UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE MEDICINA

TESIS DOCTORAL

Efecto a largo plazo de la estimulación magnética transcraneal en la afasia progresiva primaria

Long-term effects of transcranial magnetic stimulation in primary progressive aphasia

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Lucía Fernández Romero

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Jordi Matías-Guiu Antem
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LIST OF ABBREVIATIONS

AAC	Augmentative and Alternative Communication
AAL	Automated Anatomical Labeling
ACE	Addenbrooke's Cognitive Examination
AD	Alzheimer's Disease
AE	Adverse Event
ANCOVA	Analysis of Covariance
BADL	Basic Activities of Daily Living
CARE	Communication Access Real-life Engagement
CART	Copy and Recall Treatment
CDR	Clinical Dementia Rating
CI	Confidence Interval
CT	Computed Tomography
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalogram
EOD	Early-Onset Dementia
FDG	Fluorodeoxyglucose
FTD	Frontotemporal Dementia
FTLD	Frontotemporal Lobar Degeneration
IADL	Instrumental Activities of Daily Living
ICC	International Consensus Criteria
IDDD	Interview for Deterioration in Daily Living in Dementia
ITT	Intention-To-Treat
LASSO	Least Absolute Shrinkage and Selection Operator
LRT	Lexical Retrieval Treatment
LSO	Lutetium Oxyorthosilicate
lv-PPA	Logopenic Varian Primary Progressive Aphasia
MLSE	Mini Linguistic State Examination
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MSE	Mean Squared Error
nfv-PPA	Non-fluent Variant Primary Progressive Aphasia

NIBS	Non-Invasive Brain Stimulation
NN	Neuronorma
NPI	Neuropsychiatric Inventory
PAS	Paired Associative Stimulation
PCA	Posterior Cortical Atrophy
PET	Positron Emission Tomography
PPA	Primary Progressive Aphasia
RMSE	Root Mean Square Error
ROCF	Rey-Osterrieth Complex Figure
ROI	Region of Interest
RSME	Root Square Mean Error
SD	Standard Deviation
SE	Standard Error
SLT	Speech and Language Therapy
SPSS	Statistical Package for the Social Sciences
SUVR	Standardized Uptake Value Ratio
sv-PPA	Semantic Variant Primary Progressive Aphasia
TBS	Theta Burst Stimulation
TDP	TAR DNA-binding Protein
TMS	Transcranial Magnetic Stimulation
VOSP	Visual Object and Space Perception
WPM	Words Per Minute
WSS	Within-Cluster Sum of Squares

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RESUMEN

La afasia progresiva primaria (APP) es un síndrome neurodegenerativo caracterizado por un deterioro progresivo del lenguaje. A diferencia de otras enfermedades neurodegenerativas, afecta de forma selectiva a las funciones lingüísticas durante las fases iniciales, sin un tratamiento farmacológico aprobado hasta la fecha. En los últimos años, ha aumentado el interés por las intervenciones de neuromodulación, como la estimulación magnética transcraneal (EMT), que han mostrado beneficios a corto plazo, combinado también con terapia del lenguaje. Sin embargo, aún no se ha establecido una intervención eficaz con efectos sostenidos en el tiempo.

En este contexto, el presente estudio se propuso investigar los efectos a largo plazo de un tratamiento combinado de EMT y terapia de lenguaje en personas con APP. Para ello, se plantearon los siguientes objetivos: 1) Comparar el efecto de la TMS combinada con terapia del lenguaje frente a la terapia del lenguaje con TMS simulada sobre la progresión de la APP, según el metabolismo cerebral medido con FDG-PET a los 6 meses. 2) Comparar el efecto de la TMS y la terapia del lenguaje frente a la terapia del lenguaje con TMS simulada sobre la denominación por confrontación en la APP, medido mediante la denominación de palabras entrenadas a los 6 meses. 3) Comparar el efecto de la TMS y la terapia del lenguaje frente a la terapia del lenguaje con TMS simulada sobre la actividad funcional en la APP, medido mediante el Mini-Linguistic State Examination (MLSE) a los 6 meses. 4) Comparar el efecto de la TMS y la terapia del lenguaje frente a la terapia del lenguaje con TMS simulada sobre el habla espontánea en la APP, medido por el número de palabras por minuto a los 6 meses. 5) Comparar el efecto de la TMS y la terapia del lenguaje frente a la terapia del lenguaje con TMS simulada sobre la actividad funcional en la APP, medido mediante la escala IDDD (Entrevista para el Deterioro en las Actividades de la Vida Diaria en la Demencia) a los 6 meses. 6) Comparar el efecto de la TMS y la terapia del lenguaje frente a la terapia del lenguaje con TMS

simulada sobre los síntomas neuropsiquiátricos en la APP, medido mediante el Inventario Neuropsiquiátrico (NPI) a los 6 meses.

Se llevó a cabo un ensayo clínico aleatorizado, doble ciego, paralelo y controlado en el que participaron 63 personas diagnosticadas con APP. Los participantes recibieron seis meses de terapia de lenguaje basada en la evidencia, combinada con TMS activa o simulada en una proporción 2:1. La intervención consistió en estimulación theta burst intermitente (iTBS) sobre el córtex prefrontal dorsolateral izquierdo (DLPFC), aplicada durante seis meses.

Los resultados muestran que el grupo que recibió el tratamiento activo a seis meses presentaron un menor declive del metabolismo de las regiones cerebrales relacionadas con la enfermedad y mejoras en las habilidades del lenguaje y capacidades lingüísticas y funcionales, así como en los síntomas neuropsiquiátricos en comparación con el grupo que recibió la estimulación simulada.

En conclusión, este estudio respalda el uso de la TMS como una herramienta terapéutica prometedora para potenciar la intervención logopédica en la PPA, con beneficios funcionales sostenidos a largo plazo**.**

ABSTRACT

Primary Progressive Aphasia (PPA) is a neurodegenerative syndrome characterised by a progressive deterioration of language. Unlike other neurodegenerative diseases, it selectively affects linguistic functions during the early stages and currently has no approved pharmacological treatment. In recent years, there has been increasing interest in neuromodulation interventions, such as transcranial magnetic stimulation (TMS), which have shown short-term benefits, especially when combined with speech and language therapy. However, an effective intervention with sustained long-term effects has not yet been established.

In this context, the present study aimed to investigate the long-term effects of a combined TMS and speech therapy treatment in individuals with PPA. To this end, the following objectives were defined: 1) To compare the effect of TMS combined with speech therapy versus speech therapy with sham TMS on the progression of PPA, as determined by brain metabolism measured with FDG-PET at 6 months. 2) To compare the effect of TMS and speech therapy versus speech therapy with sham TMS on confrontation naming in PPA, as measured by naming of trained words at 6 months. 3) To compare the effect of TMS and speech therapy versus speech therapy with sham TMS on functional activity in PPA, as measured by the Mini-Linguistic State Examination (MLSE) at 6 months. 4) To compare the effect of TMS and speech therapy versus speech therapy with sham TMS on spontaneous speech in PPA, as measured by the number of words per minute at 6 months. 5) To compare the effect of TMS and speech therapy versus speech therapy with sham TMS on functional activity in PPA, as measured by the IDDD scale (Interview for Deterioration in Daily Living Activities in Dementia) at 6 months. 6) To compare the effect of TMS and speech therapy versus speech therapy with sham TMS on neuropsychiatric symptoms in PPA, as measured by the Neuropsychiatric Inventory (NPI) at 6 months.

A randomized, double-blind, parallel, controlled clinical trial was conducted with 63 participants diagnosed with PPA. Participants received six months of evidence-based speech therapy combined with either active or sham TMS in a 2:1 ratio. The intervention consisted of intermittent theta burst stimulation (iTBS) applied to the left dorsolateral prefrontal cortex (DLPFC) over a six-month period.

The results show that the group receiving active treatment exhibited less decline in the metabolism of disease-related brain regions and improvements in language abilities, linguistic and functional capacities, as well as neuropsychiatric symptoms, compared to the group receiving sham stimulation.

In conclusion, this study supports the use of TMS as a promising therapeutic tool to enhance speech and language intervention in PPA, with sustained long-term functional benefits.

1. INTRODUCTION

1.1 History of primary progressive aphasia

Primary Progressive Aphasia (PPA) is a neurodegenerative syndrome characterized by a gradual speech and/or language impairment, with relative preservation of other cognitive functions (such as memory and visuospatial abilities) at least during the initial stage of the disease (Mesulam, 2003).

PPA was first described in the recent literature by Mesulam (1982) when he reported six patients with a "slowly progressive aphasia" that occurred without generalized dementia. Although previous cases with similar characteristics had been reported in the literature, his work played a pivotal role in recognising PPA as a distinct clinical syndrome. In subsequent years, additional reports of patients with similar language impairments and disease progression were published, reinforcing the concept of PPA as a unique syndrome. (Weintraub et al., 1990; Yamamoto et al., 1990).

Initially, PPA was considered a relatively uniform language disorder. The patients described by Mesulam, in addition to anomia, had hypofluent spontaneous speech and made grammatical errors. This manifestation was later presented as non-fluent variant (nfv-PPA). However, further research demonstrated that it encompassed multiple subtypes with distinct clinical features. Warrington (1975) described three patients with fluent spontaneous speech, but with impaired semantic memory. This condition was later described by other authors (Basso et al., 1988). Early classifications proposed two main variants: a non-fluent variant (nfv-PPA) and a fluent variant, later known as the semantic variant (sv-PPA) (Snowden et al., 1992; Hodges & Patterson, 1996).

The nfv-PPA was characterized by effortful, halting speech with distorted articulation and prosodic abnormalities, often accompanied by apraxia of speech (Grossman et al., 1996). In contrast, the sv-PPA presented with severe anomia and impaired single-word comprehension

due to a loss of semantic memory, while syntax and phonology remained relatively preserved (Hodges & Patterson, 1996).

Over time, the two-variant classification was reconsidered as an oversimplification. Researchers observed that some PPA cases were associated with Alzheimer's pathology, leading to the identification of a third variant. In an attempt to improve the characterization of PPA and differentiate it from AD patients, Kertesz et al. (2003) described a form of logopenic PPA, characterized by word-finding difficulties, but preserving the syntactic and phonetic aspects of language. In 2004, Gorno-Tempini and colleagues provide a better description of the logopenic variant (lv-PPA), which was distinct in both cognitive and neuroanatomical characteristics. The lv-PPA was characterized by slow and hesitant speech, significant word-finding difficulties, and impaired sentence repetition. Unlike nfv-PPA, the hesitancy in lv-PPA was due to lexical retrieval deficits rather than motor speech impairments. Compared to sv-PPA, lv-PPA patients exhibited relatively preserved word comprehension and semantic knowledge, but their language production was less fluent. Structural neuroimaging revealed that sv-PPA, nfv-PPA, and lv-PPA had distinct patterns of brain atrophy, corresponding to different language-processing areas (Gorno-Tempini et al., 2004; Rohrer & Warren, 2010; Migliaccio et al., 2009). The 2011 International Consensus Diagnostic Criteria (ICC) formally recognized lv-PPA as the third distinct variant of PPA (Gorno-Tempini et al., 2011).

1.2. Epidemiology, classification and clinical features of PPA

PPA has been identified across various regions worldwide, with no evidence of specific geographic concentration. Prevalence estimates are relatively consistent across different regions, ranging from 3 to 7 cases per 100,000 individuals (Magnin et al., 2016). Within Memory Clinics, it is estimated that between 0.5% and 2.5% of patients diagnosed with a

neurodegenerative disorder have PPA. In the general population, the overall prevalence is estimated at approximately 1 in every 100,000 people (Baumann et al., 2009; Ortiz et al., 2025). In a large study Chiari et al. (2021) analyzed the clinical presentations of early-onset dementia (EOD). Among all cases of Alzheimer's disease (AD), 17.7% presented with the lv-PPA, while 7.9% were diagnosed with PPA of unspecified variant. Within the frontotemporal dementia (FTD) spectrum, 15.3% of patients had the sv-PPA, and 2.5% had the nfv-PPA. When considering all clinical subtypes of EOD, lv-PPA was the third most common presentation after amnestic AD and behavioral variant FTD (bvFTD), followed by sv-PPA and posterior cortical atrophy (PCA).

A study conducted by Magnin et al. (2016), based on a nationwide French cohort, estimated the prevalence of PPA at 3.1 per 100,000 individuals, with the highest rates observed in people aged 70 to 80 years. Notably, the nfv-PPA and lv-PPA were more common in older individuals and more frequently diagnosed in females, particularly after the age of 80. In comparison, the sv-PPA had an earlier onset and showed a longer diagnostic delay. The length of the disease can differ greatly, typically ranging between 4 and 14 years, with an average course of about 8 years.

