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**Primary Progressive Aphasia: Semantic  
Variant and the Loss of Humor  
Understanding**

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## Table of Contents

|                                                                                                                    |    |
|--------------------------------------------------------------------------------------------------------------------|----|
| <i>Abstract</i> .....                                                                                              | 1  |
| <i>Clinical presentation of aphasia</i> .....                                                                      | 2  |
| 1.1 Definition of aphasia .....                                                                                    | 2  |
| 1.2 Causes of aphasia .....                                                                                        | 2  |
| 1.3 Aphasias due to cerebral strokes, infections, injuries, tumors and aphasia models .....                        | 3  |
| 1.4 Aphasia due to dementia: Primary Progressive Aphasia .....                                                     | 9  |
| 1.4.1 Variants of Primary Progressive Aphasia.....                                                                 | 10 |
| 1.4.2 Diagnosis of PPA.....                                                                                        | 10 |
| <i>Semantic Variant of Primary Progressive Aphasia</i> .....                                                       | 20 |
| 2.1 Clinical presentation of Semantic Variant of Primary Progressive Aphasia .....                                 | 20 |
| 2.2 Differential diagnosis: Semantic Variant of Primary Progressive Aphasia and its<br>diagnostic lookalikes ..... | 23 |
| 2.2.1 Semantic Variant of Primary Progressive Aphasia versus Alzheimer’s Disease ....                              | 23 |
| 2.2.2 Semantic Variant of Primary Progressive Aphasia and Wernicke’s Aphasia .....                                 | 25 |
| 2.2.3 Semantic Variant of Primary Progressive Aphasia and Behavioral Frontotemporal<br>Dementia.....               | 26 |
| 2.3 Humor perception in patients with Semantic Variant of Primary Progressive Aphasia                              | 27 |
| <i>Conclusions and management of PPA</i> .....                                                                     | 31 |
| 3.1 Summa.....                                                                                                     | 31 |
| 3.2 Therapeutic interventions and future directions for research.....                                              | 31 |
| <i>References</i> .....                                                                                            | 34 |



## **Abstract**

This thesis explores the concept of aphasia, a complex language disorder that can arise either from brain damage or neurodegenerative conditions, with a specific focus on Primary Progressive Aphasia or PPA.

The first section examines aphasia, defining its major characteristics and subtypes, that can stem from cerebral strokes, infections, brain injuries and tumors, explained within the major aphasia models. It then focuses on aphasia due to dementia, specifically PPA, with its variants and diagnosis. One of the three variants of PPA, the semantic variant (svPPA), is better explored in the second section. Here, particular attention is given to differential diagnosis and distinction between svPPA and other conditions— such as Alzheimer’s Disease (AD), Wernicke’s aphasia and the behavioral variant of frontotemporal dementia (bvFTD). The link between svPPA and humor impairment is precisely discussed in this section, considering humor alteration not as an isolated feature, but rather as a part of a broad disruption of semantic knowledge, highlighting the progressive difficulty these patients have in understanding symbolic and socially nuanced language. This helps illustrate how svPPA affects not only language, but also everyday communication and social functioning. Lastly, the final section focuses on a few treatments that the research has identified so far, including speech therapy, cognitive rehabilitation, and neuroimaging techniques. This thesis concludes by highlighting some directions for future research (e.g. anendophasia), emphasizing the need for personalized therapeutic strategies to enhance communication with and quality of life of affected individuals.

## **Clinical presentation of aphasia**

### **1.1 Definition of aphasia**

Aphasia is an acquired neuropsychological disorder of linguistic communication.

It affects a person's ability to speak, understand, read, or write, usually caused by damage to areas of the brain responsible for language, such as the lateral frontal areas (located within the inferior and middle frontal gyri) and lateral temporal areas (located within the superior and middle temporal gyri, stretching from the temporal pole to the posterior extent of the temporal lobe). "*These areas are lateralized to the left hemisphere in most individuals*" (Fedorenko et al., 2024). Depending on the type and severity, a person with aphasia may struggle to find the right words, struggle with the production of sentences, and/or may have problems with comprehension of what others are saying.

### **1.2 Causes of aphasia**

Aphasia can be the end point of many different types of impairments (Grossman & Irwin, 2021). The known causes of aphasia are stroke, brain injury, infection and brain tumor, developmental disabilities or dementia. Among these, stroke is the most common cause (Code, 2021). A stroke is an abrupt, unpredicted interruption of cerebral blood supply; consequently, the brain does not receive oxygen and nutrients, and the brain tissue is damaged. There are two main types of strokes; the first is ischemic stroke, which accounts for about 87% of all strokes, and is an occlusion of blood vessels. Ischemic strokes are due either to atheroma and thrombi (athero-thrombotic stroke), or to emboli (embolic stroke).

Blood vessels are formed by three membranes: the intima, the inner, the media or intermediate, and the adventitia, the outer one. When fatty tissue and cholesterol build up between the intima and media layer, a thick atherosclerotic plaque (atheroma) develops that restricts the blood vessel. The atheroma grows and, when inner pressure is too high, the intima ruptures and the atheroma starts travelling in the blood stream. A blood clot forms at the site of the plaque rupture. A thrombus develops when the blood clot enlarges to completely block the artery, causing all the tissues supplied by the artery to die below the blockage. This is known as an athero-thrombotic stroke. On the contrary, when the plaque ruptures, tiny pieces of plaque and clotted blood travel in the bloodstream to the brain. These foreign masses, called emboli, can lodge in a small artery, blocking blood flow: this is an embolic stroke.

There is a subtype of ischemic stroke, the Transient Ischemic Attack or TIA. This is a “warning stroke” that happens when the blockage of blood flow is transient and symptoms disappear within 24 hours. Unlike other types of ischemic strokes, a TIA does not cause any permanent damage to the brain.

The second type of stroke is hemorrhagic stroke. It happens when there is a tear in a blood vessel. There are two subtypes of hemorrhagic strokes: Intra Cerebral Hemorrhage or ICH, caused by the burst of a small artery that bleeds into the brain, and Subarachnoid Hemorrhage (SAH), caused by the burst of an aneurysm— an abnormal outward lump.

Aphasia can also be due to infectious brain disease (e.g. meningitis, the infection of dura mater, arachnoid mater or pia mater, and encephalitis, viral infections of brain tissues) or to brain injuries. There are two broad types of Traumatic Brain Injuries or TBIs, that are the result of brain lesions caused by external forces to the head. The first type is the penetrating (or open) TBI, in which the skull is pierced by an object that enters brain tissue; the second is non-penetrating (or closed) TBI, in which the outside force is strong enough to move the brain within the skull.

Although aphasia typically results from a stroke or a brain injury, it can also be triggered by the presence of cerebral tumors. Cerebral tumors are pathological, space-occupying, progressive masses of cells that grow in the brain. Tumors can be further classified into primary tumors, about 20% of brain tumors, and secondary tumors, about 80% of brain tumors. Primary tumors start within the brain, from cells in the central nervous system. They can be either benign or non-cancerous— encapsulated and that don’t form metastasis— or malignant or cancerous— not encapsulated, that invade surrounding tissues and do metastasize. Secondary tumors, on the contrary, start outside the brain from other body organs and metastasize within the brain. Secondary tumors are always of the malignant type.

Among the causes of aphasia also lie developmental disabilities, for example Down syndrome, Attention-Deficit/ Hyperactivity Disorder (ADHD), Tourette syndrome, and learning disabilities.

### **1.3 Aphasias due to cerebral strokes, infections, injuries, tumors and aphasia models**

Having examined some of the causes of aphasia, it is now important to distinguish the resulting types of this condition.

To better understand the different categories, we use the Wernicke-Lichtheim model or Lichtheim's "House" in Figure 1. This model, by Ludwig Lichtheim, is based on the findings of Broca and Wernicke. In 1861, Pierre Paul Broca described a patient with motor aphasia in which damage to the inferior frontal gyrus— now known as Broca's area— impaired speech production, leaving speech comprehension intact (Sliwinska, 2015). This type of aphasia, also known as Broca's aphasia or expressive aphasia, is a non-fluent aphasia because speech is laborious, hesitant and slow; comprehension of single words and of syntactically simple sentences is intact, whereas comprehension of passive or reversible sentences is impaired. One major symptom is agrammatism, which is a reduction of sentences to a few words only (Axer et al., 2000). In fact, there is a deficit of function words, that convey syntactic structure, like articles, prepositions, etc; omission of functors (e.g. the sentence "The lion was killed by the leopard" becomes "Lion killed leopard") and omission of word endings (e.g. the sentence "The lion was killed by the leopard" becomes "Lion kill leopard") are present. Finally, motor aphasic patients are aware of their difficulties and can show frustration. In contrast, Wernicke described patients in which lesions to the superior temporal gyrus, known as Wernicke's area, caused speech comprehension impairments but left speech production intact (Sliwinska, 2015). Patients with this so called sensory or receptive aphasia present fluent speech and good articulation; yet sentences lack meaningful and comprehensible content since Wernicke's aphasics produce literal paraphasias (i.e. sounds within words are changed or left out) and verbal paraphasias (i.e. use of wrong words). Some patients produce meaningless sentences (jargon) or words (neologism) (Axer et al., 2000). Wernicke worked on a neurocognitive model of language as well, which Lichtheim later formalized and which Geschwind also expanded. Lichtheim's "House" involves three main centers: 'M' represents the motor pole of the network or Broca's area and 'A' the perceptual pole or Wernicke's area. 'B' represents the abstract notion of a 'concept center' (O'Sullivan et al., 2019).

