

Language Breakdown in Primary Progressive Aphasias

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Abstract

Dementias with predominant language involvement, called primary progressive aphasias provide us with unique insight into systematic breakdown of language in neurodegenerative diseases and the structures and networks involved. Clinical and neuroimaging models quite distinct from those seen in stroke aphasias have evolved. In this short overview, we will discuss the cognitive processes involved in expressive and receptive verbal communication and how these processes are affected in the different variants of primary progressive aphasia producing distinctive clinical patterns. We will also discuss the brain's language network and how different components of the network break down in each of the primary progressive aphasia variants.

Keywords: Dementia, language network, logopenic variant, nonfluent variant, primary progressive aphasia, semantic variant

Guest editor's notes: After stroke, the second most important cause of neurogenic language and communication deficits are degenerative dementias. Their prevalence is bound to increase as the population ages. The clinical profiles of language function in Alzheimer's and Fronto-Temporal dementias are very distinct than in post stroke state and are one of the hot frontiers of research, enhancing our understanding of organisation of language and related cognitive functions in brain.

INTRODUCTION

Dementias with predominant language involvement, called primary progressive aphasias (PPA)^[1,2] provide us with unique insight into systematic breakdown of language in neurodegenerative diseases and the structures and networks involved. Clinical and neuroimaging models quite distinct from those seen in stroke aphasias have evolved.^[3] In this short overview, we will discuss the cognitive processes involved in expressive and receptive verbal communication and how these processes are affected in the different variants of PPA producing distinctive clinical patterns. We will also discuss the brain's language network and how different components of the network break down in each of the PPA variants.

The PPAs are characterized by an early and prominent breakdown in speech and language, accounting for most of the functional difficulties in the patient, in the absence of other diseases that could have better explained the symptoms.^[1,4-6] Other cognitive and behavioral functions remain relatively unaffected until later. Changes in language production, naming, repetition, syntax, and word and sentence comprehension are seen to result from a progressive breakdown of the phonological, semantic, syntactic, and motoric pathways. Degeneration occurs predominantly in key areas over the left hemispheric language network although some right hemispheric involvement is also recognized.^[7,8] On the basis of distinctive clinical and radiological findings, three PPA variants are currently recognized. These are nonfluent agrammatic variant PPA (nfvPPA), semantic variant PPA (svPPA) and logopenic variant PPA (lvPPA).^[6] Whereas nfvPPA and svPPA

are classified under frontotemporal lobar degenerations, lvPPA most commonly represents underlying Alzheimer's disease (AD) pathology.

With advances in neuroimaging models, it is now clear that the language network is distributed much more extensively than understood earlier from classical aphasiology works, much of which were derived from research on stroke aphasias.^[3] In classical aphasiology, the core regions in the perisylvian language network comprise the Broca's area [near the left inferior frontal gyrus (IFG)], the Wernicke's area (left posterior superior temporal gyrus and the temporoparietal junction region), and the arcuate fasciculus linking the two. Broca's area and adjoining regions have been associated with grammatical structure and fluency and a vascular lesion in this area affects both. Wernicke's area has traditionally been associated with language comprehension. An intact arcuate fasciculus is

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required for language repetition. Unlike in stroke aphasias, the breakdown of the language network in PPA depends not on the vascular territory affected but starts in specific areas of the brain vulnerable to deposition of toxic proteins, triggering a slow and progressive trans-synaptic spread of the degeneration process. This results in a progressive and somewhat predictable loss of function but also provides an opportunity for reorganization and compensatory mechanisms to come into play. Further, an important third center in the language network, the anterior temporal lobe, has been recognized that is fundamental to our understanding of the meaning of words (left anterior temporal lobe), as well as objects and faces and other modalities of presentation (right anterior temporal lobe). Another distinctive difference caused by selective degeneration even within a given part of the network with preservation of adjacent areas, at least in the initial stages, is exemplified by the disengagement of agrammatism from fluency in some PPA patients.^[9] This is in contradiction to the teaching in classical aphasiology where the presence of agrammatism is equated with nonfluent speech pattern.