PPA most commonly begins between the ages of 50 and 65, with earlier studies reporting a mean age of onset around 59 years (Westbury & Bub, 1997; Cerami et al., 2012). However, the age at symptom onset can vary substantially, ranging from as early as the 30s to as late as the 80s (Johnson et al., 2005; Le Rhun et al., 2005). Recent evidence from Watanabe et al. (2025) places the average age of onset at 63.5 years, reflecting a shift toward slightly older age in more recent cohorts. Subtype-specific patterns have also emerged. For instance, Johnson et al. (2005) found a mean onset of 63 years (±9.7) for nonfluent PPA and 59 years (±8.2) for the semantic variant. Hodges et al. (2010) reported a later onset for semantic variant PPA (64.2 years ±7.1), while Gorno-Tempini et al. (2004) described mean onset ages of 63

years for sv-PPA, 67.9 years for nfv-PPA, and 72 years for lv-PPA. Interestingly, a subsequent study by the same group focusing on lv-PPA reported a younger onset of 58.8 years (Gorno-Tempini et al., 2008).

Sex-related patterns have become increasingly evident in recent research. While earlier studies, such as that by Weistbury and Bub (1997), indicated a slight predominance of PPA in males, and Gorno-Tempini et al. (2004) suggested no significant sex differences or even a higher prevalence in females, more recent data provide a clearer picture. For example, Pengo et al. (2022) found that bvFTD was more prevalent in men, whereas women were more frequently diagnosed with PPA. Likewise, in one of the largest FTLD cohorts, Illán-Gala et al. (2021) reported that patients with bvFTD included a higher proportion of men (72%), whereas among those with the non-fluent variant of PPA, only 28% were male.

For the diagnosis of PPA, certain diagnostic criteria must be met, based on Mesulam (2001). These criteria are fundamental for distinguishing PPA from other neurodegenerative disorders and ensuring accurate diagnosis. The key features of these diagnostic criteria are summarized in the Table 1 below:

Table 1. Diagnostic Criteria for Primary Progressive Aphasia: Based on criteria by Mesulam (2001)

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 living 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

It is now recognized to encompass three distinct subtypes: nfv-PPA, sv-PPA and lv-PPA. These subtypes are differentiated by clinical features, anatomical patterns of brain atrophy, and pathological findings.

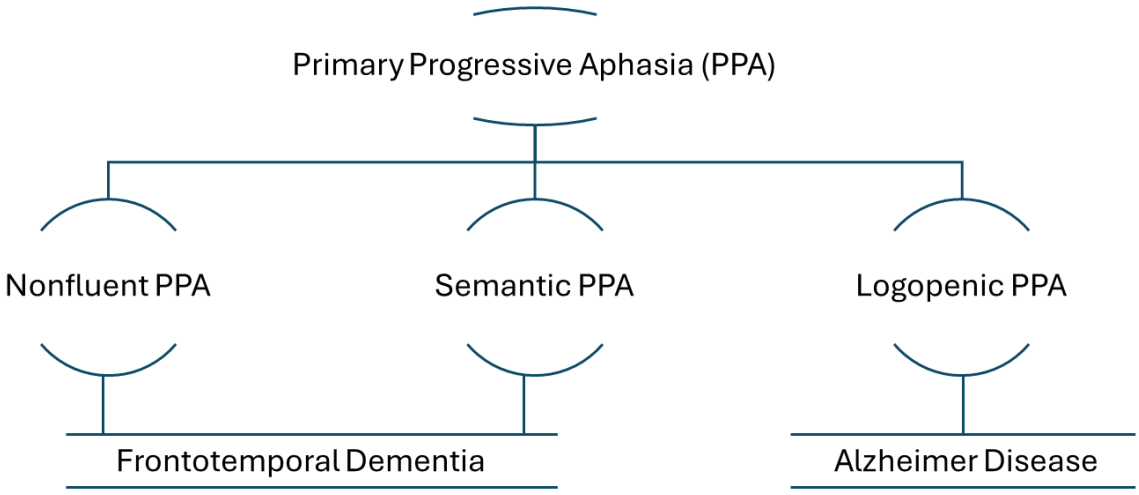

Figure 1. Clinical Variants of Primary Progressive Aphasia and Their Associated Neuropathologies.

1.2.1. Nonfluent/Agrammatic Variant (nfv-PPA)

The nfv-PPA is primarily characterised by a progressive impairment in speech production. Individuals with this subtype typically present with effortful, halting speech that is often grammatically incorrect, a phenomenon referred to as agrammatism. In the early stages, patients may experience difficulty forming words, resulting in disjointed and fragmented

speech. This is frequently accompanied by apraxia of speech, a motor planning disorder that further disrupts verbal communication.

Clinical Features (Rohrer et al., 2010; Gorno-Tempini et al., 2011):

- Speech becomes slow, effortful, and distorted.
- Grammatical construction deteriorates, with frequent omission of function words (e.g., "is," "the") and difficulty with verb conjugation.
- Difficulties are observed in both spontaneous speech and repetition tasks.
- As the disease advances, the ability to produce fluent and comprehensible speech declines markedly.

Anatomical and Pathological Features:

- Anatomically, nfv-PPA is associated with atrophy in the left posterior frontal lobe, especially in regions critical for speech production, such as the left inferior frontal gyrus (Broca's area), which plays a key role in motor speech and syntactic processing (Mandelli et al., 2016; Montembeault et al. 2018).
- From a pathological perspective, nfv-PPA is most linked to tauopathies. Different TDP-43 proteinopathies are also associated (Spinelli et al., 2017).

Table 2. Diagnostic features for the nonfluent/ agrammatic variant PPA by Gorno-Tempini et al. (2011)

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 or
    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., FTLD-tau, FTLDTDP, AD, other)
3. Presence of a known pathogenic mutation

Abbreviations: *PPA* = Primary Progressive Aphasia; *MRI* = Magnetic Resonance Imaging; *SPECT* = Single Photon Emission Computed Tomography; *PET* = Positron Emission Tomography; *FTLD* = Frontotemporal Lobar Degeneration; *FTLD*-tau = FTLD with tau pathology; *FTLD-TDP* = FTLD with TDP-43 pathology; *AD* = Alzheimer's Disease.

1.2.2. Semantic Variant (sv-PPA)

The semantic variant of Primary Progressive Aphasia (sv-PPA) is marked by a profound impairment in the comprehension of word and object meaning, despite relatively preserved speech production in the early stages of the disease (Snowden et al., 1989; Gorno-Tempini et al., 2011). Individuals with sv-PPA progressively lose access to semantic memory—that is, the store of knowledge about words, objects, people, and concepts. As a result, they struggle to understand the meaning of spoken and written words, which underlies their difficulties with comprehension. Although their speech remains fluent and grammatically correct, it often

becomes empty or vague due to the degradation of word meaning. Over time, this semantic deterioration extends beyond language, leading to marked impairments in the recognition of familiar objects, people, and faces (Montembeault et al., 2017).

Clinical Features:

- Individuals with sv-PPA exhibit progressive word comprehension difficulties, particularly for words that represent concepts or objects.
- Speech is generally fluent and grammatical, but the content becomes increasingly nonsensical or vague.
- Patients often have trouble naming objects and people (anomia) and may use vague terms or make semantic errors (e.g., calling a dog a "cat" or a "pet").
- As the disease progresses, the ability to recognize objects, faces, and specific words diminishes, leading to severe impairments in social communication and interaction.

Anatomical and Pathological Features:

- Anatomically, sv-PPA is characterized by atrophy in the anterior temporal lobes, particularly on the left side. The anterior temporal lobe plays a crucial role in semantic processing and the storage of conceptual knowledge (Mesulam et al., 2009).
- Pathologically, sv-PPA is closely associated with TDP-43 type C pathology (Spinelli et al., 2017).

Table 3. Diagnostic criteria for the semantic variant PPA by Gorno-Tempini et al. (2011)

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 diagnostic 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 PPA 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, FTLDTDP, AD, other)
3. Presence of a known pathogenic mutation

Abbreviations: *PPA* = Primary Progressive Aphasia; *SPECT* = Single Photon Emission Computed Tomography; *PET* = Positron Emission Tomography; *FTLD* = Frontotemporal Lobar Degeneration; *FTLD-tau* = FTLD with tau pathology*; FTLD-TDP* = FTLD with TDP-43 pathology; *AD* = Alzheimer's Disease.

1.2.3. Logopenic Variant (lv-PPA)

The lv-PPA is characterized by difficulties in word retrieval and word-finding pauses during speech. While patients may initially retain the ability to construct grammatically correct sentences, they experience frequent interruptions in speech due to the inability to retrieve words quickly. This variant is often associated with a reduced ability to repeat sentences or complex phrases, which primarily arises from an impairment of phonological short-term memory. (Gorno-Tempini et al., 2008).

Clinical Features:

- The hallmark feature of lv-PPA is difficulty in word retrieval, which leads to frequent pauses in speech as the individual struggles to find the correct words.
- Individuals with lv-PPA may have difficulty repeating complex sentences, which distinguishes it from other forms of aphasia.
- Despite frequent pauses, grammar and sentence structure tend to remain intact in the early stages of the disease.
- Phonological errors are common, where patients may substitute similar-sounding words or syllables in their attempts to retrieve the correct word.

Anatomical and Pathological Features:

- Anatomically, lv-PPA is associated with atrophy in the posterior perisylvian region of the left hemisphere, particularly in areas that connect language processing regions, including the posterior temporal lobe and the angular gyrus (Spinelli et al., 2017).
- Pathologically, lv-PPA is most often linked to Alzheimer's disease pathology, with the presence of amyloid plaques and tau tangles in the posterior temporal and parietal regions (Rohrer et al., 2012).

Table 4. Diagnostic criteria for the logopenic variant PPA by Gorno-Tempini et al. (2011)

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 diagnostic 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 PPA diagnosis
Both of the following criteria must be present:
1. Clinical diagnosis of logopenic variant PPA
2. Imaging must show one or more of the following results:
a. Predominant left posterior perisylvian or parietal atrophy
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., FTLD-tau, FTLDTDP, AD, other)
3. Presence of a known pathogenic mutation

Abbreviations: *PPA* = Primary Progressive Aphasia; *SPECT* = Single Photon Emission Computed Tomography; *PET* = Positron Emission Tomography; *FTLD* = Frontotemporal Lobar Degeneration; *FTLD-tau* = FTLD with tau pathology; *FTLD-TDP* = FTLD with TDP-43 pathology; *AD* = Alzheimer's Disease.

1.3. Treatment of primary progressive aphasia

From a therapeutic standpoint, there is currently no effective pharmacological treatment for PPA. No medication has been shown to halt or reverse the progression of the disease. Since the lv-PPA is considered an atypical form of Alzheimer's disease, cholinesterase inhibitors and memantine (commonly used for Alzheimer's) are sometimes prescribed, but their actual benefits in PPA remain uncertain. As a result, treatment for PPA is largely supportive, with speech and language therapy being the main intervention aimed at alleviating symptoms and improving communication.

Despite the potential benefits of language therapies, many patients do not receive appropriate therapy due to a lack of awareness, limited access to specialist services and a therapeutic nihilism associated with the disease (Volkmer et al., 2020). This is particularly concerning given the significant impact of PPA on daily life, as it progressively impairs communication skills, leading to social isolation, emotional distress, and a decline in overall quality of life. Furthermore, considering that frontotemporal dementia is one of the most common forms of early-onset dementia, the consequences for patients, their families, and caregivers can be devastating, affecting work, relationships, and social interactions. There is therefore an urgent need for new therapeutic approaches that go beyond symptomatic management.

This section will describe the available pharmacological and non-pharmacological treatment options PPA, providing a review of the current literature.

1.3.1. Pharmacological treatment in PPA

To date, there is no established pharmacological treatment that halts or reverses the progression of PPA. As a clinical syndrome resulting from various underlying neurodegenerative pathologies, such as frontotemporal lobar degeneration (FTLD) and atypical

Alzheimer's disease (AD), several attempts have been made to assess the efficacy of medications commonly used in these conditions.

Some studies have explored the use of acetylcholinesterase inhibitors (such as galantamine) and memantine, drugs routinely prescribed for Alzheimer's disease. However, findings have been inconsistent. While isolated case reports and small-scale studies have reported stabilization or mild improvements in language and cognition, larger clinical trials have not consistently demonstrated significant benefits (Kertesz et al., 2008; Boxer et al, 2009; Johnson et al., 2010). More recently, a retrospective study compared the effect of cholinesterase inhibitors in patients with lvPPA and in those with amnestic AD, showing that lvPPA patients exhibited a similar pattern of decline on the MMSE up to two years after treatment initiation. ChEIs also had a positive impact on activities of daily living, while neuropsychiatric symptoms remained stable. These findings provide preliminary but promising evidence that ChEIs may offer comparable benefits in lvPPA and amnestic AD, although further prospective studies are needed to confirm their efficacy (Carrier-Auclair et al., 2025).