Lichtheim acknowledged that a concept center did not exist, but that conceptual knowledge was in fact distributed among many different brain areas (Rutten, 2022). Figure 2 represents the complete version proposed by Lichtheim, where 'a' is the pathway connecting Broca's area and motor nerves, 'm' is the pathway connecting Wernicke's area and acoustic nerves (Wang & Siok, 2021), 'E' is the area containing motor memory images for control of the hand musculature for writing, and 'O' is the optic area containing visual memory images (Graves, 1997).

Adding on to the Wernicke-Lichtheim model, Geschwind theorized what is known as the 'Wernicke-Lichtheim-Geschwind model' (Figure 3) according to which language functions are

not solely localized in one cerebral area but involve a series of connections within the brain. The necessary information exchanges between Broca's and Wernicke's area are done via the arcuate fasciculus, a major fiber bundle connecting language areas in temporal cortex (Wernicke's area) and frontal cortex (Broca's area) (Hagoort, 2013).

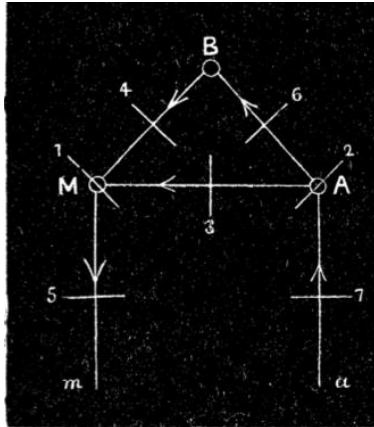


**Figure 1** The Wernicke-Lichtheim model and following lesions (Lichtheim, 1885)

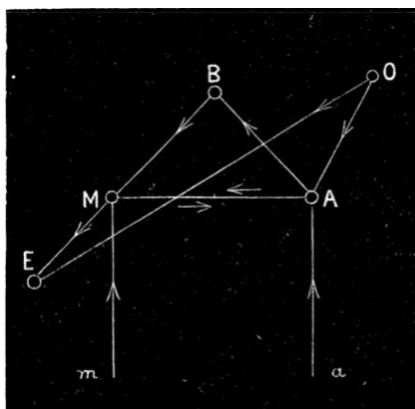


**Figure 2** The Wernicke-Lichtheim model (Lichtheim, 1885)

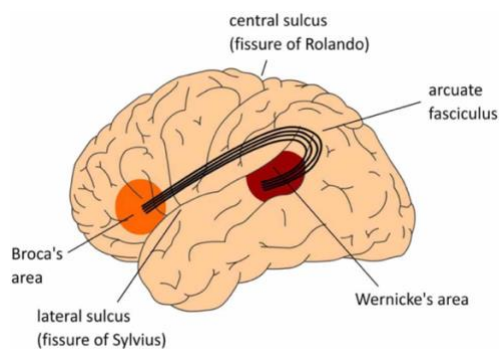


**Figure 3** The Wernicke-Lichtheim-Geschwind model (Hagoort, 2013)

Lichtheim's "House" only predicts five patterns of aphasia: (1) Broca's aphasia and (2) Wernicke's aphasia, whose symptoms have already been mentioned, both due to lesion at the two corresponding centers; (3) conduction aphasia, that impairs repetition of spoken words, is the result of a lesion between Broca's and Wernicke's areas; (4) transcortical motor aphasia, that leads to damaged oral fluency and naming, due to a lesion between the concept store and Broca's area; (5) transcortical sensory aphasia, resulting in a deficit in oral comprehension and naming, due to the damaged connection between the concept store and Wernicke's area (Cappa et al., 2025). Additionally, (6) depicts motor speech disorders like speech apraxia or anarthria (i.e. difficulty in articulatory programming for speaking) and (7) depicts pure word deafness (i.e. difficulty in understanding spoken language, repeating or writing from dictation, yet intact speaking, reading and writing).

However, Lichtheim's model didn't account for anomic aphasia, transcortical mixed aphasia and global aphasia, which can also be a byproduct of cerebral strokes, infections, injuries and tumors. In the first, only object naming is compromised; speech is typically fluent and grammar is correct, as well as comprehension and repetition. Transcortical mixed aphasia consists of damaged production and comprehension, but repetition is intact. Lastly, in global aphasia (also called total aphasia) all language modalities are affected; often communication is not possible at all (Axer et al., 2000).

The Wernicke-Lichtheim-Geschwind model remains one of the most widely used approaches in the assessment of aphasia, although a large body of evidence now suggests that it does not accurately reflect clinical reality (Fernández-Del Olmo & Medina-Valera, 2022). At a neuroanatomical level the classical model neglects the contribution of the right hemisphere, gives an imprecise delimitation of Broca's and Wernicke's areas, and does not fully account for the contribution of subcortical structures. Additionally, the Wernicke-Lichtheim-Geschwind model considers language as an isolated cognitive function, excluding its interconnection with other processes (e.g. working memory). On a diagnostic level, the model is unable to explain many signs observed in patients with aphasia falling outside diagnostic criteria, such as apraxia, nor the overlap of signs between categories (Fernández-Del Olmo & Medina-Valera, 2022). In light of the issues mentioned above, studies from the late 20th century have attempted to provide a comprehensive model of language processing. It is the case of the model proposed by Ellis and Young (see Figure 4). As Fernández-Del Olmo and Medina-Valera report "*The model includes 2 pathways of speech production, one containing a mechanism of auditory-phonological conversion for the repetition of meaningless sounds, and*

another beginning in the semantic system in order to convert thoughts into words. The authors signal the importance for language comprehension of matching words heard with known meanings, the phonological input lexicon, and the set of known words.” (Fernández-Del Olmo & Medina-Valera, 2022).

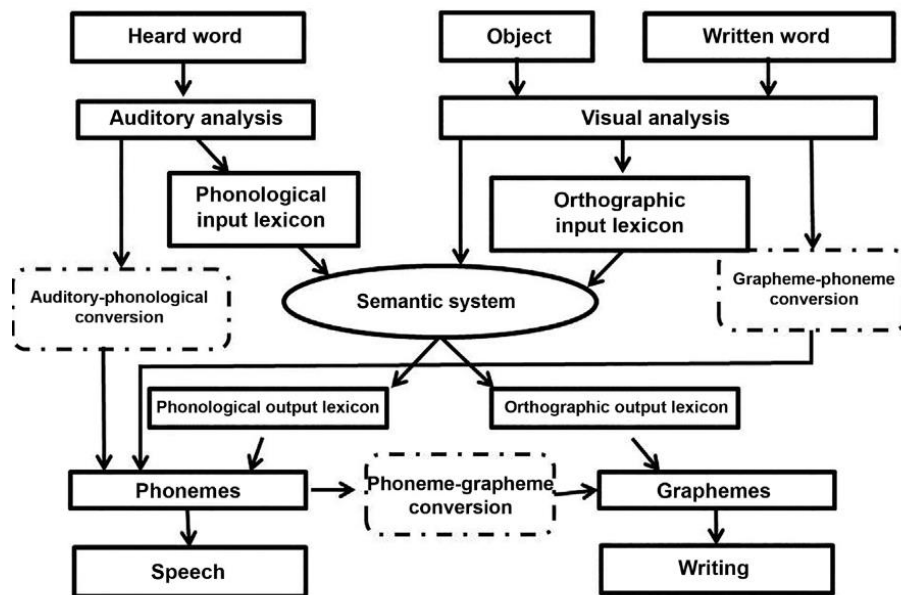


**Figure 4** The Ellis and Young model (Fernández-Del Olmo & Medina-Valera, 2022)

Neuroimaging techniques developments enabled Hickok and Poeppel to refine their two-stream model, that can be seen in Figure 5.

According to this model, early stages of speech perception depend on pathways that start from the medial geniculate body of the thalamus, that sends auditory signals to Heschl’s gyri and neighboring cortical fields on the dorsal plane of the superior temporal gyri (STG). These areas perform spectrotemporal analysis— which analyzes sound, looking at how its frequency changes over time— and project to the middle posterior portions of the superior temporal sulcus (STS), that represents the phonological network. “Subsequently, the system diverges into two broad streams, a dorsal pathway (blue) that maps sensory or phonological representations onto articulatory motor representations, and a ventral pathway (pink) that maps sensory or phonological representations onto lexical conceptual representations” (Figure 5a) (Hickok & Poeppel, 2007). The ‘how’ stream, shaded in blue and strongly left dominant, is composed of the sensorimotor interface— corresponding to the Sylvian parietal temporal area— that connects phonological representations to motor representations. The articulatory network— involving the posterior inferior frontal gyrus (pIFG), the premotor cortex (PM) and the anterior

insula— that controls the phonological loop which implements auditory short-term memory, is also part of the dorsal stream. Whereas the ‘what’ pathway, shaded in pink and bilaterally organized, is formed by the lexical interface— in the posterior middle and inferior portions of the temporal lobes— that connects the phonological representations with the semantic representations; and the combinatorial network, which integrates the complete meaning of phrases, that corresponds to the anterior middle and inferior temporal lobe, predominantly on the left (Figure 5b) (Hickok & Poeppel, 2007). To summarize, the superior or dorsal stream— which overlaps completely with the classical model— is related to verbal production, and the inferior or ventral stream, related to verbal comprehension. The ventral stream, or ‘what’ pathway, is the innovation of the model: it comprises projection from Wernicke’s area to the temporal lobe, and particularly to the anterior temporal lobe (ATL), a structure not mentioned in the classical models (Fernández-Del Olmo & Medina-Valera, 2022).