Nevertheless, the core components of the language network continue to be around the left Sylvian fissure and can be segregated into two streams, namely, a dorsal articulatory-phonological pathway which includes the left IFG and deals with phonological encoding, grammar, and fluency, and a ventral lexico-semantic pathway mainly in the left temporal lobe, which deals with word meaning.^[10,11] The posterior perisylvian parietotemporal region connects the two streams and is thought to be responsible for visual to verbal conversion. Peak areas of atrophy within this language network correspond to the characteristic clinical observations of the different aphasias, as will be covered later.^[12,13]

As a cardinal requirement for the diagnosis of PPA, one should demonstrate early and progressive loss of language functions even when other cognitive and behavioral functions are mostly preserved, at least in the first 1–2 years of the illness.^[2] Day-to-day functional impairment during this early period and also throughout the course of illness should primarily be accountable by the increasing loss of language functions.^[6]

A good starting point to examine language breakdown in progressive aphasias is to understand the steps and cognitive processes related to expressive and receptive language functions. It is the selective loss of some of these processes with preservation of the others that define the syndromes that we will be discussing later.

For conveying a verbal message, first an idea of the message needs to be created. This is immediately followed by a mental plan of how the message should be communicated. Next come the words that need to be used and therefore be retrieved from the vocabulary. The semantic store is searched for the most suitable words, discarding words that are similar or close in meaning but are inappropriate for the occasion. The selected words should now be organized in a grammatically correct order for the message to be conveyed. The phonemes should be

correctly encoded, the motor programming of the articulatory apparatus should be flawless, and the peripheral articulatory processes should be functioning correctly.

Impairment of each of these steps is associated with characteristic errors. Poor generation of idea could result in the message not being initiated. Poor planning of how to deliver the message could result in a disorganized message being sent. Poor retrieval of words would produce anomia, especially to nouns, or cause long pauses in speech. Patients may circumlocute to make up for the anomia. Impaired ability to select from the semantic store would result in semantic paraphasias, use of high-frequency words, or use of generic words in related categories. Poor ordering of selected words results in agrammatism. If encoding of phonemes is defective, phonological errors result. Poor motor programming of speech results in hesitant and effortful speech, dysprosodic speech, or frank speech apraxia. Defective peripheral articulatory process produces dysarthria.

For receiving a verbal message, one needs to recognize the speech sounds correctly including ones like “b” and “p” that sound very similar to the ear. The message needs to be held long enough to be analyzed. The grammatical processing of the message needs to be correct and the meaning of the words used in the received message should be understood in the context of the message.

Errors in speech sound recognition cause auditory verbal agnosia. If the message cannot be held long enough due to defective phonological working memory, interpretation of long or grammatically complex sentences is lost. Defective grammatical processing of received message leads to syntactic comprehension errors and is especially noticeable with complex commands, for example, those with embedded clauses or passives. Inability to interpret the meaning of familiar words due to loss of vocabulary may lead the patient to ask for the meaning of the word or to respond incorrectly to a command.

Repeating a message that has otherwise been comprehended correctly requires intact phonological working memory and intact motor programming. Errors in the former are best observed with long sentences. Asking the subject to quickly repeat polysyllabic words several times exposes motor programming errors.

In the next part of this review, we will discuss how different components of language production, reception, and repetition are selectively affected in each of the three PPAs.

LANGUAGE BREAKDOWN IN NONFLUENT AGRAMMATIC VARIANT PPA (nfvPPA)

Patients with nfvPPA typically present with slow and hesitant spontaneous speech, word-finding difficulty, and early speech-sound errors. Tripping over words and an effort to correct them become a constant struggle that increases as the disease progresses. Pronunciation errors may initially be particularly prominent during times of stress or when

speaking too quickly. Grammatical errors occur early and initially tend to affect function words. A childhood stammer may sometimes return. Confusion between “yes” and “no” responses in conversation has consistently been noticed in nfvPPA patients.^[14] Patients may have difficulty following conversation and especially following long and complex sentences. They may also complain of difficulty in writing.

Clinical interview and formal neuropsychological tests reveal predominant language impairment especially in the initial stages of the illness. Speech is hesitant and patients have difficulty structuring their words and sentences during a spontaneous conversation. Agrammatism, one of the cardinal features of nfvPPA, may be evident in the improper use or loss of function words (pronouns, conjunctions, prepositions, for example)^[15] affecting sentence formation and giving them a telegraphic quality. Difficulty in comprehending grammatically complex sentences (passives, embedded clauses, for example) could occur early but single word comprehension is typically preserved.^[16] Motor speech errors could cause dysarthria or frank apraxia of speech (AOS), the latter characterized by variable occurrence of distortions, deletions, insertions, transpositions, and substitutions of phonemes.^[17–19] Speech is dysprosodic, vowels may be prolonged, and consonants abnormally stressed. The AOS is typically worsened when the person tries to speak fast or at times of stress.^[18] AOS may be the initial primary symptom in nfvPPA although in the majority, agrammatism eventually becomes evident.^[20] Anomia may occur due to speech sound errors although object recognition and object knowledge is retained. Anomia could be more for verbs than nouns.^[21,22] Repetition is affected and is best evident with polysyllabic words and complex sentences. Writing may be apraxic and may also provide a clue to agrammatism.