In the sv-PPA and the nfv-PPA—both most commonly associated with FTLD pathology—no pharmacological agent has demonstrated clear therapeutic efficacy. Some studies have investigated the use of selective serotonin reuptake inhibitors (SSRIs), antipsychotics, or stimulants to manage behavioral symptoms such as apathy and disinhibition, rather than targeting the core language deficits. One study also evaluated the potential benefit of bromocriptine, an ergoline derivative and D2 dopamine receptor agonist used in the treatment of pituitary disorders and Parkinson's disease (Reed et al., 2004). Although these medications may provide symptomatic relief in selected cases, they have not been shown to slow the progression of language deterioration.

More recently, Coleman et al. (2025) investigated the effects of intranasal oxytocin on apathy in patients with frontotemporal dementia, including individuals with semantic and

nonfluent variants of PPA. They found that oxytocin administered every third day was well tolerated and associated with a small reduction in apathy.

Given the current lack of effective disease-modifying therapies, clinical attention has increasingly shifted toward non-pharmacological interventions, including speech and language therapy and neuromodulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). These approaches have shown greater promise in preserving functional communication and improving the quality of life in individuals with PPA.

1.3.2. Language therapy in PPA

Given the progressive nature of PPA and the lack of effective pharmacological treatments, speech and language therapy has emerged as the main intervention aimed at managing communication difficulties and improving functional language skills. Several therapeutic approaches have been developed targeting different aspects of language processing. The following table presents the main language therapy approaches commonly used in the literature (Volkmer et al., 2020):

Table 5. Summary of Language Therapy Approaches

Treatment	Summary	Key Studies
Word Retrieval Interventions	Targeted semantic and phonological treatments improve naming and word retrieval; generalisation more likely in nonfluent and lv-PPA; maintenance requires continued practice.	Henry et al. (2013, 2019), Crook et al. (2020), Volkmer et al. (2020)
Script Training and Fluency Approaches	Focus on improving speech fluency and grammatical accuracy, especially in nfv-PPA; includes verb production training and script rehearsal with benefits lasting up to 1 year.	Henry et al. (2018), Jokel et al. (2014), Cherney et al. (2016)
Compensatory-Based	Includes communication partner training and AAC; targets functional communication and daily interaction; strategies are often adapted from stroke aphasia literature.	Volkmer et al. (2020), Savundranayagam et al. (2015), Fried-Oken et al. (2009)
Group Education and Support	Provides emotional and practical support through group interaction; facilitates strategy sharing and peer support; shown to improve confidence and reduce isolation.	Kindell et al. (2013), Taylor et al. (2014), Volkmer et al. (2020)
Person-Centred Therapeutic Models	Integrates impairment-based and compensatory goals with patient and family input; prioritises meaningful engagement and therapy aligned with life participation goals.	Simmons-Mackie & Kagan (2007), Volkmer et al. (2020), Carey et al. (2016)

Abbreviations: *lv-PPA* = logopenic variant Primary Progressive Aphasia; *nfv-PPA* = nonfluent/agrammatic variant Primary Progressive Aphasia; *AAC* = Augmentative and Alternative Communication.

Different ways of managing PPA through language therapy have been studied. Among these, word retrieval interventions are the most frequently explored. These include semantic and phonological cueing strategies aimed at improving naming abilities, which is a core deficit across all PPA variants. Studies such as those by Henry et al. (2013, 2019), Crook et al. (2020), and Volkmer et al. (2020) have demonstrated that structured word retrieval training can produce immediate benefits, particularly in individuals with nonfluent and logopenic variants. However, the extent of generalisation and the durability of gains tend to depend on continued practice and the use of personalised, functionally relevant stimuli.

Another approach with growing support is script training, which aims to enhance fluency and grammatical structure through the repeated rehearsal of personally meaningful dialogues. This technique has been especially beneficial in nfv-PPA, where speech production is often effortful and syntactically impaired. Studies by Henry et al. (2018), Jokel et al. (2014), and Cherney et al. (2016) highlight how structured practice with scripted phrases can lead to more fluent, intelligible, and automatic speech, with effects sustained for several months post-intervention.

Compensatory-based approaches have also gained traction, particularly as the condition progresses and restorative gains become less achievable. These interventions include communication partner training and the use of augmentative and alternative communication (AAC) systems, both high-tech and low-tech. They are designed to support daily interactions and improve the effectiveness of communication despite declining verbal output. Volkmer et al. (2020) as well as earlier work by Savundranayagam et al. (2015) and Fried-Oken et al. (2009) provide evidence that such strategies can improve quality of life and reduce frustration for both patients and their families.

In addition to individual therapy, group education and support interventions have shown positive psychosocial outcomes. These sessions provide a forum for individuals with PPA and

their care partners to learn communication strategies, share experiences, and receive emotional support. Studies such as Kindell et al. (2013), Taylor et al. (2014), and Volkmer et al. (2020) report that group programmes help reduce social isolation and empower participants by fostering a sense of community and resilience.

More recently, Rogalski et al. (2025) evaluated the Communication Bridge program in a randomized clinical trial involving 95 dyads of people with PPA and their communication partners. The intervention, delivered via video chat, was designed to enhance communication participation and quality of life, while reducing caregiver burden. The results demonstrated that remote delivery of structured, person-centred interventions is feasible and provides a promising model for rigorous non-pharmacologic trials in PPA and related dementias.

Lastly, the field is moving toward more person-centred therapeutic models. These integrate impairment-based and compensatory approaches while aligning therapy goals with the personal values, identity, and everyday priorities of the individual. Frameworks such as the Life Participation Approach to Aphasia (Simmons-Mackie & Kagan, 2007) and the CARE Pathway (Carey et al., 2016) emphasise meaningful communication and quality of life, rather than purely linguistic outcomes.

It is important to note that interventions in PPA present unique challenges compared to post-stroke aphasia. Unlike stroke-related aphasia, which typically stabilizes after an initial recovery period, PPA is a progressive neurodegenerative condition, meaning language abilities continue to decline over time. This progressive nature requires therapy to be continually adapted to each individual's evolving profile. Moreover, the heterogeneity of symptoms across PPA variants and the variability in the rate of progression make treatment planning more complex. Interventions must therefore be flexible, personalized, and focused on communication goals that are meaningful to the patient, highlighting the need for strategies

that can maximize engagement, generalization, and functional outcomes in the context of an ongoing decline.

1.4. Non-invasive brain stimulation

Non-invasive brain stimulation (NIBS) encompasses a set of techniques designed to modulate neuronal activity without the need for surgical intervention. Among the most commonly used modalities are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). These approaches have gained increasing importance in neuroscience and clinical research due to their potential to improve cognitive and motor functions, as well as to serve as therapeutic tools for various neurological and psychiatric disorders (Miniussi et al., 2013; Lefaucheur et al., 2020).

TMS is a non-invasive neuromodulation technique based on the principle of electromagnetic induction, through which an electric field is generated in targeted brain regions by brief, high-intensity magnetic pulses delivered through a coil placed on the scalp. When the intensity of these pulses is sufficient, they can induce neuronal depolarization and directly trigger action potentials, influencing cortical excitability and activity in functionally connected brain networks. Although TMS was initially developed as a diagnostic and neurophysiological tool, it has evolved into a versatile technique with both research and therapeutic applications.

In neuroscience, TMS is used for cortical mapping and to assess the excitatory state of the nervous system. Clinically, it is increasingly applied in the treatment of neurological and psychiatric disorders, including depression (Baeken et al., 2011), stroke-related aphasia (Koch et al., 2019), Parkinson's disease (Lee et al., 2013), and in neurodegenerative conditions such as PPA. The neuromodulatory effects of TMS depend on specific stimulation protocols. When applied as single-pulse TMS (spTMS), it typically does not produce lasting changes in neural

activity; however, when configured into repetitive patterns, TMS can induce long-term plasticity in the brain.

These neuromodulatory protocols are generally divided into two categories: (1) Repetitive TMS (rTMS), which involves high-frequency trains of pulses (typically between 1 and 50 Hz) applied consistently at a single brain site; and (2) Paired Associative Stimulation (PAS), which synchronizes spTMS with another stimulus—either endogenous or exogenous—based on precise temporal and neural pathway coordination. Among these, rTMS has been shown to induce significant and lasting changes in synaptic transmission and cortical plasticity.

The effects of TMS on the cortex are influenced by various stimulation parameters, including pulse frequency, duration of pulse trains, application pattern, pulse intensity, magnetic pulse shape, and the total number of pulses delivered. Specific rTMS paradigms, such as intermittent theta burst stimulation (iTBS), have been designed to enhance excitability and are particularly promising due to their shorter administration time and strong modulatory effects.

Overall, TMS represents a powerful tool for influencing neural function, with growing relevance in cognitive rehabilitation and neurodegeneration. In the context of PPA, it could offer the potential to support residual language function, promote compensatory network activity, and enhance the effectiveness of behavioral interventions through synergistic mechanisms of neuroplasticity.

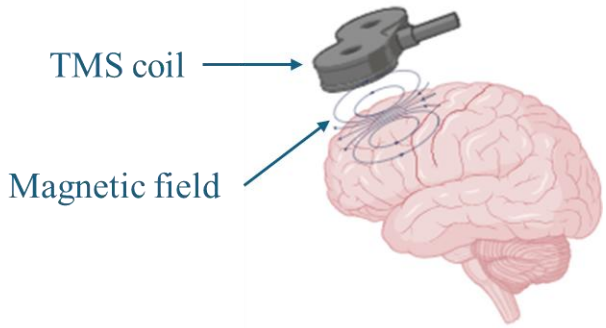

Figure 2. Mechanism of TMS: Coil Positioning and Magnetic Field Induction

1.4.1. Non-Invasive Brain Stimulation in PPA

Initial studies using non-invasive brain stimulation (NIBS) demonstrated improvements in naming and general language function, particularly in the nonfluent and semantic variants. For instance, Cotelli et al (2014), using tDCS, and Pytel et al. (2021), using TMS, reported that NIBS applied to language-related cortical areas resulted in enhanced spontaneous speech, reduced apathy, and increased metabolic activity in regions linked to language and the default mode network. In another study, Teichmann et al. (2016) demonstrated that tDCS can specifically enhance semantic processing in patients with svPPA, showing significant effects in verbal tasks following excitatory stimulation of the left hemisphere and inhibitory stimulation of the right. More recently, Huang et al. (2023) conducted a parallel trial with 40 participants across all three PPA variants and observed rTMS applied to the DLPFC significantly improved language performance compared to sham stimulation following 20 sessions of rTMS for one month. These improvements were consistent across PPA variants and sustained for up to 6 months. Smaller studies, such as those by Antczak et al. (2018) and Margolis et al. (2019), also indicated subjective cognitive benefits from rTMS, although their short duration and small sample sizes limit the generalizability of the results.

An increasing number of studies has focused on the use of tDCS in PPA, with a greater amount of published research exploring its clinical applications. This technique has been evaluated both as a standalone intervention and, importantly, in combination with language therapy. The combined use of tDCS and speech-language therapy has received particular attention for its potential to amplify and sustain treatment gains through synergistic effects on neuroplasticity. McConathey et al. (2017) reported benefits in multiple language domains in individuals with nonfluent and logopenic PPA, while Ferrucci et al. (2018) found that patients with lower baseline performance experienced greater gains from tDCS. The largest study to date is the previously mentioned Huang et al. (2023) with 40 participants, followed by Zhao et

al. (2021) with 39, and Tsapkini et al. (2018) and Wang et al. (2022), each with 36 participants. Zhao et al. (2021) showed that both groups improved on trained items, but the active tDCS group demonstrated greater improvement and generalization to untrained words. Tsapkini et al. (2018) randomized participants to receive either active tDCS over the left inferior frontal gyrus or sham stimulation, both followed by language therapy, and observed significant improvements in spelling and naming performance, particularly in the nonfluent and logopenic variants. Building on the randomized trial by Tsapkini et al. (2018), De Aguiar et al. (2020) examined brain volumes as predictors of tDCS outcomes in PPA and found that regions associated with language, attention, and working memory contributed to the maintenance and generalization of the stimulation effects. These results suggest that tDCS may influence not only the stimulated region but also anatomically or functionally connected areas. Wang et al. (2022) similarly reported that semantic fluency improved significantly more in the active tDCS group after 12 sessions over three weeks, supporting the potential for generalization beyond trained lexical items. Additional studies have consistently found that short-term tDCS protocols can enhance language performance, especially in tasks involving naming and verbal fluency (Gervits et al. 2016; Teichmann et al. 2016; Hosseini et al. 2019; Benussi et al. 2020). The combination of tDCS with speech-language therapy has been particularly effective. Studies have demonstrated that combined interventions not only improve trained language tasks but also lead to generalization to untrained items, and in some cases, to broader improvements in sentence-level processing and comprehension (Roncero et al. 2017; Sheppard et al. 2022; Wang et al. 2022; Zhao et al. 2021; De Aguiar et al. 2020). Sheppard et al. (2025) and Zhao et al. (2021) showed that gains extended beyond lexical retrieval, suggesting a reinforcing effect of non-invasive neuromodulation techniques on therapy-induced plasticity. However, not all studies have found beneficial effects of tDCS. Borrego-Écija et al. (2023), in a study with 15 patients with PPA, did not find differences between active and sham tDCS stimulation in

clinical scores of language function. Similarly, more recently, Teichmann et al. (2025), in a study with 12 patients with lvPPA, found no benefits of active tDCS compared to sham stimulation, highlighting the need to explore factors influencing stimulation effects and to conduct studies with larger sample sizes.