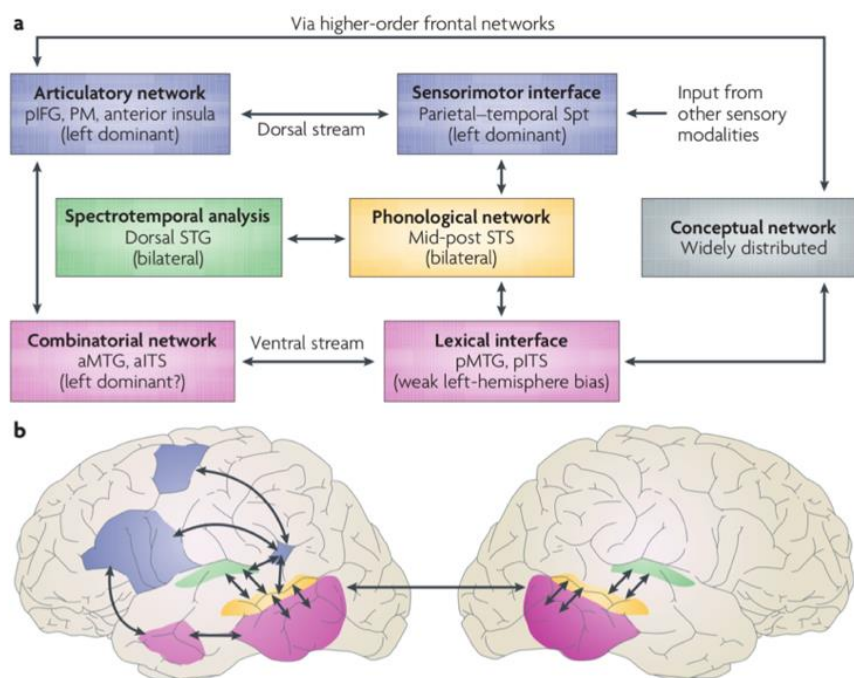


**Figure 5** The dual-stream model of the functional anatomy of language. **a)** Schematic diagram of the dual-stream model. **b)** Approximate anatomical locations of the model components (Hickok & Poeppel, 2007)

“Friederici and Gierhan studied these pathways in greater depth, dividing the dorsal and ventral pathways into 2 new segments. The dorsal pathway connects the Broca and Wernicke areas via 2 fascicles, the arcuate fasciculus (included in the classical model) and the superior longitudinal fasciculus (which has important links with the angular gyrus); the authors

associate these pathways with grammar and with phonology/repetition, respectively. The previously overlooked ventral pathway is divided into the inferior front-occipital fasciculus (IFOF) and the uncinate fasciculus (UF), related to the comprehension of isolated words and the comprehension of complex sentences, respectively.” (Fernández-Del Olmo & Medina-Valera, 2022). The original two-stream model and the renewed Friederici-Gierhan model can be seen in Figure 6a and Figure 6b.

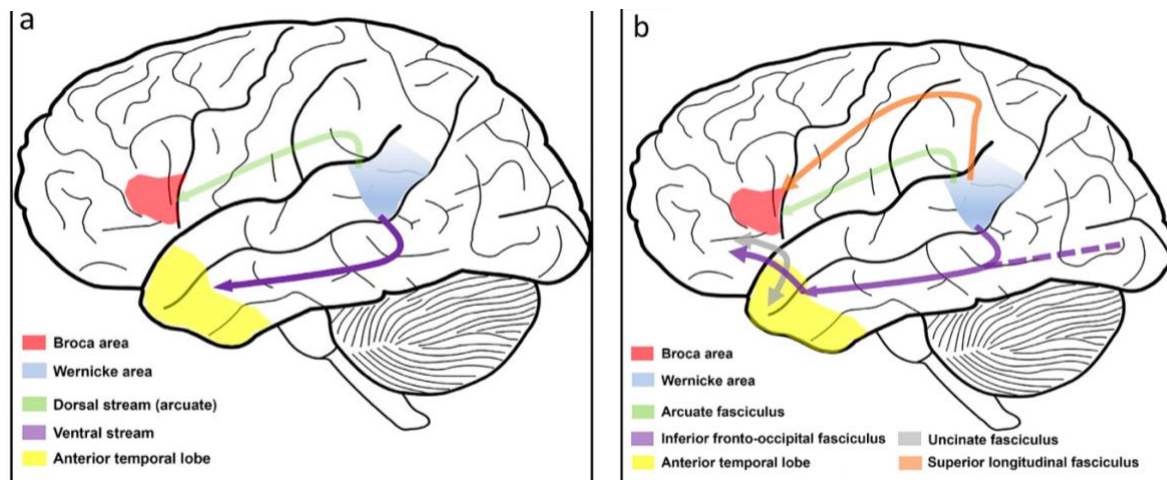


**Figure 6 a)** Representation of the two-stream model. **b)** Extended Friederici-Gierhan two-stream model (Fernández-Del Olmo & Medina-Valera, 2022)

#### 1.4 Aphasia due to dementia: Primary Progressive Aphasia

Aphasia can also be the result of dementia. This section examines the current state of knowledge regarding Primary Progressive Aphasia (PPA).

Primary Progressive Aphasia is a form of frontotemporal lobar degeneration or FTLT. Frontotemporal lobar degeneration is an umbrella term that refers to all non-AD (i.e. not Alzheimer’s disease) brain pathologies that are found in people with frontotemporal dementias. Frontotemporal dementia (FTD) is a neurodegenerative disease, one of a series of disorders in which specific populations of neurons, in the frontal and/or temporal lobes on one side of the brain or bilaterally, die. Dementias are defined as syndromes of deterioration of cognitive function, sufficient to cause disability or affect activities of daily living (Kirshner, 2014).

Given the points above, how is it that the term “aphasia” is still used in this context?

The hallmark feature of FTD is the presentation with “focal” syndromes, like PPA, that mimic pathological states— such as cerebral stroke, injury or tumor— that typically result in aphasia.

Frontotemporal dementia affects brain regions that control language, emotions, personality and behaviors— mostly, social behaviors (Setién-Suero et al., 2022).

As Grossman and Irwin (2018) report “*‘Primary’ refers to the absence of obvious structural abnormalities, including absence of stroke, space-occupying lesion, or head traumas; ‘progressive’ refers to the gradual worsening of the language deficit over several years.*” Compared with stroke or tumor aphasia, manifestations of PPA appear gradually.

#### **1.4.1 Variants of Primary Progressive Aphasia**

There are multiple forms of PPA, just as there are different types of aphasia due to stroke; the first is known as semantic variant PPA (svPPA), which, like Wernicke’s aphasia, is a fluent form of aphasia. The symptoms of the semantic variant of PPA include impairments in naming and word meanings. The second variant is the non-fluent/agrammatic variant PPA (naPPA), also known as progressive non-fluent aphasia or PPA-G, and it usually overlaps in the locus of disease with stroke aphasia, therefore having similar syndromes. naPPA weakens word production, as well as the understanding of grammatical characteristics of language needed to assemble words; this can lead to slow speech and compromised comprehension and expression. The third and final variant is the logopenic variant, also known as lvPPA or PPA-L. The logopenic variant is characterized by a word-finding difficulty, meaning impaired word retrieval, and damaged repetition, although comprehension, grammar and motor speech are preserved (Mendez et al., 2023).

#### **1.4.2 Diagnosis of PPA**

In the article “*Classification of primary progressive aphasia and its variants*”, Gorno-Tempini explains how the diagnosis for PPA works (Gorno-Tempini et al., 2011).

Initially, for a patient to be diagnosed with a specific variant of Primary Progressive Aphasia, it is necessary to meet the basic criteria for PPA, based on Mesulam’s guidelines. Table 1 shows the inclusion and exclusion criteria for its diagnosis, which requires an isolated language deficit, namely aphasia, loss of daily activities related to language (e.g. conversing, ordering food, reading, writing notes or to-do lists), with the exclusion of other neurological or psychiatric causes. “*Other cognitive functions may be affected later on, but language remains the most impaired domain throughout the course of the illness*” (Gorno-Tempini et al., 2011). As far as the exclusionary criteria go, they include absence of aphasia due to stroke or tumor,

patterns of episodic or nonverbal memory loss or visuospatial impairments. Behavioral disturbances and other deficits can also be present; however, they are not the main cause of dysfunction.

|                                                                                                             |
|-------------------------------------------------------------------------------------------------------------|
| <b>Inclusion and exclusion criteria for the diagnosis of PPA: Based on criteria by Mesulam</b>              |
| Inclusion: criteria 1-3 must be answered positively                                                         |
| 1. Most prominent clinical feature is difficulty with language                                              |
| 2. These deficits are the principal cause of impaired daily activities                                      |
| 3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease  |
| Exclusion: criteria 1-4 must be answered negatively for a PPA diagnosis                                     |
| 1. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders |
| 2. Cognitive disturbance is better accounted for by a psychiatric diagnosis                                 |
| 3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments                        |
| 4. Prominent, initial behavioral disturbance                                                                |

**Table 1** Mesulam's criteria for PPA diagnosis (Gorno-Tempini et al., 2011)

Moreover, a brief clinical evaluation of the main domain of language is needed to classify patients with a subtype of PPA. The tasks are reported in Table 2.