Imaging in nfvPPA typically shows posterior frontal and insular atrophy with variable superior temporal atrophy over the dominant hemisphere on MRI scans or hypometabolism over the same areas on FDG-PET scans. Structural and functional connectivity studies show early involvement of the left IFG (pars opercularis) and premotor area. Subsequent longitudinal progression of atrophy occurs from this epicenter along the “speech production network” variably to the anterior insula, supplementary motor cortex, prefrontal cortex, basal ganglia, and supramarginal gyrus.^[18,23] Indeed, this variability of network degeneration defines the clinical evolution of the nfvPPA syndrome. For example, a dissociation between verbal fluency and grammatical performance has been shown in nfvPPA.^[9] Lack of fluency has been attributed to atrophy of the premotor cortex and degeneration of the frontal aslant tract (the white matter tract connecting the IFG to the supplementary motor area) while agrammatism is related to thinning of the left IFG and the left supramarginal gyrus. Phonological and syntactic processing has been attributed to damage to the left temporoparietal junction and arcuate fasciculus. Impaired repetition corresponds to left posterior superior temporal lobe atrophy.^[9,23] However, a recent study has proposed a revised neuroanatomical model for repetition demonstrating the

importance of the temporoparietal junction and the “indirect pathway” between the Broca’s and Wernicke’s regions comprising the posterior and anterior segments of the arcuate fasciculus and located in the inferior parietal lobe.^[24] According to this model, true repetition defect, due to phonological working memory impairment, relates to posterior segment of the arcuate fasciculus, whereas impaired reproduction of polysyllabic words with retained phonological working memory is due to degeneration of the anterior segment. Mixed repetition defects are associated with damage to the inferior parietal lobe and both anterior and posterior segments of the arcuate fasciculus.^[24]

Like in many other neurodegenerative diseases including AD and behavioral variant frontotemporal dementia (bvFTD), degeneration of the language network proceeds along defined pathways as a result of trans-synaptic propagation of toxic protein accumulation. Misfolded tau protein (4R more than 3R) is the commonest pathological deposit in nfvPPA, followed by transactive response DNA binding protein 43kDa (TDP 43) (types A or B) deposits in some patients. In keeping with this predominant 4R tau deposition pattern, the disease most frequently evolves with time into progressive supranuclear palsy (PSP) or corticobasal degeneration. Patients with a 3R deposition pattern may develop Pick’s disease.^[25–29]

LANGUAGE BREAKDOWN IN SEMANTIC VARIANT PPA (svPPA)

Patients with svPPA have a fluent speech but with profound anomia.^[30,31] Low familiarity and low-frequency words are lost first. Normal day-to-day conversation, which does not depend on such low-frequency words, could therefore mask the presence of svPPA in the early stages. Some word finding pauses could occur and with disease progression increasing compensatory circumlocutions and a tendency to use “this,” “that,” or “thing” to describe items are common. Semantic errors made during naming are usually within-category errors but with increasing preference for higher frequency nouns in that category (“chair” for “sofa,” “clock” for “timer,” and “horse” for “zebra”). More generic terms (“animal” for “horse”) are used with further loss of vocabulary.^[32] Eventually, names are lost altogether and speech, although fluent, becomes empty and incomprehensible. In spite of the abundant anomia, a core symptom required to establish a diagnosis of svPPA is the loss of word meaning. Single-word comprehension deficit is usually not volunteered by the caregivers but may come out when carefully probing the history. Families and colleagues may have been taken aback when a die-hard gardening enthusiast did not understand what “spade” meant, or a physician, when asked to pass the ophthalmoscope on the consulting table, said, “What is ophthalmoscope? I don’t know what ophthalmoscope is.”