Although these studies offer encouraging findings, it is important to highlight that all interventions reported in the literature to date have been conducted over short timeframes, generally ranging from one to four weeks. To date, no long-term trials have been published assessing the sustained impact of neuromodulation techniques in PPA beyond the immediate or subacute post-treatment phase.

TMS is a particularly relevant technique for intervention in PPA because it delivers focal stimulation to specific brain regions, which aligns with the typically focal pattern of cortical degeneration observed in this syndrome (Rohrer et al. 2009; Rogalski et al. 2011).

Moreover, several studies have combined these techniques with language therapy, reporting promising short-term improvements in various linguistic functions. However, despite these encouraging results, there is still a lack of evidence regarding their long-term efficacy. Most existing studies are limited by small sample sizes and short follow-up periods, which hinder the generalisability of findings. In many cases, crossover designs have been used, potentially introducing carry-over effects that may confound the interpretation of treatment outcomes. Additionally, the language therapy protocols employed are often poorly described or insufficiently standardised, making replication and comparison across studies difficult. A further challenge lies in the nature of the outcome measures, as many studies rely on non-validated or ad-hoc assessments with limited sensitivity to change. Notably, the majority of research to date has focused on tDCS, while the evidence for TMS in PPA remains relatively scarce. These methodological limitations have been highlighted in a recent systematic review by Alrasheed (2025), which concluded that due to the heterogeneity in study designs,

administration methods, small sample sizes, and lack of standardized measurement tools, drawing firm conclusions remains difficult. The review stresses the need for further studies to establish evidence-based treatment protocols. Complementing this, a recent meta-analysis by Lomi et al. (2025) suggests that deeper analytical approaches yield valuable insights. Specifically, stratifying studies by design revealed that parallel-group trials reported stronger effects than crossover trials, and longitudinal trends showed an increase in estimated effect sizes over time. Importantly, although not statistically significant, studies that combined non-invasive brain stimulation (NiBS) with speech and language therapy (SLT) showed slightly higher effect sizes than those using NiBS alone, indicating that this combined approach deserves further investigation in future research.

Table 6. Summary of Treatment Studies in Primary Progressive Aphasia

	Participants	Design	Treatment	Treatment duration	Main findings
Pharmacological treatment					
Reed et al. (2004)	6 PPA (not specified)	Crossover	Bromocriptine	Max dose: 3 times a day (7 weeks)	Increased mean length of utterance but showed no significant benefits on other language measures
Kertesz et al. (2008)	22 PPA (not specified), 17 bvFTD		Galantamine	Open-label (18 weeks) + placebo-controlled phase (8 weeks)	In PPA, a trend toward efficacy was observed, with overall severity scores favoring galantamine and language stability compared to placebo
Boxer et al. (2009)	21 FTD, 13 sv-PPA, 9 nfv-PPA	Opel-label trial	Memantine	26 weeks	PPA group remained relatively stable on ADAS-cog, NPI, TFLS.
Johnson et al. (2010)	18 PPA (not specified)	Crossover	Memantine	26 weeks	No statistically significant differences between treatment and placebo phases, but trend toward less decline in WAB-AQ during memantine phase.
Coleman et al. (2025)	76 FTD, 5 nfv-PPA, 13 sv-PPA	Crossover	Oxytocin	6 weeks / intermittent dosing	Slight reduction in apathy
Non-invasive neuromodulation					
Transcranial Magnetic Stimulation					
Antczak et al. (2018)	2 PPA, 9 bvFTD		rTMS	10 sessions (2 weeks)	Improvement in some cognitive tests and subjective impression
Margolis et al. (2019)	8 PPA (not specified)	-	rTMS	2 sessions (1 day)	-
Pytel et al. (2021)	14 nfv-PPA, 6 sv-PPA	Mixed	rTMS	15 sessions (4 weeks)	Improvement in spontaneous language, apathy and increased regional brain metabolism

Huang et al. (2023)	16 nfv-PPA, 12 sv-PPA, 12 lv-PPA	Parallel	rTMS	20 sessions (4 weeks)	Improvement in language function
Transcranial direct current stimulation					
Gervits et al. (2016)	2 nfv-PPA, 4 lv-PPA		tDCS	10 sessions (2 weeks)	Improvement in language production
Teichmann et al. (2016)	12 sv-PPA	Crossover	tDCS	1 session	Improvement in semantic association tasks compared to sham group.
McConathey et al. (2017)	6 nfv-PPA, 1 lv-PPA	Crossover	tDCS	10 sessions (2 weeks)	Improvement in multiple language components, with varying degrees of benefit depending on the severity of the initial impairment
Ferruci et al. (2018)	5 PPA (not specified)	Crossover	tDCS	5 sessions (1 week)	Lower baseline performance predicted greater tDCS-related gains in language, while higher performers showed slight benefits in speech repetition.
Roncero et al. (2019)	12 PPA (not specified)	Crossover	tDCS	10 sessions (2 weeks)	Improvement in naming, especially trained items
Hosseini et al. (2019)	3 nfv-PPA, 3 lv-PPA	Crossover	tDCS	10 sessions (2 weeks)	Improvement in verbal fluency deficits
Benussi et al. (2020)	18 nfv-PPA, 12 sv-PPA	Parallel	tDCS	10 sessions (2 weeks)	Increase of intracortical connectivity and improvement in clinical scores and behavioral disturbances
Transcranial direct current stimulation + language therapy					
Cotelli et al. (2014)	16 nfv-PPA	Parallel	tDCS + language therapy	10 sessions (2 weeks)	Greater improvement on trained items
Roncero et al. (2017)	6 nfv-PPA, 2 lv-PPA, 2 sv-PPA	Crossover	tDCS + language therapy	10 sessions (3 weeks)	Improvement in naming on trained and untrained items
Tsapkini et al. (2018)	14 nfv-PPA. 12 lv-PPA, 10 sv-PPA	Crossover	tDCS + language therapy	15 daily sessions (3 weeks)	Improvement in spelling naming compared to sham group, especially nfv-PPA and lv-PPA

Zhao et al. (2021)	18 nfv-PPA, 7 sv-PPA, 14 lv-PPA,	Parallel	tDCS + language therapy	15 sessions (3 weeks)	Both groups improved in trained words, but tDCS showed greater improvement and generalization to untrained words
Nissim et al. (2022)	2 nfv-PPA, 2 sv-PPA, 7 lv-PPA	Crossover	tDCS + language therapy	10 sessions (2 weeks)	Enhancement in naming performance after active stimulation
Wang et al. (2022)	13 nfv-PPA, 9 sv-PPA, 14 lv-PPA	Parallel	tDCS + language therapy	12 sessions (3 weeks)	Semantic fluency improved significantly more in the active tDCS
Sheppard et al. (2022)	2 nfv-PPA, 1 lv-PPA	Crossover	tDCS + language therapy	15 sessions (3 weeks)	Generalization to untrained verbs in non-fluent PPA
Herrmann et al. (2022)	7 nfv-PPA, 11 lv-PPA, 5 sv-PPA	Crossover	tDCS + language therapy	12 sessions (3weeks)	The effects of tDCS were only greater in participants who slept better
Borrego-Écija et al. (2023)	5 nfv-PPA, 4 sv-PPA, 4 lv-PPA	Crossover	tDCS + language therapy	10 sessions (2 weeks)	No differences were found between active and sham tDCS stimulation in clinical scores of language function in PPA patients.
Sheppard et al. (2025)	8 PPA (not specified)	Crossover	tDCS + language therapy	15 sessions	Generalization to untrained verbs, sentence production, and comprehension.

Abbreviations: *PPA* = Primary Progressive Aphasia; *sv-PPA* = semantic variant PPA; *nfv-PPA* = nonfluent/agrammatic variant PPA; *lv-PPA* = logopenic variant PPA; *FTD* = Frontotemporal Dementia; *tDCS* = transcranial direct current stimulation; *TMS* = transcranial magnetic stimulation; *WAB-AQ* = Western Aphasia Battery – Aphasia Quotient; *ADAS-cog* = Alzheimer's Disease Assessment Scale – cognitive subscale; *NPI* = Neuropsychiatric Inventory; *TFLS* = Texas Functional Living Scale.

2. HYPOTHESES AND OBJECTIVES

2.1. Hypotheses

Main Hypothesis

The treatment with TMS and language therapy reduces disease progression in primary progressive aphasia, as determined by brain metabolism at 6 months, compared to language therapy and sham TMS.

Secondary Hypotheses

Secondary Hypothesis 1: The treatment with TMS and language therapy improves naming ability following language therapy, as determined by naming trained words, compared to language therapy and sham TMS.

Secondary Hypothesis 2: The treatment with TMS and language therapy improves the global language functioning in primary progressive aphasia, as measured by the Mini-Linguistic State Examination (MLSE) at 6 months, compared to language therapy and sham TMS.

Secondary Hypothesis 3: The treatment with TMS and language therapy improves spontaneous speech, as determined by the number of words per minute, compared to language therapy and sham TMS.

Secondary Hypothesis 4: The treatment with TMS and language therapy improves functional activity in daily life, as determined by the IDDD scale, compared to language therapy and sham TMS.

Secondary Hypothesis 5: The treatment with TMS and language therapy reduces neuropsychiatric symptoms in primary progressive aphasia, as determined by the NPI scale at 6 months, compared to language therapy and sham TMS.

Exploratory Hypothesis

Exploratory Hypothesis 1: Certain baseline demographic, clinical, and neurocognitive factors may predict clinical progression over a 6-month period in patients with PPA receiving language therapy.

Exploratory Hypothesis 2: Specific individual characteristics, including cognitive and neuroimaging variables, are significantly associated with a positive clinical response to TMS treatment.

2.2. Objectives

Main Objective

To compare the effect of TMS and language therapy with language therapy and sham TMS on the progression of primary progressive aphasia, as determined by brain metabolism on FDG-PET at 6 months.

Secondary Objectives

Secondary Objective 1: To compare the effect of TMS and language therapy with language therapy and sham TMS on naming abilities in primary progressive aphasia, as measured by the naming of trained words at 6 months.

Secondary Objective 2: To compare the effect of TMS and language therapy with language therapy and sham TMS on global language functioning in primary progressive aphasia, as measured by the Mini-Linguistic State Examination (MLSE) at 6 months.

Secondary Objective 3: To compare the effect of TMS and language therapy with language therapy and sham TMS on spontaneous speech in primary progressive aphasia, as measured by the number of words per minute at 6 months.

Secondary Objective 4: To compare the effect of TMS and language therapy with language therapy and sham TMS on functional activity in primary progressive aphasia, as measured by the IDDD scale (Interview for Deterioration in Daily Living Activities in Dementia) at 6 months.

Secondary Objective 5: To compare the effect of TMS and language therapy with language therapy and sham TMS on neuropsychiatric symptoms in primary progressive aphasia, as measured by the Neuropsychiatric Inventory (NPI) at 6 months.

Exploratory Objectives

Exploratory Objective 1: To evaluate the predictive factors associated with clinical progression over a 6-month in patients with PPA receiving language therapy.

Exploratory Objective 2: To determine the factors associated with clinical response to TMS.

3. MATERIAL AND METHODS

3.1. Study design

This was a prospective, randomized, controlled, double-blind, parallel-group clinical trial designed to evaluate the efficacy and safety of TMS combined with language therapy compared to language therapy alone on brain metabolism, language, and neuropsychiatric symptoms in patients with primary progressive aphasia.