| <b>Task for assessment of speech and language functions in PPA</b> |                                                                                                                                            |                                                                                                                                                                                                |                                                                                                |
|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| <b>Speech/language function</b>                                    | <b>Task</b>                                                                                                                                | <b>Behavioral measures</b>                                                                                                                                                                     | <b>Variant in which impaired</b>                                                               |
| <b>Speech production</b>                                           |                                                                                                                                            |                                                                                                                                                                                                |                                                                                                |
| <b>Grammar</b>                                                     | Picture description task; story retelling (e.g., picture aided); constrained-syntax sentence production task                               | Grammatical structure; mean length of utterance; speech rate; accuracy of content; melody; prosody; specific error types in word selection; articulation                                       | naPPA                                                                                          |
| <b>Motor speech</b>                                                | Motor speech evaluation, including multiple repetitions of multisyllabic words; diadochokinesis of speech articulators; spontaneous speech | Effortfulness; hesitations; presence of apraxia of speech or dysarthria; specific types of speech sound errors; factors that affect articulation (e.g., word length in syllables)              | naPPA                                                                                          |
| <b>Confrontation naming</b>                                        | Single-word retrieval in response to pictures, sounds, foods, and odors                                                                    | Error rate; delay in naming; factors that affect naming accuracy (e.g., familiar vs unfamiliar items, nouns vs verbs, semantic category); error types (e.g., semantic errors, phonemic errors) | Severe deficits in svPPA with semantic errors; moderate deficits in lvPPA with phonemic errors |

|                                  |                                                                                                               |                                                                                                                                                                          |                                                                             |
|----------------------------------|---------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| <b>Repetition</b>                | Oral repetition of words, pseudowords, phrases, and sentences                                                 | Factors that affect repetition accuracy (e.g., predictability of the phrase, sentence length, grammatical complexity); error types                                       | lvPPA with phonological errors                                              |
| <b>Sentence comprehension</b>    | Matching orally presented sentences to pictures; answering yes/no questions; following directions             | Factors that affect comprehension (e.g., grammatical complexity; reversibility of the sentence, e.g., The boy was kicked by the girl vs The ball was kicked by the girl) | naPPA, effect of grammatical complexity; lvPPA, length and frequency effect |
| <b>Single-word comprehension</b> | Word-to-picture matching; word-to-definition matching; synonym matching                                       | Factors that affect comprehension (e.g., familiarity; frequency; grammatical word class)                                                                                 | svPPA                                                                       |
| <b>Object/people knowledge</b>   | Picture-picture matching; odd-one-out; semantic associations; gesture-object matching; sound-picture matching | Factors that affect object knowledge (e.g., familiarity, semantic category)                                                                                              | svPPA                                                                       |

|                         |  |                                                                                                                                                                                        |                                                                    |
|-------------------------|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <b>Reading/spelling</b> |  | Factors that affect reading/spelling accuracy (e.g., regularity, frequency, word class); error types (e.g., regularization, phonologically plausible errors; articulatory distortions) | svPPA with ‘regularization’ errors; lvPPA with phonological errors |
|-------------------------|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|

**Table 2** *Task for assessment of speech and language functions in PPA (Gorno-Tempini et al., 2011)*

Once a PPA diagnosis is clear, classification into one variant is specified by three levels: clinical, imaging-supported and pathological diagnosis (Gorno-Tempini, 2011). The first level consists of the presence of the specific speech and language features that are characteristic of each variant. These features have already been outlined in the previous paragraph, and they can be found summarized in the first part of Table 3 (nonfluent/agrammatic variant PPA), Table 4 (semantic variant PPA) and Table 5 (logopenic variant PPA).

|                                                                                     |                                                                                                         |
|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| <b>Diagnostic features for the nonfluent/agrammatic variant PPA</b>                 |                                                                                                         |
| I.                                                                                  | Clinical diagnosis of nonfluent/agrammatic variant PPA                                                  |
| At least one of the following core features must be present:                        |                                                                                                         |
| 1.                                                                                  | Agrammatism in language production                                                                      |
| 2.                                                                                  | Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)     |
| At least 2 of 3 of the following other features must be present:                    |                                                                                                         |
| 1.                                                                                  | Impaired comprehension of syntactically complex sentences                                               |
| 2.                                                                                  | Spared single-word comprehension                                                                        |
| 3.                                                                                  | Spared object knowledge                                                                                 |
| II.                                                                                 | Imaging-supported nonfluent/agrammatic variant diagnosis                                                |
| Both of the following criteria must be present:                                     |                                                                                                         |
| 1.                                                                                  | Clinical diagnosis of nonfluent/agrammatic variant PPA                                                  |
| 2.                                                                                  | Imaging must show one or more of the following results:                                                 |
| a.                                                                                  | Predominant left posterior fronto-insular atrophy on MRI                                                |
| b.                                                                                  | Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET               |
| III.                                                                                | Nonfluent/agrammatic variant PPA with definite pathology                                                |
| Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present: |                                                                                                         |
| 1.                                                                                  | Clinical diagnosis of nonfluent/agrammatic variant PPA                                                  |
| 2.                                                                                  | Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLN-tau, FTLN-TDP, AD, other) |
| 3.                                                                                  | Presence of known pathogenic mutation                                                                   |

Abbreviations: AD Alzheimer disease; FTLN frontotemporal lobar degeneration; PPA primary progressive aphasia.

**Table 3** Features of diagnosis for naPPA (Gorno-Tempini, 2011)

|                                                                                                            |
|------------------------------------------------------------------------------------------------------------|
| <b>Diagnostic features for the semantic variant PPA</b>                                                    |
| I. Clinical diagnosis of semantic variant PPA                                                              |
| Both of the following core features must be present:                                                       |
| 1. Impaired confrontation naming                                                                           |
| 2. Impaired single-word comprehension                                                                      |
| At least 3 of the following other features must be present:                                                |
| 1. Impaired object knowledge, particularly for low-frequency or low-familiarity items                      |
| 2. Surface dyslexia or dysgraphia                                                                          |
| 3. Spared repetition                                                                                       |
| 4. Spared speech production (grammar and motor speech)                                                     |
| II. Imaging-supported semantic variant diagnosis                                                           |
| Both of the following criteria must be present:                                                            |
| 1. Clinical diagnosis of semantic variant PPA                                                              |
| 2. Imaging must show one or more of the following results:                                                 |
| a. Predominant anterior temporal lobe atrophy                                                              |
| b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET                           |
| III. Semantic variant PPA with definite pathology                                                          |
| Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:                        |
| 1. Clinical diagnosis of semantic variant PPA                                                              |
| 2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other) |
| 3. Presence of known pathogenic mutation                                                                   |

Abbreviations: AD Alzheimer disease; FTLD frontotemporal lobar degeneration; PPA primary progressive aphasia.

**Table 4** Features of diagnosis for svPPA (Gorno-Tempini, 2011)

|                                                                                     |                                                                                                            |
|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| <b>Diagnostic features for the logopenic variant PPA</b>                            |                                                                                                            |
| I.                                                                                  | Clinical diagnosis of logopenic variant PPA                                                                |
| Both of the following core features must be present:                                |                                                                                                            |
|                                                                                     | 1. Impaired single-word retrieval in spontaneous speech and naming                                         |
|                                                                                     | 2. Impaired repetition of sentences and phrases                                                            |
| At least 3 of the following other features must be present:                         |                                                                                                            |
|                                                                                     | 1. Speech (phonologic) errors in spontaneous speech and naming                                             |
|                                                                                     | 2. Spared single-word comprehension and object knowledge                                                   |
|                                                                                     | 3. Spared motor speech                                                                                     |
|                                                                                     | 4. Absence of frank agrammatism                                                                            |
| II.                                                                                 | Imaging-supported logopenic variant diagnosis                                                              |
| Both of the following criteria must be present:                                     |                                                                                                            |
|                                                                                     | 1. Clinical diagnosis of logopenic variant PPA                                                             |
|                                                                                     | 2. Imaging must show at least one of the following results:                                                |
|                                                                                     | a. Predominant left posterior perisylvian or parietal atrophy on MRI                                       |
|                                                                                     | b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET      |
| III.                                                                                | Logopenic variant PPA with definite pathology                                                              |
| Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present: |                                                                                                            |
|                                                                                     | 1. Clinical diagnosis of logopenic variant PPA                                                             |
|                                                                                     | 2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLT-tau, FTLT-TDP, AD, other) |
|                                                                                     | 3. Presence of known pathogenic mutation                                                                   |

Abbreviations: AD Alzheimer disease; FTLT frontotemporal lobar degeneration; PPA primary progressive aphasia.

**Table 5** *Features of diagnosis for lvPPA (Gorno-Tempini, 2011)*

The previous three tables also show the other two levels of classification.

Since specific language impairments are associated with distinct regions of anatomical damage, neuroimaging— either structural or functional imaging— provides support to the clinical diagnosis: this is referred to as an imaging-supported diagnosis.

In the case of nonfluent/agrammatic variant PPA, imaging abnormalities are present in the left

posterior fronto-insular region (i.e. inferior frontal gyrus, insula, premotor and supplementary motor areas). Atrophy of ventral and lateral portions of the anterior temporal lobes bilaterally, although mostly in the left, is necessary to make a diagnosis of imaging-supported semantic variant PPA. Additionally, for the logopenic variant PPA abnormalities in the left temporo-parietal junction area (i.e. posterior temporal, supra-marginal and angular gyri) are present.