Single word comprehension deficits may be seen more abundantly during formal neuropsychological testing, during verbal to visual task (such as “point to” tasks) or verbal-verbal

tasks (such as when asked to describe about a named item). Comprehension of nouns is initially more affected and names of living items such as animals, fruits, and vegetables are most difficult to recognize. Later, comprehension of all word classes is impaired. Initially, patients may retain a vague familiarity of probably having heard the word somewhere even when they can provide no other information. Only low-frequency words may be affected first and words learnt in a second language may also be lost earlier. In a recent study looking at picture naming and word comprehension in 16 bilingual svPPA patients from India, the authors found a striking loss of performance in both the categories in L2 compared to L1 in all svPPA patients.^[33]

Reading and writing tests may bring out “regularization” errors where patients pronounce as they read (surface dyslexia) and spell as they hear (surface dysgraphia).^[30,31] Thus, the word “glove” may be written as “gluv” and “knight” read as “k-nite.” Unlike nvPPA, grammar and syntax as well as repetition and sentence comprehension, even for polysyllabic words and complex sentences, respectively, are relatively preserved. With disease progression, and extension of degeneration of the semantic language network, there is an amodal loss of concept of objects starting with low-frequency and low-familiarity ones, another of the characteristic findings in svPPA.^[6,34]

Neuroimaging in svPPA typically shows bilateral anterior temporal atrophy on MR or CT brain scans at presentation but with greater left temporal involvement in most patients, accounting for early loss of verbal semantics. Atrophy involves the inferior and lateral aspects, extending to the temporal pole. The anterior hippocampus is also affected but the posterior hippocampus, concerned with episodic memory, is typically preserved. White matter damage is seen in the inferior longitudinal fasciculus and uncinate fasciculus.^[35] Right anterior temporal atrophy is prominent in around 30% of patients and may be associated with prosopagnosia for familiar and famous faces and other visual agnosias and behavioral dysfunction including a bvFTD pattern in some.^[36–40] With time the contralateral anterior temporal lobe, the ipsilateral posterior temporal lobe, and the orbitofrontal cortex are affected.

A recent whole brain seed-based intrinsic connectivity network study using resting state functional MRI imaging isolated three networks linked to distinct regions in the inferior parietal lobe that are variably involved in language processing in svPPA.^[41] A ventral semantic network between the left anterior middle temporal and left angular gyrus; a dorsal articulatory-phonological system between the left IFG and the left supramarginal gyrus; a third network between the left posterior temporal region and the left intraparietal sulcus region that probably deals with sublexical orthography to phonology conversion. The authors found that the ventral semantic network is disrupted in svPPA and that there appears to be a possible compensatory increase in connectivity in the dorsal articulatory-phonological system. They suggested that with a loss of the semantic processing ability possessed by the ventral network, there would be increasing

use of compensatory verbalization and phonological strategies by the patient necessitating the reorganization of the dorsal network and the temporoparietal orthography-phonology conversion network. The posteriorly located temporoparietal orthography-phonology conversion network is typically spared until late in svPPA where degeneration starts anteriorly in the temporal lobe. The intraparietal sulcus in this latter network is activated during sublexical reading as typically occurs with nonlexical pseudo-word reading or in svPPA patients when a word is not recognized as a meaningful unit in its entirety. In both cases, reading is through sublexical processes where the patient breaks up the word into plausible graphemes and converts them phonemes. This pattern is also seen in surface dyslexia in svPPA.^[41]

TDP 43 Type C is by far the commonest abnormal protein deposition in the anterior temporal lobe and the connecting pathways in svPPA. Tau pathology is uncommon in svPPA and such patients typically have Pick’s disease. AD pathology has been found at autopsy in a few patients.^[42,43]

LANGUAGE BREAKDOWN IN LOGOPENIC VARIANT PPA (lvPPA)

This third variety of aphasia is characterized by marked word-finding difficulties and long pauses during spontaneous speech in the absence of agrammatism and motor speech disorders.^[6,44] Repetition of long sentences is impaired but the repetition of words is comparatively less affected, distinguishing lvPPA from nvPPA. Also, unlike nvPPA, in spite of the pauses, the patient with lvPPA does not struggle with pronunciation. Confrontational naming is impaired but to a lesser extent than in svPPA. “Tip of the tongue” phenomenon is common. Phonological errors, especially as syllable substitution, may become evident in speech. Longer polysyllabic words or long sentences may bring out the error more. The frequent pauses, false starts, the phonological errors, and attempted repair of speech impart a nonfluent character to the speech in lvPPA. Single-word comprehension is relatively preserved but sentence comprehension is affected, especially if the sentence is long. Fundamental to these symptoms of lvPPA is an impairment of phonological working memory. In keeping with this, the peak areas of atrophy are seen in the left superior temporal lobe and the adjoining inferior parietal lobe in the posterior perisylvian region (temporoparietal junction), areas that serve for phonological working memory.^[44–46] However, the area of atrophy in lvPPA appears much more extensive than in the other PPA syndromes and also includes the left precuneus, posterior cingulate gyrus and the medial temporal lobes,^[46,47] all recognized to be part of the default mode network and characteristically involved early in AD. Indeed, most cases of lvPPA have AD pathology. The recent International Working Group Criteria on AD recognize lvPPA as an atypical variant of AD subject to demonstration of AD specific biomarkers.^[48] Over time the atrophy spreads anteriorly, not only along the dorsal articulatory-phonological