3.2. Study population

The study included patients over 18 years of age who were diagnosed with primary progressive aphasia according to the criteria established by Gorno-Tempini et al. (2011).

3.2.1. Patient inclusion criteria

Eligible subjects for inclusion in this study must meet all the following criteria:

1. Diagnosis of PPA according to the consensus criteria by Gorno-Tempini, supported by neuroimaging (FDG-PET and/or Magnetic Resonance Imaging).
2. Clinical Dementia Rating (CDR) score of 1 or less.
3. Language is the patient's primary deficit.
4. Signed informed consent provided by the patient or their legal representative.

3.2.2. Patient exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study:

1. Patients diagnosed with a condition other than PPA that may cause language impairment.
2. History of epilepsy or evidence of focal epileptiform pathology on EEG recordings.
3. Presence of contraindications related to the treatments or procedures to be used (TMS and MRI), such as:

a. Magnetically sensitive metal in the head or within 30.5 cm of the TMS coil that cannot be removed. Examples include aneurysm clips or coils, carotid or cerebral stents, implanted stimulators, electrodes, ferromagnetic implants in the ears or eyes, bullets or shrapnel fragments, and magnetically activated dental implants.
b. Pregnancy.

4. Patients who are breastfeeding, pregnant, or planning to become pregnant within the next year. Fertile women must agree to use contraception throughout the study. If there is uncertainty at the time of inclusion, a pregnancy test will be conducted.
5. Patients with a terminal medical condition with a life expectancy of less than one year.
6. Patients with active malignant disease in the past two years.
7. Any condition that prevents participation or follow-up in the study.
8. Alcohol or substance abuse within the past year.
9. Major psychiatric disorders (e.g., schizophrenia, schizoaffective disorders, bipolar disorder, obsessive-compulsive disorders, or personality disorders).
10. Absolute inability to communicate (mutism) or poor language proficiency that prevents participation in the study, as determined by the investigator.
11. Severity of PPA that prevents the patient from following the study interventions or assessments at the time of inclusion.
12. Participation in another clinical trial within the past 4 months.
13. Chronic use of medications that could influence study outcomes:
    a. Antiepileptic drugs are permitted if on a stable dose for 3 months prior to inclusion. If required during the study due to a seizure episode, they may be added.

b. Diazepam and derivatives are permitted only if on stable doses 3 months prior to inclusion. Adjustments are allowed during the study.
c. Donepezil, Galantamine, Rivastigmine, and Memantine are permitted if on stable doses 3 months prior to inclusion.
d. SSRIs (Selective Serotonin Reuptake Inhibitors) are permitted only if on stable doses 3 months prior to inclusion. They may be added if necessary, during the study.
e. Medications that can lower the seizure threshold (e.g., tricyclic antidepressants, antipsychotics) are permitted if on stable doses 3 months prior to inclusion. They may be added if necessary, during the study.

3.3. Procedures

The initial screening visit occurred at the Department of Neurology of the Hospital Clínico San Carlos, Madrid, Spain. Clinical information was collected from the patient, including date of birth, sex, years of formal education, year of PPA diagnosis, relevant prior medical conditions and medication. Patients who met the eligibility criteria were informed about the study both verbally and in writing. Once the patient decided to participate in the study, they signed two copies of the informed consent (Appendix). Within 30 days of this visit, treatment visits began with a baseline visit that included a comprehensive neurologic, language, and cognitive assessment, and FDG-PET. At this stage, the patient was randomised to one of the two study arms through a computerised randomisation procedure, performed by the investigator who administered the TMS (https://www.studyrandomizer.com/). Before beginning TMS treatment, a pre-treatment assessment was conducted and then repeated at 3 and 6 months, the end of the treatment, including: MLSE, naming word list, number of words

per minute in spontaneous speech, NPI, and IDDD. In the final visit, FDG-PET imaging was also performed.

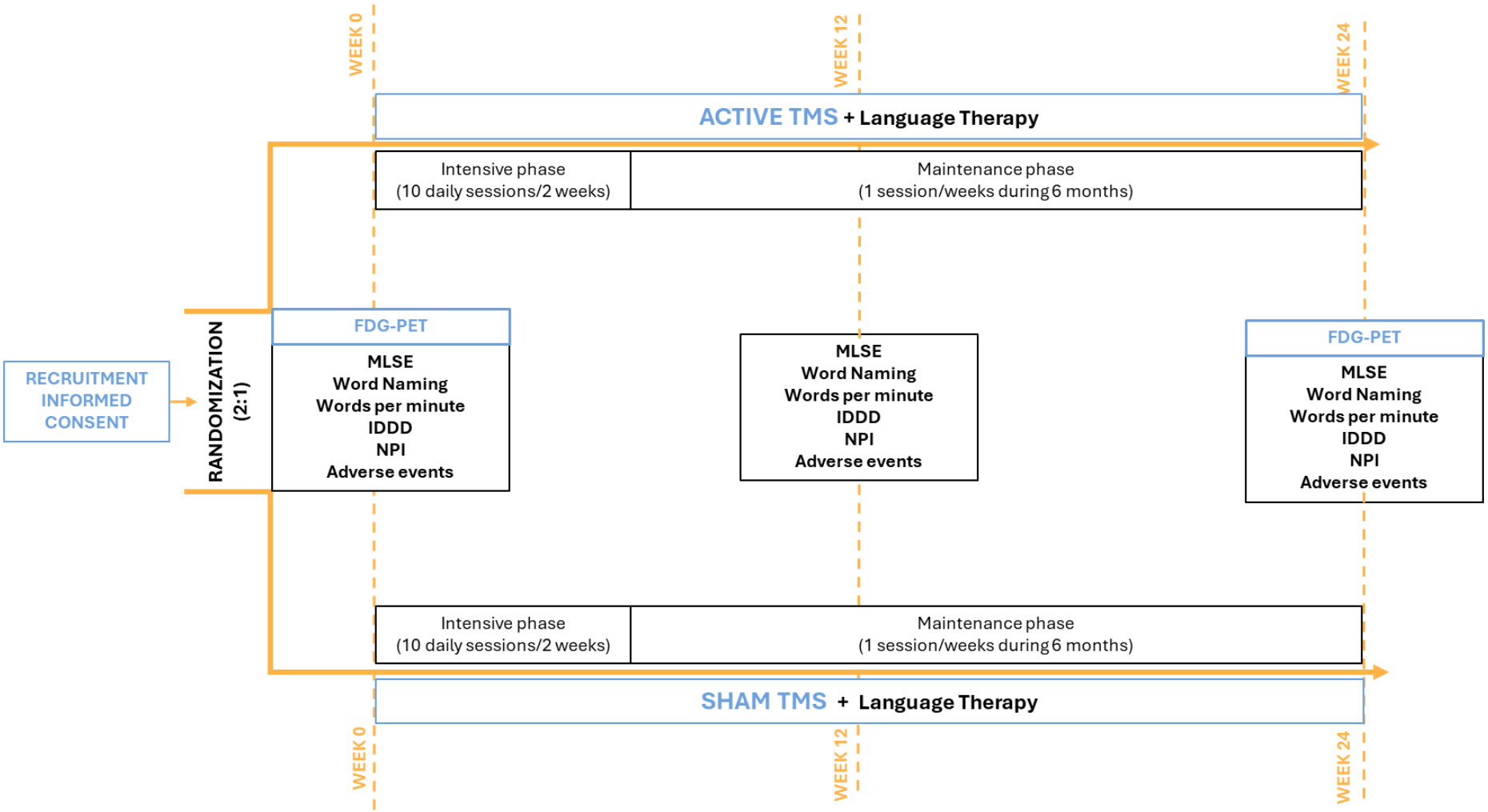

Figure 3. Study Design

3.4. Tasks and measures

3.4.1. Baseline assessment

Before beginning the treatment, participant data were collected, and a comprehensive language and cognitive assessment was conducted. This evaluation was essential to verify each participant's diagnosis, confirm that they met the inclusion criteria, and determine their baseline cognitive and language abilities at the start of the study.

3.4.1.1. Data collection

Clinical and demographic data were collected through an interview with the patient and/or their family members or caregivers. The information gathered included age, date of birth, sex, handedness, nationality, and native language, as well as other languages spoken. Additionally, educational background and profession were collected. Relevant clinical history was also documented, including date of symptom onset, current medications, and any comorbid conditions.

3.4.1.2. Neuropsychological assessment

- **Addenbrooke's Cognitive Examination III (ACE-III)**

Before beginning the treatment, all participants underwent the Spanish version the ACE-III (Matias-Guiu et al., 2015). It is a widely used cognitive screening tool designed to assess multiple cognitive domains, particularly for detecting dementia and other neurocognitive disorders. ACE-III is an updated version of the ACE-Revised (ACE-R; Mioshi et al., 2006) and evaluates five key cognitive areas: attention and orientation [/18], memory [/26], verbal fluency [/14], language [/26], and visuospatial abilities [/16]. The test provides a total score ranging from 0 to 100, with higher scores indicating better cognitive performance.

The ACE-III is commonly used in the assessment of neurodegenerative conditions such as Alzheimer's disease, frontotemporal dementia, and primary progressive aphasia (PPA)

(Flanagan et al., 2014; Matias-Guiu et al., 2017; Foxe et al., 2021; Fernández-Romero et al., 2024).

- **Neuronorma battery (NN)**

Before beginning the treatment, all participants completed a selection of tests from the NN battery. This battery consists of a collection of tests that provide normative data for the Spanish population, considering age and years of education (Peña-Casanova et al., 2009).

It includes tests designed to evaluate key cognitive domains, such as attention, memory, language, executive functions, and visuospatial skills. A detailed description of the tests completed from the battery can be found in Table 7.

Table 7. Summary of Cognitive Assessment Tests in PPA

Digit Span	Forward Backward
Corsi Block-tapping Test	Forward Backward
Trail Making Test (TMT)	Part A: numbers only Part B: numbers and letters
Symbol Digit Modalities Test (SDMT)	Number of correct items in 90 seconds
Visual Object and Space Perception Battery (VOSP)	Object decision: n of correctly identified objects Progressive silhouettes: score based on the last correctly solved item in each series. Position discrimination: n of items correctly localised. Number location: n of items where the point matched the correct number.
Judgement of Line Orientation (JLO)	Number of correct items
Tower of London Drexel University	Total correct items, total moves, initiation time (IT), resolution time (RT), execution time = RT - IT
Rey Osterrieth Complex Figure Test	Copy accuracy and time 3 minutes recall 30 minutes recall
Stroop Test	Word reading (45 seconds) Color naming (45 seconds) Interference condition (45 seconds)

- **Language assessment**

All participants were administered a battery of specific language tests. This battery consisted of various tests assessing different language domains, including: reading, comprehension, repetition, spontaneous speech, agrammatism, naming, and semantic memory.

The tasks are as follows: Cookie Theft picture; Paradis narrative sequence picture; reading narrative text, words, capitalized words, foreign words, and non-words; omission of the initial phoneme; spelling words; repetition of words, non-words, syllables, and sentences; semantic association; naming pictures and actions; word-picture matching; synonyms; picture-action matching; orophonatory praxis; verb tense agreement; and sentence comprehension.

3.5. Outcomes measures

3.5.1. Primary measure

Standardized Uptake Value Ratio (SUVR)

The primary outcome measure of the study was the change in regional brain metabolism, quantified using the Standardized Uptake Value Ratio (SUVR). This change was assessed by FDG-PET imaging, comparing measurements taken at baseline and at the end of the treatment.

Recent studies support the use of advanced neuroimaging techniques due to their high sensitivity and objectivity in detecting clinical changes, as well as their strong correlation with disease severity (Staffaroni et al., 2019; Boxer et al., 2020; Panza et al., 2020). In this context, FDG-PET has proven especially useful, as it reflects patterns of synaptic dysfunction—an aspect closely linked to the pathophysiology of neurodegenerative conditions. FDG-PET findings show a high degree of correlation with cognitive and language performance, as well as with overall clinical staging, making it a valuable tool for tracking disease progression. In addition, the ability to perform quantitative or semi-quantitative analyses helps reduce inter-

observer variability and improves the reliability and reproducibility of the results (Minoshima et al., 2021). As such, FDG-PET is considered an appropriate technique for assessing longitudinal changes in clinical trials (Bejanin et al., 2020).

FDG-PET scans were conducted using a Siemens Biograph TruePoint PET/CT scanner, equipped with an advanced detector system featuring lutetium oxyorthosilicate (LSO) crystals. To ensure optimal imaging conditions, participants were required to fast for at least six hours before the scan. The radiotracer dose was administered 30 minutes prior to image acquisition, following the current European guidelines for FDG-PET brain imaging (Varrone et al., 2009).