The last level of classification is the pathology diagnosis: cases that present typical clinical characteristics of each variant, independently of neuroimaging evidence, along with a genetic mutation. Specifically, in the nonfluent/agrammatic PPA patients will often show FTLD-tau or FTLD-TDP pathologic changes; in semantic PPA, FTLD-TDP is the most common finding; in logopenic PPA, Alzheimer's disease is the most common underlying pathology.

The above-mentioned "*Classification of primary progressive aphasia and its variants*" by Gorno-Tempini was also used in 2022 by the Association for Frontotemporal Degeneration (AFTD) to compile a *Diagnostic Checklist*. This checklist is designed to help identify possible PPA symptoms, evaluating problems in language production and comprehension.

It highlights difficulties with slow, labored speech, as well as with naming people and objects. It is worth noting that this checklist is not a diagnosis, but a tool to guide the healthcare provider in the assessment of PPA. The checklist also includes a back page, intended for the neurologist or geriatric neuropsychologist, in which the three levels of criteria needed for a PPA diagnosis are reported.

*"The publication of the 2011 international consensus criteria by Gorno-Tempini and colleagues marked a critical advancement in the clinical conceptualization of PPA"* (Macoir et al., 2025). Nonetheless, it presents many limitations: overlapping, evolving, or atypical presentations call for greater diagnostic flexibility and the inclusion of non-linguistic features in definitions (Macoir et al., 2025). Since the same clinical variants can arise from diverse pathological processes and, conversely, identical pathologies can manifest through different linguistic profiles, there is the need for a multidimensional model (Macoir et al., 2025).

Moreover, despite the many advances in the clinical diagnosis of PPA, there is still limited availability of standardized and appropriate diagnostic tools, not to mention the challenge of using tools that have been created for English-speaking, Western populations, on other cultures (Macoir et al., 2025). Therefore, an investment towards developing culturally sensitive tests is essential for an accurate diagnosis. It is crucial to distinguish PPA variants with their closest diagnostic lookalikes. For example, lvPPA presents word-finding pauses and phonological

errors that resemble early AD symptoms. However, in lvPPA speech remains grammatical, comprehension is preserved and phonological errors are prominent; whereas, in Alzheimer's disease, a visuospatial impairment is striking and there is a broader cognitive decline. A similar distinction applies to svPPA and behavioral variant frontotemporal dementia (bvFTD), which will be further explored in the next section. Both present behavioral and socio-emotional changes, such as loss of empathy, rigid behaviors and altered dietary preferences; though svPPA patients present profound loss of word meaning and surface dyslexia/agraphia, whereas bvFTD patients have preserved naming and comprehension, while having important executive impairments. Lastly, naPPA and apraxia of speech diagnoses can be difficult: they both share symptoms of effortful speech and motor deficits. However, they maintain distinct profiles: naPPA patients show agrammatism and impaired sentence comprehension, while in speech apraxia patients' syntax is often preserved, showing mostly speech sound distortions or motor-planning deficits (Macoir et al., 2025).

Focusing on prodromal symptoms can be helpful in early recognition of Primary Progressive Aphasia. Possible risk factors may include mild language difficulties, reduced fluency, phonological deficits (e.g. difficulty repeating long or complex words) for lvPPA, behavioral changes such as altered social behavior or reduced empathy for svPPA. Neuroimaging and biomarkers can also be of aid for early detection; "*atrophy or hypometabolism in left anterior temporal lobe, posterior temporo-parietal regions or inferior frontal gyrus may indicate early vulnerability*" (Ortiz et al., 2025), as well as elevated tau and genetic screenings for mutations (Ortiz et al., 2025).

## Semantic Variant of Primary Progressive Aphasia

### 2.1 Clinical presentation of Semantic Variant of Primary Progressive Aphasia

One of the three variants of Primary Progressive Aphasia (PPA) is the semantic variant.

Semantic variant PPA now subsumes the term “semantic dementia” (SD), denoting the loss of word meaning. In fact, previously categorized disorders of semantic memory that were divided into two categories—those with an isolated verbal deficit (unimodal impairment, often referred to as APP) and those with multimodal impairment (semantic dementia)—, are now grouped under the same umbrella term “semantic PPA” (Ortiz et al., 2025). Moreover, since *“approximately 25% of frontotemporal lobar degeneration (FTLD) cases meet the criteria for primary progressive fluent aphasia”* (Ortiz et al., 2025), the right temporal variant of frontotemporal dementia (rtvFTD) is also regarded as a subtype of svPPA (Ortiz et al., 2025).

Although the diagnostic criteria of svPPA have been presented above (see paragraph 1.4.2, *“Diagnosis of Primary Progressive Aphasia”*), a more detailed examination of diagnostic criteria and symptoms is appropriate to better understand this complex condition.

*“Semantic dementia consists of a progressive loss of semantic knowledge or ‘learned knowledge about the world’ ”* (Cole et al., 2023). Patients lose comprehension of single words, which, with time, may grow into a difficulty in understanding superordinate terms; these impairments lead to lacking sentence comprehension and sentence expression. Consequently, meaningful communication is compromised: everything is reduced to being referred to as “that” or “thing”, since superordinate terms are lost and significance of words becomes increasingly vague as the disease progresses (Grossman & Irwin, 2018). Over time, learned properties of objects and more abstract conceptual knowledge, including moral and societal rules, fail as well, as do non-linguistic domains like voice recognition, tactile stimuli and object use knowledge (Cole et al., 2023).

All the previous difficulties can be assessed with fluency tests. There are two types of fluency to test for: semantic or categorical fluency—examined by asking the patient to generate as many words as possible that belong to a specific semantic category (e.g. flowers, garments) within a limited time frame—and letter fluency—evaluated by asking the subject to recall as many words as possible that begin with a given letter. During the test, patients employ the mental strategies of switching—the ability to change subcategories during the task (e.g. words beginning with BA to words beginning with BO)—and of clustering, meaning the ability to

organize words together under the same category. Researchers showed that subjects with dementia progressively lose their switching ability during the prodromal phase (approximately five years before diagnosis), even though their overall performance remains intact. Further studies have shown that svPPA patients exhibit a significant deficit in categorical fluency tasks (Ortiz et al., 2025).

Furthermore, svPPA patients also present a profound confrontation naming difficulty: there is severe impairment in naming picture objects or using these words in spontaneous speech. Typical naming errors consist in substituting the name of a prototype (e.g. calling a camel “horse”) or using the name of a more common, familiar object sharing features with the target object (e.g. calling a pelican “robin”); more general, superordinate terms are used when a basic level name of a specific object is difficult (e.g. calling a pelican “bird” or “animal”) (Grossman & Irwin, 2018). Confrontation naming is assessed with the object naming section, a subset within the language domain in the Addenbrooke’s Cognitive Examination III (ACE-III). Originally developed as an extension of the Mini-Mental State Examination, the ACE-III tests cognitive domains of attention, memory, fluency, language and visuospatial skills (Figure 7), and it requires engagement of semantic memory and access to the mental lexicon (store of words) (Matías-Guiu, Fernández-Bobadilla, & Cortés-Martínez, 2008; Bruno & Schurmann Vignana, 2019; Cole et al., 2023).

| Cognitive domains | Tasks                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Sub-total score |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Attention         | Attention is tested by asking the patient about the date, including the season and the current location; repeating back three simple words; and serial subtraction                                                                                                                                                                                                                                                                                                  | 18 points       |
| Memory            | Memory is tested by asking the patient to recall three words previously repeated; memorizing and recalling a fictional name and address; and recalling widely known historical facts                                                                                                                                                                                                                                                                                | 26 points       |
| Fluency           | Fluency is tested by asking the patient to say as many words as they can think of starting with a specified letter within 1 minute; and naming as many animals as they can think of in 1 minute                                                                                                                                                                                                                                                                     | 14 points       |
| Language          | Language is tested by asking the patient to complete a set of sequenced physical commands using a pencil and piece of paper such as “place the paper on top of the pencil,” to write two grammatically complete sentences, to repeat several polysyllabic words and two short proverbs; to name the objects shown in 12 line drawings, and to answer contextual questions about some of the objects; and to read words with irregular sound-spelling correspondence | 26 points       |
| Visuospatial      | Visuospatial abilities are tested by asking the patient to copy two diagrams, to draw a clock face with the hands set at a specified time, to count sets of dots, and to recognize four fragmented letters                                                                                                                                                                                                                                                          | 16 points       |

**Abbreviation:** ACE-III, Addenbrooke’s cognitive examination III.

**Figure 7** Cognitive domain, tasks and sub-total score of ACE-III (Bruno & Schurmann Vignana, 2019)

Having established the clinical features and diagnostic criteria of svPPA, next we will examine its underlying neuroanatomical substrate. The semantic variant of Primary Progressive Aphasia is characterized by progressive bilateral atrophy of the anterior and ventral gray matter regions of the temporal lobe, predominantly on the left side. Atrophy commonly involves the anterior

hippocampus and the amygdala, as well as the posterior and superior gray matter regions of the right temporal lobe. Degeneration also extends dorsally to the insula and to the ventral frontal lobe (Grossman & Irwin, 2018). Brain scans highlight an evident link between semantic tasks and the anterior, ventral and posterior regions of the temporal lobe (Grossman & Irwin, 2018). Specifically, neuroimaging suggests a marked atrophy of the anterior temporal lobe (ATL), compromising the superior temporal gyrus as well, with right-lateralized atrophy occurring in 30% of cases (Cole et al., 2023). As svPPA advances, right hemispheric cortical involvement becomes more pronounced (Cole et al., 2023).

