words or digits to multiple digits, words, phrases, and sentences [14,16,19,25,28,33]. Although naming deficits may also occur [13,16,17,20,24-28], errors on these tasks often involve a lack of response [16,19,20,31], and are believed to result from speech hesitation or impaired working memory, rather than loss of semantic information [14,30]. Semantic knowledge is generally preserved as evidenced through tasks of single word comprehension and semantic associations [19,25,29]. Reading errors often are present as a result of phonological dyslexia, likely due to impairment in phonological processing [28]. Additional domains of neuropsychological functioning may also be reduced, including the encoding and short term recall of verbal information [19,24,25,28,32], attention, and executive functioning [20,24,28,29,35]. While visuospatial perception and visual recognition skills are typically preserved [13,19,24,35], findings are mixed regarding visuospatial constructional abilities [19,24,28,29] and verbal long term memory [13,25]. Future research should further clarify the neuropsychological profile of patients with PPA-L throughout various disease stages to aid in the differentiation of this variant from PPA-A and PPA-S.
REFERENCES