FDG-PET preprocessing and analysis

The preprocessing of FDG-PET images was performed using Statistical Parametric Mapping 12 (SPM12), developed by the Wellcome Trust Centre for Neuroimaging, Institute of Neurology, London. First, the images were manually realigned to match the bi-commissural plane. Next, they were normalized to the Montreal Neurological Institute (MNI) reference space, using a template that has been specifically validated for FDG-PET imaging in dementia research (Della Rosa et al., 2014).

For the analysis of cerebral metabolism, a region of interest (ROI) was defined, covering a large portion of the left hemisphere. This ROI was determined through voxel-based analysis by comparing a cohort of 70 PPA patients assessed at two time points. It also served as the basis for sample size calculation.

To evaluate metabolic changes over time, the relative FDG uptake within this ROI was measured at baseline and again after six months of treatment. The whole cerebellum was used as the reference region for normalization.

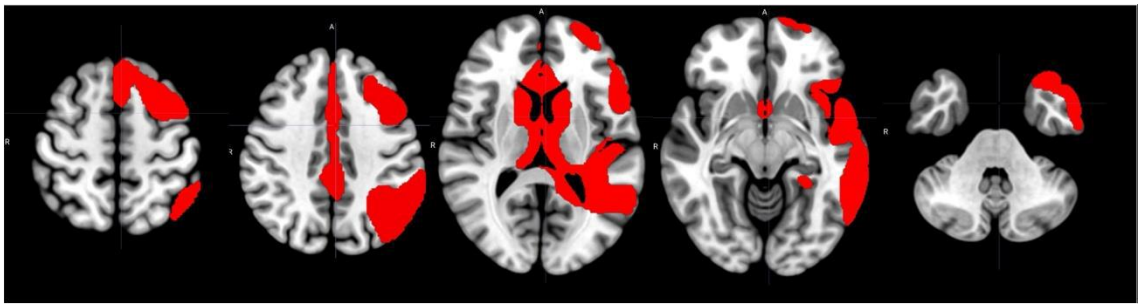

Figure 4. ROI Used for Longitudinal FDG-PET Analysis in PPA Patients

3.5.2. Secondary measures

- **Mini Linguistic State Examination (MLSE)**

The MLSE Spanish version (Matias-Guiu, 2021) was administered to the patients at the beginning of the treatment, three months later, and at the end of the treatment. The MLSE is a brief screening tool designed to assess language impairments in various neurodegenerative disorders, particularly in PPA. It consists of 11 subtasks that target key linguistic domains commonly impacted in PPA, (Patel et al., 2021). These subtasks are designed to reflect broader functional aspects of language production and comprehension, specifically motor speech, semantic knowledge, phonology, syntax, and working memory. Test scoring focuses on identifying the nature of a participant's language impairment by quantifying errors associated with each domain, resulting in a five-dimensional profile score. The total score is calculated as the sum of the five language domains, and higher scores represent better language performance.

- **Naming of trained words**

A list of 261 words was developed, covering eight semantic categories: animals, food, clothing, body parts, transport, objects, furniture, and places. The list was constructed using high-frequency, commonly used words in daily communication in Spain, ensuring cultural and linguistic relevance for Spanish-speaking participants. This word list was presented twice on two different days each time the assessment was administered. The purpose of these

assessments was to evaluate word naming abilities and to select words for training during the language therapy sessions.

Naming was assessed at three time points: before the treatment began, three months after the start of treatment, and at the end of the treatment. During the assessment, participants were shown a single image of each target word in a PowerPoint presentation on a computer and were required to name it aloud. A response was only considered correct if the participant spontaneously produced the word without any cueing. The complete word list used is provided in the Appendix.

- **Words per minute in spontaneous speech**

Three minutes of spontaneous speech were recorded and assessed through storytelling with the wordless picture books "Frog Stories" at the beginning of the treatment, three months later, and at the end of the treatment. The patient had to tell a story based on the pictures in the book for three minutes. All the words spoken by the patient were counted and divided by the total seconds of the recording (approximately 180 seconds). The result was multiplied by 60 seconds to obtain the number of words per minute. Audiotranscription was performed by an expert rater blinded to the treatment and period of examination.

- **Interview for Deterioration in Daily Life in Dementia (IDDD)**

The Spanish version was completed by the patients' relatives or caregivers at the beginning of the treatment, three months later, and at the end of the treatment (Teunisse et al. 1997; Böhm et al., 1998). It is a scale designed to assess initiative and performance in basic and household activities of daily living. It consists of 33 items divided into two sections: 16 items about "personal care" (basic activities of daily living, BADL) and 17 items about "complex activities" (instrumental activities of daily living, IADL). Each item is scored as 1 if the patient does not need help, 2 if the patient occasionally needs help, and 3 if the patient always needs help. If the response was unknown or not applicable, it is scored as 8 or 9. All

items rated 1 to 3 were summed up. They then were divided by the number of items rated 1 to 3. Therefore, the total score range between 1 and 3 in each section.

- **Neuropsychiatric Inventory (NPI)**

The NPI (Cummings et al., 1994; Boada et al, 2002) was completed by the patients' relatives or caregivers at the beginning of the treatment, three months later, and at the end of the treatment. It is a structured interview developed to assess psychopathology in patients with dementia. It assesses 12 different symptom domains, which include: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, night-time behavioral disturbances and appetite/eating disturbances. For each symptom, there is a false-negative rate question followed by subquestions if the response to the initial question suggests the presence of abnormalities. The caregiver rates the frequency on a scale of 1 to 4 (1 = occasionally, less than once per week; 4 = very frequently, once or more per day or continuously) as well as their severity (1 = mild, 2 = moderate, 3 = severe). The total score for each domain is calculated by multiplying the frequency by the severity. A total score is calculated by adding all the domain scores together.

Table 8. Summary of Tests Administered at Each Visit

Baseline	**Visit 1 (week 0)**	**Visit 2 (week 12)**	**Visit 3 (week 24)**
Data collection	FDG-PET	MLSE	FDG-PET
Cognitive assessment	MLSE	Spontaneous speech	MLSE
Language assessment	Spontaneous speech	Naming of trained words	Spontaneous speech
	Naming of trained words	IDDD	Naming of trained words
	IDDD	NPI	IDDD
	NPI		NPI

Abbreviations: *FDG-PET* = Fluorodeoxyglucose Positron Emission Tomography; *MLSE* = Mini Linguistic State Examination; *IDDD* = Interview for Deterioration in Daily Living Activities in Dementia; *NPI* = Neuropsychiatric Inventory.

3.6. Treatment

There were two treatment arms:

1. Active TMS + language therapy
2. Sham TMS + language therapy

Patients were randomized in a 2:1 ratio, stratified by PPA variant (nfv-PPA, sv-PPA and lv-PPA).

3.6.1. Transcranial Magnetic Stimulation

The stimulation protocol consisted of a six-month treatment period, beginning with an induction phase that included ten sessions over two consecutive weeks, with a break on the weekend between the two weeks. This was followed by a 22-week maintenance phase, during which the same treatment was administered once per week.

All sessions utilized an intermittent theta-burst stimulation (iTBS) protocol, delivering a total of 600 pulses at a frequency of 50 Hz. These pulses were grouped into 20 cycles, each containing three pulses, with 10-second intervals between cycles. The entire stimulation session lasted approximately three minutes.

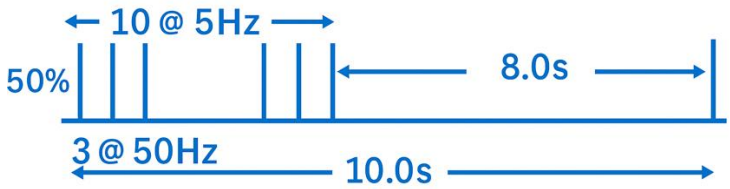

Figure 5. Structure of an iTBS Train

The treatment was applied at 120% of the resting motor threshold, with a maximum intensity of 50% of the stimulator's output capacity. Brain stimulation was performed with neuronavigation guidance, using a Magstim Rapid2 stimulator (Magstim, Whitland, UK) equipped with a figure-of-eight coil positioned over the left dorsolateral prefrontal cortex (DLPFC).

Moreover, in a study by Moral-Rubio et al. (2025), different TMS protocols were tested in a preliminary phase, including excitatory versus inhibitory stimulation and various cortical targets. The results showed that excitatory protocols led to more favourable outcomes. Among the regions examined, the left inferior frontal gyrus and the dorsolateral prefrontal cortex were identified as the most responsive, with the left DLPFC ultimately selected as the optimal site for excitatory stimulation because of a positive effect in both non-fluent and semantic variants.

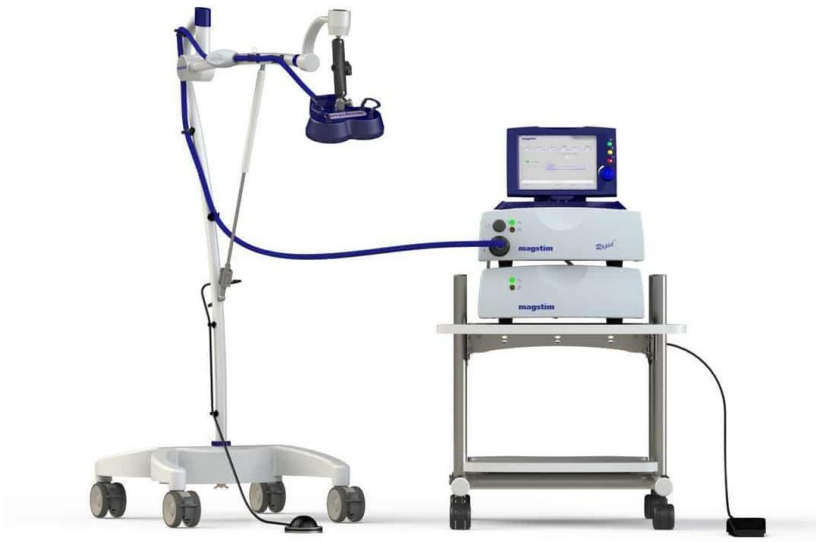

Figure 6. Transcranial Magnetic Stimulation Device Used in the Study

For the sham TMS condition, a sham coil was used, designed to be indistinguishable from the active TMS coil. Sham sessions followed the same frequency, duration, and target location as active TMS, with neuronavigation ensuring accurate coil positioning.

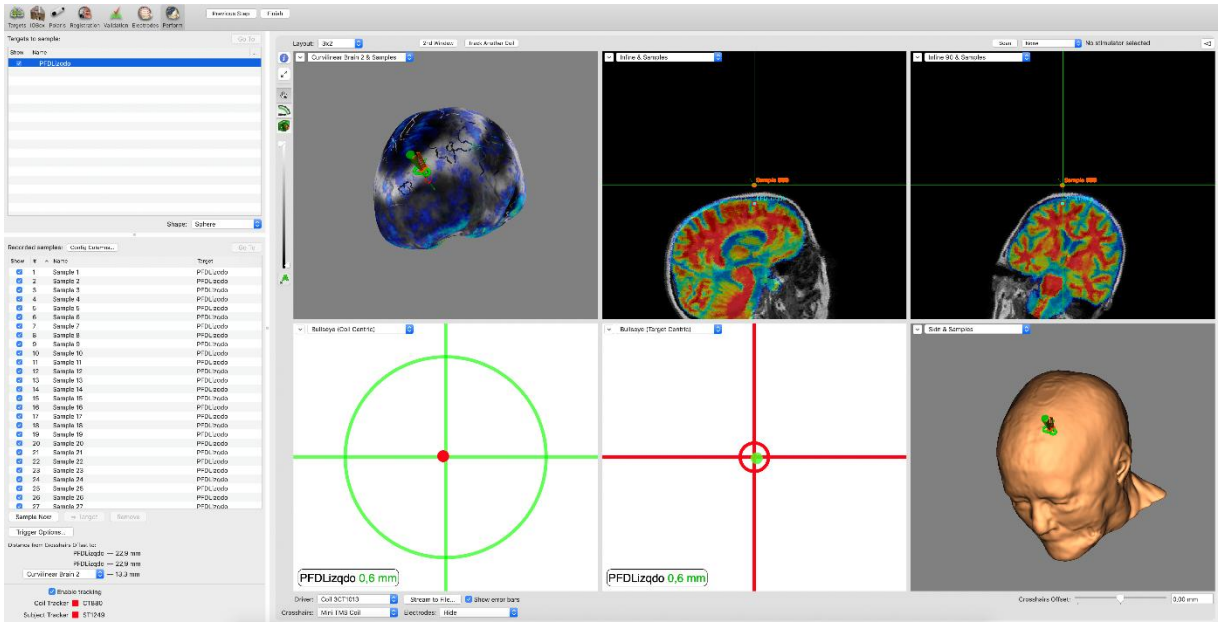

Figure 7. Neuronavigation System Display for TMS Treatment Administered Over the Left DLPFC.