These anatomical features are particularly relevant since the affected regions form part of the ventral pathway (see paragraph 1.3, “*Aphasia due to cerebral strokes, infections, injuries, tumors and aphasia models*”). Friederici and Gierhan have theorized that “*the previously overlooked ventral pathway is divided into the inferior front-occipital fasciculus (IFOF) and the uncinate fasciculus (UF), related to the comprehension of isolated words and the comprehension of complex sentences, respectively.*” (Fernández-Del Olmo & Medina-Valera, 2022). In this perspective, the ventral pathway now becomes a multimodal structure, rather than solely a language pathway, as it connects frontal, temporal, and occipital lobes (Fernández-Del Olmo & Medina-Valera, 2022).

According to this same view, the ventral pathway includes a central hub or node, the anterior temporal lobe (ATL), which receives information from the other cortical regions distributed across various spokes. Given this “hub and spokes” model, lesions can be classified either as unimodal or multimodal: if a specific spoke is affected, the lesion will be unimodal, whereas impairment of the central hub will result in a multimodal lesion (Fernández-Del Olmo & Medina-Valera, 2022). In fact, “*People with neurodegeneration of the anterior temporal lobe (ATL) demonstrate not only verbal but also non-verbal semantic impairments*” (Cole et al., 2023).

Embodied theories of semantic memory align with this multimodal view: conceptual knowledge in semantic memory is grounded in sensory-motor systems (e.g. visual concepts recruit visual cortex, while actions engage the motor areas). Damage to the ATL in svPPA therefore disrupts the integration of modality-specific information into coherent semantic representations. For instance, the ATL integrates the elementary visuo-perceptual features (i.e. color and shape), processed by the posterior temporal lobe, to semantic knowledge; while the ventral temporal lobe is the locus of the visual association cortex, which coordinates mental imagery, high-level visual perception and object representations. svPPA-related atrophy in

these regions impairs the mapping between visual representations and semantic knowledge. Therefore, patients with svPPA become progressively unable to use visual features to recognize and assign meaning to objects, while other types of meaning (e.g. knowledge of number concepts or appreciation of musical meaning) that rely on non-visual systems can be relatively preserved (Grossman & Irwin, 2018). The progression of the disease in semantic PPA often results in associative agnosia—the person can't assign meaning to an object, despite it being accurately perceived—and behavioral disorders, when atrophy spreads to the insular and orbitofrontal cortices and to the contralateral anterior temporal lobe (Ortiz et al., 2025).

## **2.2 Differential diagnosis: Semantic Variant of Primary Progressive Aphasia and its diagnostic lookalikes**

Differential diagnosis is the process of identifying which condition, among multiple possibilities, is causing a patient's symptoms. Differential diagnosis is helpful in clinical decision-making because it indicates the correct treatment protocol and facilitates the prediction of the treatment's outcome. It also lowers the chance of missed or delayed diagnosis, by considering all likely causes; differential diagnosis also helps identify conditions with serious or life-threatening implications.

In the case of svPPA and its clinical lookalikes, differential diagnosis is crucial because it distinguishes semantic variant from other overlapping disorders that have similar memory, language and behavioral symptoms.

These next sections will examine semantic variant of Primary Progressive Aphasia and the conditions that might be mistaken for it.

### **2.2.1 Semantic Variant of Primary Progressive Aphasia versus Alzheimer's Disease**

An important aspect of diagnosing semantic variant of Primary Progressive Aphasia lies in separating it from Alzheimer's disease (AD), especially given that their symptoms can overlap. Often the progressive loss of semantic knowledge in svPPA is misdiagnosed by clinicians as memory loss due to Alzheimer's disease. However, as Figure 8 shows, there are distinct features that help clinicians distinguish svPPA from AD. Both conditions involve progressive cognitive or behavioral decline that interferes with daily functioning, but misdiagnosis is often due to the presence of word finding difficulty and semantic deficits in both diseases. Nonetheless, severe language impairment is the hallmark of svPPA—in contrast with

Alzheimer's disease, where language problems are usually less prominent or occur later (Mendez & Nasir, 2023). Compared with Alzheimer's disease patients, individuals with svPPA show greater difficulties in naming tasks. In fact, a familiarity effect is usually present in the object naming section of the Addenbrooke's Cognitive Examination III (ACE-III): patients with svPPA are able to remember commonly-used words, but struggle to recall lower-frequency words. Although Alzheimer's patients may also experience this effect, the two conditions can be differentiated by providing retrieval cues (e.g. the first letter or syllable of the word) or by offering a multiple-choice selection; patients with Alzheimer's disease are often able to identify the target word when provided with cues, whereas individuals with svPPA are unable to do so due to loss of underlying semantic knowledge (Cole et al., 2023).

Patients with svPPA also present irregular word reading and face recognition but better perform on episodic memory and visuospatial skills than Alzheimer's patients. Common svPPA symptoms also include poor single-word comprehension and surface dyslexia/dysgraphia (reading and writing based on sound patterns), which are not typical of Alzheimer's disease. Neuroimaging findings in svPPA typically reveal a more severe ATL atrophy or ATL hypometabolism, compared with AD, as shown in Figure 9 (Mendez & Nasir, 2023).

| Feature                                                                                                                                                                             | svPPA/SD [7]           | Dementia/AD [4]                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|-------------------------------------------------------|
| <b>PRESENTATION</b>                                                                                                                                                                 |                        |                                                       |
| Cognitive or behavioral symptoms that interfere with the ability to function at work or at usual activities                                                                         | Yes                    | Yes                                                   |
| Cognitive or behavioral symptoms that represent a decline for previous levels of functioning and performing                                                                         | Yes                    | Yes                                                   |
| Insidious onset over months to years                                                                                                                                                | Yes                    | Possible for dementia, Yes for AD                     |
| Clear-cut history of progressive worsening of cognition by report or observation                                                                                                    | Yes                    | Possible for dementia, Yes for AD                     |
| Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment | Yes                    | Yes                                                   |
| The cognitive or behavioral impairment involves a minimum of two cognitive domains (memory, executive, visuospatial, language, personality and behavior)                            | No                     | Yes for dementia; can have just severe amnesia for AD |
| <b>PROMINENT SYMPTOM(S)</b>                                                                                                                                                         |                        |                                                       |
| Prominent initial episodic memory, visual memory, visuo-perceptual impairments                                                                                                      | No                     | Probable                                              |
| Prominent, initial behavioral disturbance                                                                                                                                           | No                     | Possible                                              |
| Language difficulty is the most prominent clinical feature                                                                                                                          | Yes                    | Possible                                              |
| Language deficits are principal cause of impaired activities of daily living                                                                                                        | Yes                    | Possible                                              |
| Aphasia (language impairment) is the most prominent deficit at symptom onset and for the initial phases of the disease                                                              | Yes                    | Possible                                              |
| <b>LANGUAGE and SEMANTIC FEATURES</b>                                                                                                                                               |                        |                                                       |
| Impaired confrontational naming                                                                                                                                                     | Yes                    | Possible                                              |
| Impaired single-word comprehension                                                                                                                                                  | Yes                    | Possible                                              |
| Impaired object knowledge                                                                                                                                                           | No in svPPA, Yes in SD | Possible                                              |
| Surface dyslexia or dysgraphia (reading and writing by sound)                                                                                                                       | Probable               | Possible                                              |
| Spared repetition                                                                                                                                                                   | Probable               | Possible                                              |
| Spared speech production (grammar and motor speech)                                                                                                                                 | Probable               | Possible                                              |
| <b>EXCLUSIONS</b>                                                                                                                                                                   |                        |                                                       |
| Not explained by delirium or medical disorders                                                                                                                                      | Yes                    | Yes                                                   |
| Not explained by major psychiatric disorder or better accounted for by a psychiatric diagnosis                                                                                      | Yes                    | Yes                                                   |
| <b>IMAGING</b>                                                                                                                                                                      |                        |                                                       |
| Predominant anterior temporal lobe atrophy                                                                                                                                          | Yes                    | No                                                    |
| Predominant anterior temporal hypoperfusion or hypometabolism                                                                                                                       | Yes                    | No                                                    |

**Figure 8** Semantic Variant Primary Progressive Aphasia (svPPA) versus Alzheimer's Disease (AD) (Mendez & Nasir, 2023)

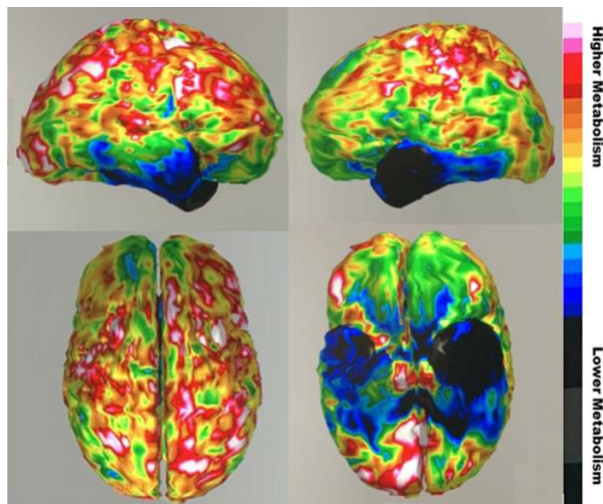


**Figure 9** Anterior Temporal Lobe (ATL) hypometabolism (Mendez & Nasir, 2023)

Additionally, reduced verbal comprehension in PPA can often mimic memory impairment found on verbal memory tasks, typical of Alzheimer’s disease. Screening tests such as the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are therefore useful for differentiating between PPA and AD. Studies using the MMSE have shown that *“patients with PPA generally perform better on temporal orientation and memory tasks than those with AD, yet they show weaker performance on language and repetition tests”* (Ortiz et al., 2025). Similarly, in MoCA assessment, PPA patients present poorer performance in language and attention tasks, whereas patients with Alzheimer’s disease showed more deficits in memory and orientation (Ortiz et al., 2025).