pathway to the IFG region but also via the ventral semantic pathway. Involvement of the right hemisphere also occurs and mirrors the area affected on the left, namely, temporoparietal junction, posterior cingulate, and precuneus. Interestingly, longitudinal studies suggest that atrophy in lvPPA tends to remain largely asymmetrically over the left hemisphere more than the right, unlike in AD where bilateral atrophy is more typical.^[47]

In spite of the diagnostic criteria currently recommended for lvPPA,^[6] there remains a lot of overlap with this and the other PPA subtypes so that it could sometimes be difficult to distinguish from nvPPA or from svPPA. Only a combination of observations during the assessment of spontaneous speech could help the astute clinician in such situations. In a recent study using connected speech, the researchers analyzed the data taken from patients who were asked to describe the picnic scene in the Western Aphasia Battery^[49] using complete sentences.^[15] When comparing lvPPA to nvPPA, an overall assessment combining presence of distorted speech sounds (nvPPA > lvPPA), verb usage (lvPPA > nvPPA), use of embeddings in sentences (lvPPA > nvPPA), maximum speech rate (lvPPA > nvPPA), repaired speech sequences (lvPPA > nvPPA), and the presence of agrammatism (nvPPA > lvPPA) could help distinguish the two.^[15]

To discriminate between lvPPA and svPPA, a combined assessment using the maximum speech rate (svPPA > lvPPA), phonological paraphasias (lvPPA > svPPA), filled pauses (lvPPA > svPPA), repaired sequences (lvPPA > svPPA), proportion of pronouns and verbs in connected speech sequence (svPPA > lvPPA), and the use of high-frequency nouns (svPPA > lvPPA) could be useful.^[15]

There also exists an indolent form of lvPPA in which the language deficits could remain stable for many years and the patient could continue to perform daily activities due to the preservation of other cognitive functions.^[50]

LANGUAGE BREAKDOWN IN OTHER DEMENTIAS

Progressive aphasias also occur in other dementias but in them, other nonlinguistic cognitive or behavioral symptoms predominate in the early stages of illness. Fluent speech with anomia as the primary problem with preserved phonology and repetition may accompany typical AD. Some semantic paraphasias may be seen but single-word comprehension and sentence comprehension should be intact. Dynamic aphasia with conversational speech initiation difficulty may accompany PSP, bvFTD or vascular dementia due to involvement of the left frontal lobe or subcortical structures. Patients respond promptly to confrontational naming tasks or repetition tasks. Patients with prominent right anterior temporal atrophy may present with language deficits resembling svPPA, face and object recognition deficits, and early behavioral problems. The term “semantic dementia”^[30,31] continues to usefully define this group. Some of the right anterior temporal atrophy patients present with a bvFTD phenotype.^[39,51]

Patients with PSP and corticobasal syndrome may have nvPPA pattern of language impairment accompanying their defining motor presentations.

In many of these dementias, the examiner has to be careful in choosing, as well as interpreting, the formal neuropsychological tests. Linguistic performance, as much as performance in other cognitive domains, could be impaired due to a gaze disorder, visuospatial problems, episodic memory loss, impaired attention, impaired working memory and other executive functions, impaired praxis, or a markedly distractible behavior.

FINAL COMMENTS

This review attempted to give an overview of how the various components of language are affected in the different PPA variants and the salient features of each clinical variant. We also discussed in short our current understanding of the language network in the brain and how the deterioration of language functions in each of the PPA variants relates with the breakdown of this language network. Our understanding of these processes is evolving and more robust characterization of variants such as the logopenic variant is awaited. Closer home, there is a huge untapped need for research on progressive aphasias and the mechanisms of language breakdown. In a country of many languages and a substantial bilingual and multilingual population, this should not be a challenge but a natural step forward.

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