3.7.2. Language therapy

All enrolled participants, regardless of whether they received active or sham TMS, underwent an adapted form of Lexical Retrieval Treatment (LRT) (Henry et al., 2013; Henry et al., 2019; Grasso et al., 2021). This therapy focuses on training lexical retrieval strategies to enhance and reinforce residual semantic, orthographic, and phonological knowledge. LRT has been previously demonstrated to be effective in individuals with PPA, in the absence of neuromodulation.

The treatment followed a structured sequence of tasks designed to engage, strengthen, and actively utilize key language processing components. The approach began with semantic self-cueing techniques and progressively incorporated orthographic and phonemic self-cues to support word retrieval. A summary of the task sequence can be found in Figure 8.

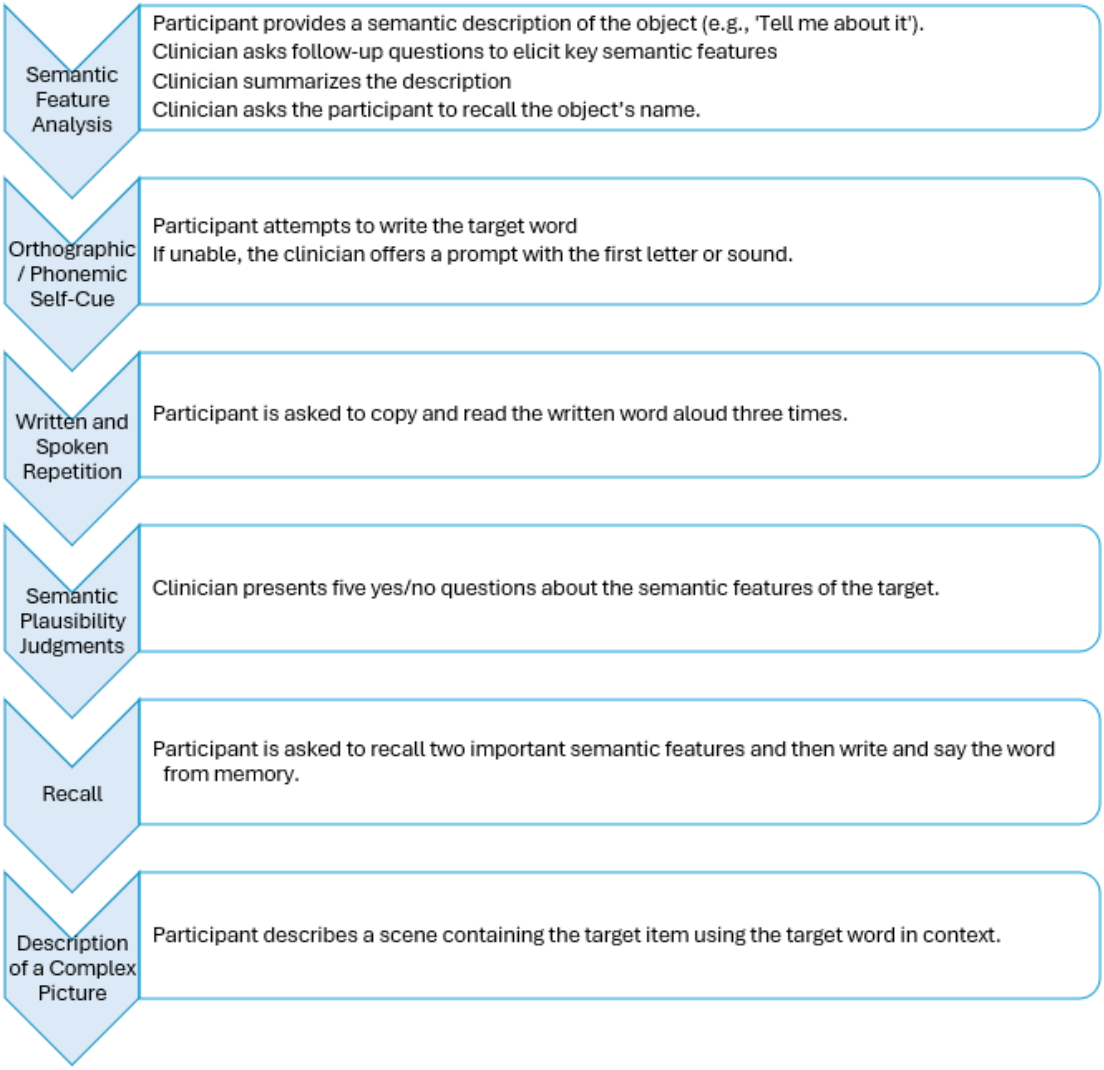

Figure 8. Steps of the Structured Lexical Retrieval Treatment Used in the Intervention

During the first two weeks, participants attended 10 intensive language therapy sessions. After this phase, each participant received one language therapy session per week throughout the six-month treatment period. These 50-minute therapy sessions were administered immediately after the TMS session. An example of the initial screen presented for each trained item is shown in Figure 9.

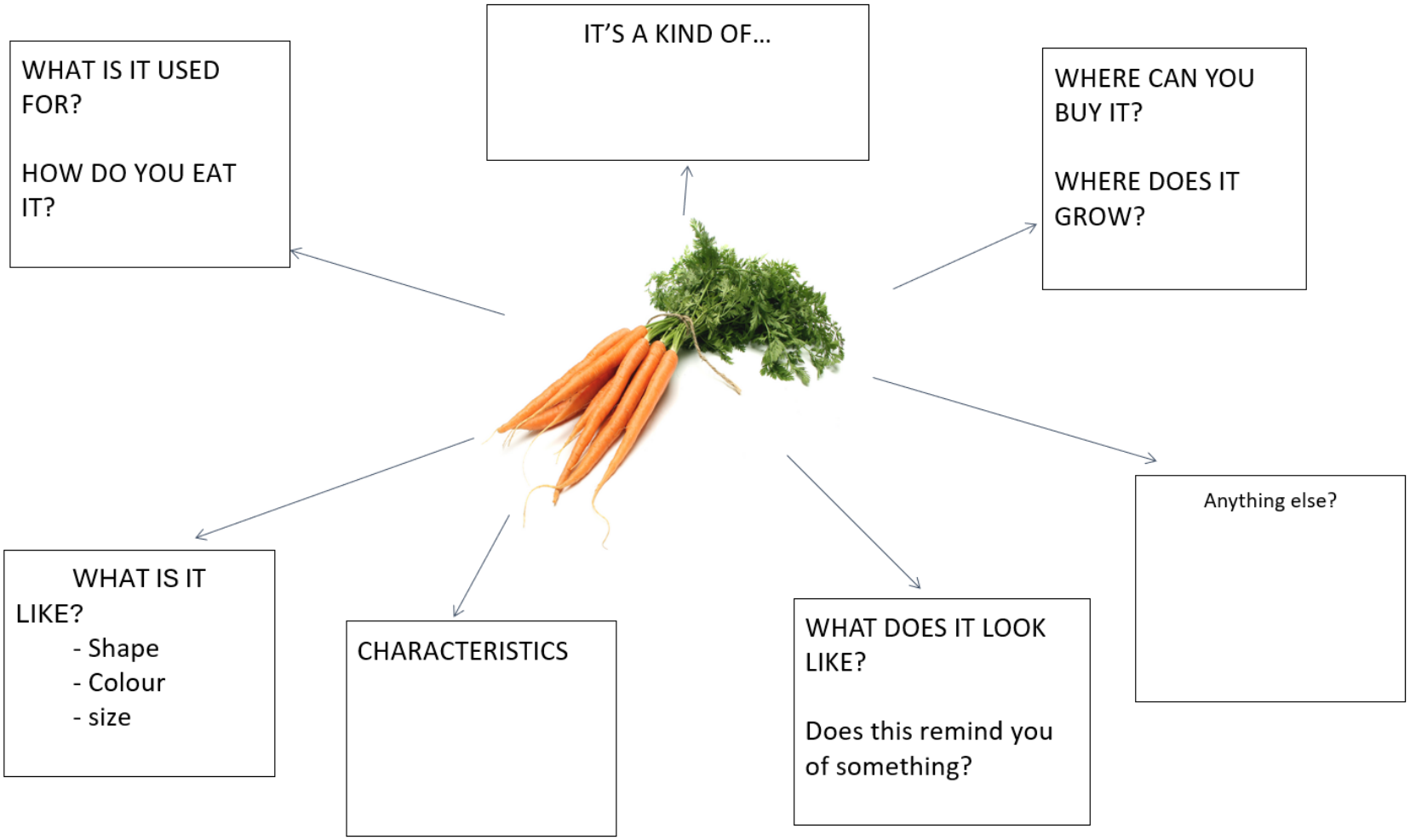

Figure 9. Semantic Feature Prompt Screen for Naming Therapy

Stimuli Selection

Each session focused on training five nouns. The words were selected from a list of 261 words, covering eight semantic categories: Animals, food, objects, places, furniture, clothing, transports and body parts.

To determine which words required training, participants completed two baseline oral naming assessments before the intervention began. Only nouns that were not named correctly or were unnamed in both assessments were selected for training.

Each therapy session introduced a new set of five eligible nouns. Once all eligible words had been used, the training cycled through previously trained words again.

Following the initial two-week intensive phase, participants were also assigned daily homework to reinforce learning. They received slides featuring images of the trained words along with their written forms. Participants were instructed to follow the Copy and Recall Treatment (CART) (Beeson & Egnor, 2006) method by copying the written word and produce the spoken word aloud 10 times. CART is a home-based practice method commonly paired with LRT in previous studies.

3.8. Statistical analysis

The statistical analysis for this study was conducted using SPSS 26.0 and RStudio 2024.04.2.

Descriptive statistics were used to summarize the data, with continuous variables presented as mean ± standard deviation and categorical variables expressed as absolute frequencies and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test. Baseline demographic and clinical characteristics were reported to provide an overview of the study sample.

To evaluate the effect of the intervention, an analysis of covariance (ANCOVA) was performed. Each primary and secondary outcome variable, such as SUVR, MLSE, naming of trained words, words per minute, IDDD and NPI at six months, was included as a dependent variable. The primary independent variable was the treatment group, distinguishing between active and sham TMS. Additional factors such as PPA variant and sex were included in the model. Baseline measurements of the dependent variable and SUVR at baseline for the secondary outcomes were included as covariates. The assumptions of the ANCOVA model, including normality of residuals and homogeneity of variances, were tested to ensure the validity of the analysis. Effect sizes were estimated using eta squared to quantify the magnitude of the intervention effect.

To further assess the impact of treatment at an earlier time point, additional ANCOVA models were estimated for secondary outcomes at three months. These models followed the same structure, adjusting for PPA variant, sex, baseline SUVR, and baseline assessment. A statistical significance threshold of $p < 0.05$ was applied throughout the analyses.

The final statistical analysis followed the intent-to-treat (ITT) principle, meaning that all randomized participants were included in the analysis. However, three patients withdrew early from the study, and their missing data were not imputed. As a result, a modified intent-to-treat approach was implemented, analysing only the available data without imputing missing values.

As an exploratory objective, the present work includes a subanalysis aimed at identifying potential predictors of clinical change after six months. We included in this analysis only those patients who completed all clinical and neuroimaging assessments throughout the entire follow-up period (n=57) (Appendix Table A1). In this case, we calculated the correlations between variables at baseline and the change in each variable using Pearson's

correlation coefficient. The magnitude of the correlation was interpreted according to the following criteria: small ($r < 0.30$), moderate ($0.30 \leq r < 0.50$) and strong ($r > 0.50$).

We used Least Absolute Shrinkage and Selection Operator (LASSO) regression to identify the most relevant predictors of clinical change at 6 months. LASSO is a machine-learning technique that performs both variable selection and regularization, shrinking the coefficients of less informative variables to zero, thereby enhancing model interpretability and reducing the risk of overfitting. For each clinical endpoint, we estimated the 6-month change score (e.g. MLSE at 6 months minus MLSE at baseline). Predictor variables included all baseline demographic, clinical, neuropsychological scores, and PET uptake in AAL regions. Predictors were standardized and entered into the model using a design matrix generated by *model.matri*x(). We used 5-fold cross-validation to identify the optimal regularization parameter (lambda) that minimized the cross-validated mean squared error. Models were fitted using the *glmnet* package with alpha = 1 to enforce the L1 penalty (LASSO). Final models included only variables with non-zero coefficients at the optimal lambda.