An important additional way of distinguishing AD-related PPA from other neurodegenerative diseases is to rely on the presence of a specific modified version of the tau protein (phosphorylated Tau or pTau) in biological samples (Ortiz et al., 2025).

### **2.2.2 Semantic Variant of Primary Progressive Aphasia and Wernicke’s Aphasia**

A key point of differential diagnosis involves distinguishing semantic variant Primary Progressive Aphasia from Wernicke’s aphasia, as both conditions are characterized by fluent speech and impaired word comprehension. Nonetheless, their difference lies in the different neuroanatomical distributions and the consequent patterns of impairment.

As Grossman and Irwin report *“In contrast to anterior and ventral temporal anatomic distribution of disease in svPPA, more posterior and superior areas of the temporal lobe are compromised in Wernicke’s aphasia”* (Grossman & Irwin, 2018). Thus, Wernicke’s aphasics

have a compromised lexical comprehension and lexical retrieval; object comprehension is well preserved, since the visual association network is intact (Grossman & Irwin, 2018). This pattern is significantly different from patients with svPPA, whose deficits involve object concepts and associated visual features. Additional features further distinguish the two conditions. Wernicke's aphasics frequently show impaired repetition, due to disruption of the arcuate fasciculus, whereas repetition difficulties are rare features in svPPA patients. Reading abilities also differ: patients with Wernicke's aphasia have preserved oral reading, while svPPA patients usually present surface dyslexia— a reading disorder characterized by mispronunciation for irregular words (Grossman & Irwin, 2018).

### **2.2.3 Semantic Variant of Primary Progressive Aphasia and Behavioral Frontotemporal Dementia**

Semantic variant of Primary Progressive Aphasia (svPPA) and behavioral variant frontotemporal dementia (bvFTD) can converge clinically as the diseases progress, therefore distinguishing the two is necessary for accurate diagnosis and management.

Over time, svPPA affects daily functioning and a behavioral syndrome emerges, characterized by mental rigidity, inflexible, repetitive or compulsive behaviors and altered food preferences. Symptoms of apathy and impaired Theory of Mind, which are usually linked to bvFTD, also appear (Cole et al., 2023). The Rascovsky criteria provide a diagnostic framework through which it is possible to distinguish bvFTD from other dementias. This framework, in Figure 10, identifies possible, probable and definite levels of bvFTD, analyzing six behavioral features of disinhibition, apathy, loss of empathy, compulsive behaviors, hyperorality and memory and visuo-spatial skills. The diagnosis that helps distinguish svPPA and bvFTD is based on the first symptoms that appear: if language impairments come first, the main diagnosis is svPPA; whereas bvFTD is diagnosed if behavioral changes are the earliest (Cole et al., 2023).

#### I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

- A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

#### II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

- A. Early\* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
  - A.1. Socially inappropriate behaviour
  - A.2. Loss of manners or decorum
  - A.3. Impulsive, rash or careless actions
- B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
  - B.1. Apathy
  - B.2. Inertia
- C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
  - C.1. Diminished response to other people's needs and feelings
  - C.2. Diminished social interest, interrelatedness or personal warmth
- D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
  - D.1. Simple repetitive movements
  - D.2. Complex, compulsive or ritualistic behaviours
  - D.3. Stereotypy of speech
- E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
  - E.1. Altered food preferences
  - E.2. Binge eating, increased consumption of alcohol or cigarettes
  - E.3. Oral exploration or consumption of inedible objects
- F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
  - F.1. Deficits in executive tasks
  - F.2. Relative sparing of episodic memory
  - F.3. Relative sparing of visuospatial skills

#### III. Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria.

- A. Meets criteria for possible bvFTD
- B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
- C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
  - C.1. Frontal and/or anterior temporal atrophy on MRI or CT
  - C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

#### IV. Behavioural variant FTD with definite FTLD Pathology

Criterion A and either criterion B or C must be present to meet criteria.

- A. Meets criteria for possible or probable bvFTD
- B. Histopathological evidence of FTLD on biopsy or at post-mortem
- C. Presence of a known pathogenic mutation

#### V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.

- A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
- B. Behavioural disturbance is better accounted for by a psychiatric diagnosis
- C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

\*As a general guideline 'early' refers to symptom presentation within the first 3 years (for further discussion see Supplementary material, Appendix 1).  
bvFTD = behavioural variant FTD.

**Figure 10** International consensus criteria for bvFTD (Rascovsky et al., 2011)

## 2.3 Humor perception in patients with Semantic Variant of Primary Progressive Aphasia

Humor is a universal social quality that plays a crucial role in shaping our everyday lives. It acts as a 'social glue', enabling individuals to connect and communicate effectively. Humor helps make interactions smoother and more enjoyable, while helping to navigate discomfort, awkward or emotionally charged situations. Yet, to understand its impact, it is important to

study humor processing at a neuroanatomical level.

Joke-specific neural activity is not confined to a single region in the brain, instead it is distributed across a network. Humor understanding is therefore a multiple-step process. The first one is the surface-level semantic analysis, supported by bilateral anterior temporal and left inferior prefrontal regions. The next stage is the interpretative integrative process, which allows the brain to detect ambiguity between the semantic representations of setup and the punch line—done by the bilateral temporo-frontal areas—; global coherence integration follows, with the activation of the anteromedial prefrontal cortex, which aids in the understanding and detection of the “twist” that defines the joke. The activity spreads anteriorly via the ventral visual stream, reaches the left-lateralized occipital area, moving forward to the anterior left temporal regions. Lastly, left-lateralized temporo-prefrontal areas contribute to the initial lexical-semantic access (Marinkovic et al., 2010). The ATLs are therefore key structures involved in the lexical-semantic stage of humor processing. However, in svPPA, the degeneration of these regions disrupts this semantic analysis mechanism, leading to an impairment in humor comprehension and appreciation.

Jokes also require mentalizing, that is our ability to represent others’ intentions. Mentalizing builds on a hierarchy of levels of intentionality (e.g. “I think that...”, “I think she thinks that...”, “she thinks that he thinks that I think that...”); the second-order intentionality is commonly known as the Theory of Mind (ToM), which is our cognitive ability to attribute and understand others’ mental states, beliefs, feelings and thoughts (Dunbar et al., 2015). Everyday conversations rely on levels above the third-order. Despite this, adults have a harder time with understanding sentences that exceed a five-level intentionality; it follows that this processing capacity also limits the level of intentionality reachable by verbal jokes. “[...] *verbal jokes that exceed the listener’s processing capacity will simply be incomprehensible*” (Dunbar et al., 2015); therefore, jokes should be tailored to push the audience’s mentalizing limits without exceeding them. Also, given that there must be a three-level intentionality to create “conversation” and that there is a natural upper limit of five levels, jokes remain processable when they involve two characters at most (Dunbar et al., 2015).

Brain imaging research has linked impairments in the Theory of Mind (ToM) to atrophy of the anterior temporal lobe, specifically right-lateralized; the right anterior temporal lobe is sensitive to socially meaningful situations (Irish et al., 2014). Consequently, damage to this region leads to the inability to interpret socioemotional information. This pattern explains why svPPA patients have particular difficulty in understanding humor that depends on social norms

or others' beliefs, as shown by Clark et al. (2015a). The study by Clark et al. (2015a) examined humor changes in forty-eight patients with a semi-structured questionnaire composed of seven elements. The answers were filled “for each patient by a normal informant who had known them well for at least 15 years” (Clark et al., 2015a). The questions are reported in Figure 11.

#### Daily Life Humour Questionnaire

---

1. Care-giver's relationship to patient:  
2. How long have you known the patient? (years):  
3. What country did s/he mainly grow up in? (to age 16)  
4. Has s/he exhibited a change in sense of humour in the course of the illness?  
If so, in what way?  
5. Does s/he find humour or laugh at things others do not find funny? Please rate:  
0, never; 1, a few times per month; 2, a few times per week; 3, daily; 4, constantly  
6. Please estimate the total hours in a typical week that s/he spends watching comedy programmes (TV or films) or looking at humorous cartoons:  
Currently: 15 years ago:  
7. Please rate his/her liking for comedy of the following kinds, according to the scale shown below  
1 10  
Dislikes very much Likes very much  
7.1 Slapstick or farcical comedy, e.g. Mr Bean, Benny Hill, Tom and Jerry  
Currently: 15 years ago:  
7.2 Satirical comedy, e.g. Yes, Minister, Punch, The New Yorker  
Currently: 15 years ago:  
7.3 Absurdist comedy, e.g. Monty Python, The Goon Show  
Currently: 15 years ago:

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The questionnaire was completed by a normal informant for each patient, in most cases their primary caregiver; healthy control participants completed a modified version of the questionnaire (comprising Questions 3,6 and 7). Informants were encouraged to seek clarification on examples of comedy genres to improve reliability and avoid bias. Patients were all known to their primary informants for >15 years.

**Figure 11** Questionnaire to assess patients' daily life humor preferences (Clark et al., 2015a)

The humor questionnaire aimed at recording patients' changes in sense of humor over the course of the illness, as well as their tendency to express humor in scenarios that are not typically funny (inappropriate laughter)— for which, informants' reports were used. The patients' total daily life comedy exposure, both in broadcast and print media, and their liking for comedy— on a 10-point Likert scale— were also measured. Specifically, the questionnaire assessed three main comedy genres: farcical or slapstick (e.g. Mr. Bean), satirical (e.g. The Simpsons) and absurdist (e.g. Alice in Wonderland). The researchers found “*Increased fatuity and relative predilection for childlike or slapstick humor and less pleasure in other comedy genres were features of all dementia syndromes, while frankly inappropriate humor in response to unpleasant or impersonal stimuli was a hallmark of bvFTD and SD.*” (Clark et al., 2015a). As shown in Figure 12, semantic dementia patients showed a reduced liking for comedy that requires social thinking, such as satire and absurdist humor. A possible explanation for this aligns with recent work that uses non-verbal cartoons to test humor perception (Clark et al., 2015b): semantic dementia and bvFTD patients have impaired recognition of humorous intent in cartoons that rely on understanding others' thoughts and social situations.

While slapstick humor typically requires detection of obvious, physical incongruities, the understanding of satirical and absurd comedy scenarios needs a mental model of social norms and others' beliefs and intentions. Usually, breaking these social norms creates surprise when the twist is understood; in SD, this interpretative process is faulty and unreliable, leading patients to attribute humor to inappropriate contexts.

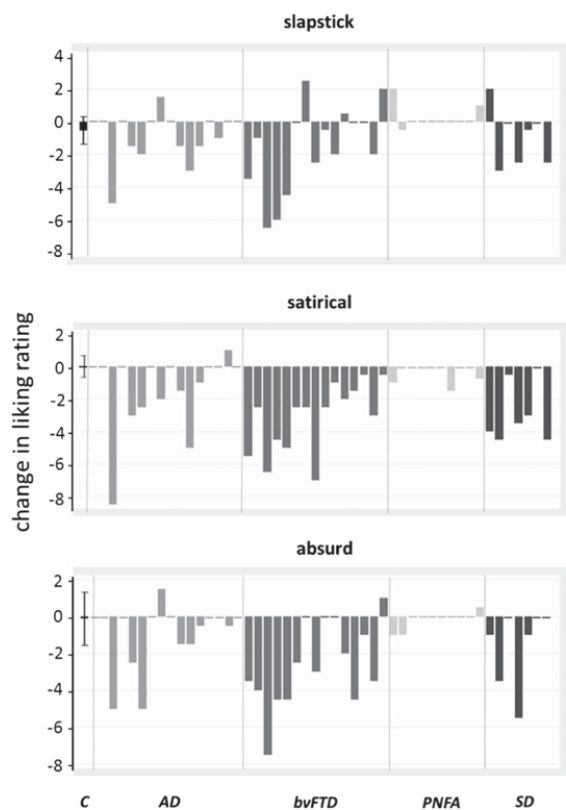


Fig. 1. Questionnaire data on changes in liking of comedy over a 15 year interval are shown for individual patients in each disease group (Alzheimer' disease, AD; behavioral variant frontotemporal dementia, bvFTD; progressive nonfluent aphasia, PNFA; semantic dementia, SD) alongside the mean change in liking for the healthy control group (C), with error bars indicating standard deviation from the mean in controls. Data for each comedy genre are plotted in separate panels. In each plot, the zero line indicates no change over the interval; values below the line indicate reduced liking and values above the line increased liking for that comedy genre, on a 10-point Likert scale (see text and Table 2 for details).

**Figure 12** Humor questionnaire data for the participant groups (Clark et al., 2015a)

In conclusion, in svPPA the loss of humor understanding is caused by the degeneration of the ATL and, consequently, of the mechanisms of ToM necessary for understanding jokes. Patients usually prefer simpler forms of humor, like slapstick, but they have problems when it comes to satire and absurdist humor. Thus, alterations in humor perception are crucial for exploring the neuroanatomical basis of social communication.

## Conclusions and management of PPA

### 3.1 Summa

This thesis has outlined the definition, causes, variants and neuroanatomical loci of Primary Progressive Aphasia (PPA), starting from the concept of general aphasia and classical aphasia models. The focus has been on the semantic variant of Primary Progressive Aphasia or svPPA, characterized by the gradual loss of word meanings, impaired naming and single-word comprehension, which extends to objects, people and the use of superordinate terms. The neuroanatomical hallmark of svPPA is anterior temporal lobe (ATL) atrophy, leading to a multi-modal disruption of semantic knowledge. Differential diagnosis with Alzheimer's disease, Wernicke's aphasia and behavioral variant frontotemporal dementia is then considered. Humor loss is examined next, since the ATL-ventral stream network and Theory of Mind mechanisms are compromised in svPPA patients, who show marked difficulties in understanding jokes and irony, linking semantic impairment to social cognition.

### 3.2 Therapeutic interventions and future directions for research

Building on this theoretical framework, current therapeutic approaches for PPA and future directions for research are reviewed.

As of today, no pharmacological treatment for PPA exists. Antidepressants are usually prescribed, since patients' awareness of the disease can lead to depressive symptoms; positive effects of antidementia drugs have been suggested, even though the results remain inconclusive (Ortiz et al., 2025). Moreover, some studies have looked at the role played by serotonin, which regulates moods, and at boosting serotonergic transmission using selective serotonin re-uptake inhibitors (SSRIs), although mixed results were found (Cole et al., 2023). Transcranial magnetic stimulation (TMS) has shown significant improvements in daily activities, but it requires further validation as well (Ortiz et al., 2025). Fernández-Romero et al. (2025) have shown that a specific type of transcranial brain stimulation (TMS)— theta-burst TMS— combined with language therapy over six months can slow PPA progression, associated with a *“reduction in decline of regional brain metabolism and improvements in trained language abilities, functional independence, and neuropsychiatric symptoms.”* (Fernández-Romero et al., 2025).

Non-pharmaceutical interventions are the most effective treatment currently available. These types of interventions revolve around educating caregivers, modifying the environment and

optimizing communication with speech therapy (Cole et al., 2023). “*Speech and language therapy (SLT) plays a crucial role in management*” (Cole et al., 2023): speech therapy is commonly suggested, as it optimizes the patients’ residual capacities (Ortiz et al., 2025). The frequency of therapy sessions should be tailored to individual needs and based on the progression of the disease (Ortiz et al., 2025). Therapy in svPPA specifically should focus on maintaining or improving access to both names and semantic representations (Suárez-González et al., 2021). “Look, listen, and repeat” (LLR) or “repetition (and reading) in the presence of picture” (RRIPP) approaches have shown to improve vocabulary, however they might lead to rigid and context-specific learning (Suárez-González et al., 2021). Naming items with residual semantic knowledge is proven to be easier to rehabilitate than that of items completely devoid of meaning. Great success in rehabilitation is achieved with familiar items, since they degenerate slower due to regularly reinforced use (Suárez-González et al., 2021). Most studies have shown good adherence of people to practice. For some patients with svPPA, 73% to 82% of the words named at the end of treatment can still be successfully named after 3 to 6 months; others show modest to low levels of retention—which might be obviated by regular revision of re-learned words. “*A consistent finding across most svPPA treatments studies is that untrained words do not improve*” (Suárez-González et al., 2021). Successful naming has been observed when svPPA patients are tested on alternative versions of trained items.

As an alternative to direct speech treatments, compensatory approaches have also been proposed. They include the use of augmentative and alternative communication (AAC) systems, where external devices improve communication (e.g. notebooks, smartphones, tablets or computers). Research has demonstrated that AAC should be integrated with other treatment approaches and used as early as possible in the disease process, so that patients have time to learn the processes and practice (Suárez-González et al., 2021). In the same vein, conversation-based, partner-inclusive therapy has shown to improve communication with svPPA patients. Teaching patients’ family members or partners how to communicate in a way that makes conversation possible for patients with svPPA is a valuable tool; having supportive conversation partners who focus on the global message and help guide the conversation forward, is helpful in improving everyday interactions (Taylor-Rubin et al., 2017). Improving conversation with family and friends was found to be crucial, since it has been shown that PPA patients express the desire for greater collaboration within their social networks and communities (Volkmer et al., 2026). Today, Artificial Intelligence can also support the assessment and rehabilitation of aphasia, but still requires refinement, particularly in understanding patients’ emotional needs (Zhong, 2024). Therefore, the optimal strategy is a

combined model, in which healthcare professionals can work with AI tools, benefitting from its strengths while still preserving human empathy (Zhong, 2024).

Future research could look more closely into the relationship between svPPA and anendophasia, or the loss of inner speech (Nedergaard & Lupyan, 2024). Since svPPA involves the progressive erosion of semantic meaning and inner speech requires access to these word meanings, it could be hypothesized that svPPA leads to anendophasia (acquired anendophasia). As meanings are lost, patients lose two fundamental abilities: the understanding and naming words, and the use of language internally— causing, in extreme cases, the complete loss of inner speech.

Exploring this relationship would give an important and innovative perspective on how degenerations like svPPA shape thought and contribute to establish a more complete neurological model of speech. It could also significantly improve clinical assessment and diagnosis of svPPA: acquired anendophasia may represent an early marker of the disease, helping clinicians understand patients' subjective experiences.

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