Furthermore, Elastic Net regression was performed to identify the most relevant predictors of clinical change. Elastic Net combines the strengths of both Ridge and LASSO regularization methods by incorporating both L1 and L2 penalties, which helps to overcome some of the limitations of Lasso regression when there are highly correlated predictors. The Elastic Net model was fitted using the *glmnet* package in R. The optimal penalty parameter (λ) was selected via 5-fold cross-validation. Specifically, the cv.glmnet() function was used to perform cross-validation, minimizing the cross-validated mean squared error (MSE) to select the best λ. The resulting model coefficients were estimated using the *glmnet()* function with the chosen λ.

Model performance was evaluated using R-squared (R^2) and Root Mean Squared Error (RSME). To avoid overinterpreting poorly performing models, only those with a cross-

validated R^2 of 0.30 or higher were retained in the main results. Models with lower performance were considered exploratory.

We performed an unsupervised clustering analysis using k-means to identify distinct subgroups of patients based on their clinical response. The analysis focused on quantifying overall patterns of change over the 6-month intervention period in the variables MLSE, naming, IDDD, and NPI. Before clustering, all change score variables were standardized (z-scores) to ensure equal weighting across different scales. The optimal number of clusters was determined using the elbow method, which examines the within-cluster sum of squares (WSS) for increasing numbers of clusters. We used 25 random starts and a maximum of 100 iterations. After clustering, we examined the characteristics of the clusters, and we compared the clinical and cognitive characteristics specifically in the group of patients receiving active TMS to identify those characteristics associated with each cluster.

3.9. Ethics Approval and Study Registration

The study was approved by the Ethics Committees for Investigation with Medicinal Products (CEIM) of the Hospital Clínico San Carlos (Code: 21/731-EC_P) and was registered at ClinicalTrials.gov (Identifier: NCT05842473). The subanalysis focusing on the prediction of clinical change was not pre-registered and has therefore been considered exploratory.

4. RESULTS

4.1. Participant characteristics

Between December 2021 and June 2024, a total of 78 individuals were assessed for eligibility. Of these, 63 participants (80.77%) met inclusion criteria and were enrolled in the study. Participants were randomized in a 2:1 ratio into two treatment arms: 42 (66.67%) were allocated to the active-TMS group and 21 (33.33%) to the sham-TMS group. There were 24 participants with nfv-PPA, 12 with sv-PPA, and 27 with lv-PPA. The last participant was randomized in January 2024.

During the follow-up period, a total of three participants in the sham-TMS group were partially or completely lost to follow-up. Two participants were diagnosed with cancer after initiating the intervention and consequently began chemotherapy around weeks 11 and 12, which led to their withdrawal from the study. Additionally, one participant in the sham group discontinued the intervention at month 3 and was therefore unable to complete the secondary outcome assessments, although the primary outcome (FDG-PET) was available. Conversely, another participant completed all secondary assessments but declined the FDG-PET scan, resulting in missing primary outcome data. As a result, 18 participants from the sham group were included in the primary outcome analysis and 18 in the secondary outcome analysis. In the active-TMS group, two participants declined to undergo the FDG-PET scan but completed all other assessments. Therefore, 40 participants of the active group were included in the primary outcome analysis, and 42 in the secondary outcome analysis. Despite these exclusions, data completeness was high across both groups.

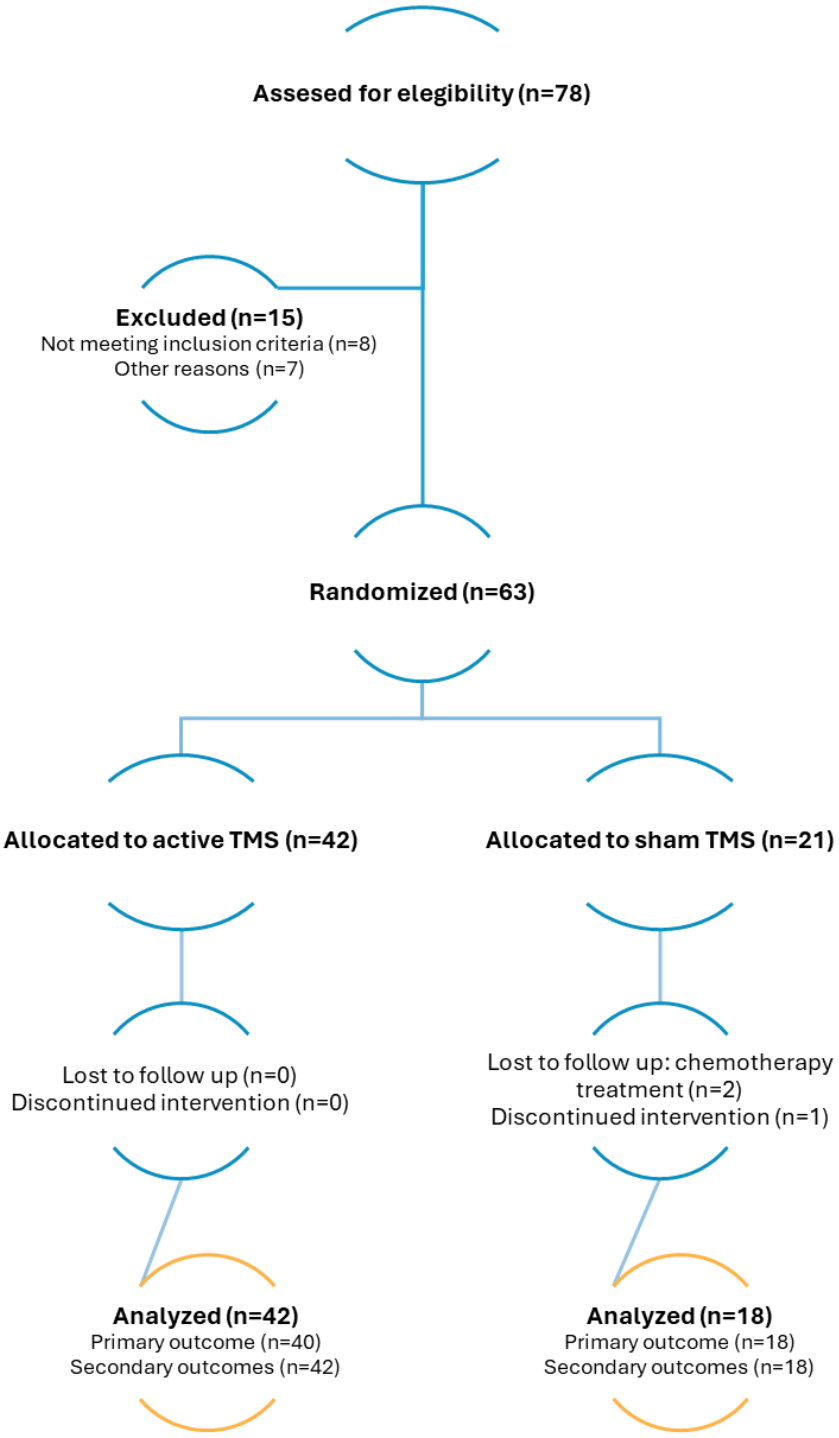

Figure 10. Flow of participants through the study.

TMS indicates transcranial magnetic stimulation.

For the participants enrolled, demographic and clinical baseline characteristics are summarised in Table 9. The two treatment groups were well matched. The mean age was 71.85 years (SD = 8.35) in the active-TMS group and 71.61 years (SD = 8.59) in the sham-TMS group ($p = 0.763$). Women represented 73.8% of the active group and 52.4% of the sham group ($p = 0.089$). Years of education was comparable between groups, with a mean of 13.76 years (SD = 5.06) and 13.57 years (SD = 4.02), respectively ($p = 0.763$). All participants were white, and all but two were native Spanish speakers (one English speaker per group).

The average time since symptom onset was 29.17 months (SD = 17.88) in the active group and 31.42 months (SD = 21.02) in the sham group ($p = 0.657$). The distribution of PPA variants across groups was similar: nfv-PPA (active: 40.5%, sham: 33.3%), sv-PPA (active: 19.0%, sham: 19.0%), and lv-PPA (active: 40.5%, sham: 47.6%) ($p = 0.838$).

Cognitive, functional, and neuropsychiatric scores did not significantly differ at baseline. SUVR values were significantly higher in the active group (M = 0.829, SD = 0.012) compared to the sham group (M = 0.743, SD = 0.016; $p < 0.001$). But no significant differences were observed in ACE-III, MLSE, naming performance, WPM, NPI, depressive symptoms, or IDDD scores (all $p > 0.05$).

Table 9. Baseline demographic and clinical characteristics (randomized sample).

		Active group (n=42)	Sham group (n=21)	U / χ^2 (p-value)
		Demographic		
Age, mean (SD), years		71.85 (8.35)	71.61 (8.59)	421 (0.763)
Sex, Females		31 (73.8%)	11 (52.4%)	2.89 (0.089)
Race, White		42 (100%)	21 (100%)	-
Education, years		13.76 (5.06)	13.57 (4.02)	421 (0.763)
Mother tongue		41 Spanish 1 English	20 Spanish 1 English	0.25 (0.61)
		Clinical		
Time since symptom onset, months		29.17 (17.88)	31.42 (21.02)	2.095 (0.657)
PPA variant	nfv-PPA	17 (40.5%)	7 (33.3%)	0.354 (0.838)
	sv-PPA	8 (19.0%)	4 (19.0%)	
	lv-PPA	17 (40.5%)	10 (47.6%)	
SUVR		0.829 (0.012)	0.743 (0.016)	123 (<0.001)
ACE-III (/100)		55.12 (18.80)	42.33 (21.43)	314 (0.065)
MLSE (/100)		78.93 (11.18)	73.43 (16.26)	370 (0.304)
Naming (/261)		122.21 (11.63)	127.12 (15.66)	306 (0.050)
WPM		68.59 (6.12)	67.47 (8.25)	202 (0.113)
NPI		8.93 (11.82)	7.76 (12.45)	381 (0.379)
Depression		8 (19%)	4 (19%)	-
IDDD		48.02 (14.35)	45.45 (10.45)	410 (0.886)
Speech therapy		11 (26.2%)	7 (33.3%)	0.350 (0.379)
		Comorbidities		
Dyslipidemia		5 (11.90%)	4 (19.05%)	0.583 (0.445)
Arterial hypertension		5 (11.90%)	4 (19.05%)	0.583 (0.445)
Diabetes mellitus		3 (7.14%)	2 (9.52%)	0.109 (0.742)
Atrial fibrillation		1 (2.38%)	1 (4.76%)	0.258 (0.611)
Other cardiopathies		1 (2.38%)	1 (4.76%)	0.258 (0.611)
		Concomitant therapies		

Cholinesterase inhibitors	5 (11.90%)	4 (19.05%)	0.583 (0.445)
Memantine	1 (2.38%)	1 (4.76%)	0.258 (0.611)
L-dopa	1 (2.38%)	0 (0%)	0.508 (0.476)
Antipsychotics	3 (7.14%)	1 (4.76%)	0.133 (0.715)
Selective serotonin reuptake inhibitors	7 (16.67%)	7 (33.33%)	2.250 (0.134)

Abbreviations: *ACE*: Addenbrooke's Cognitive Examination; *IDDD*: Interview for Deterioration of Daily Living in Dementia; *MLSE*: Mini-Linguistic State Examination; *NPI*: Neuropsychiatric Inventory; *PPA*: Primary Progressive Aphasia; *nfv-PPA*: nonfluent/agrammatic variant Primary Progressive Aphasia; *sv-PPA*: semantic variant Primary Progressive Aphasia; *lv-PPA*: logopenic variant Primary Progressive Aphasia.

4.2. Treatment efficacy

In this section, the results regarding the efficacy of the intervention are described. The analysis includes both the primary and secondary outcome measures, comparing the active-TMS and sham-TMS groups at different timepoints. The corresponding adjusted means and statistical comparisons for each variable are presented in Tables 10 and 11.

Table 10. Summary of Primary and Secondary Outcomes at 6 Months by Treatment Group

Outcome	Group	Adjusted Mean (95% CI)	F	p	η^2
Primary outcome					
	a-TMS	0.784 (0.774–0.794)	4.17	0.046	0.077
SUVR	s-TMS	0.766 (0.752–0.780)			
Secondary outcomes					
MLSE	a-TMS	79.06 (76.48–81.64)	11.07	0.002	0.173
	s-TMS	71.35 (67.76–74.94)			
Naming	a-TMS	143.81 (137.26–150.35)	15.97	<0.001	0.238
	s-TMS	119.99 (110.79–129.19)			
WPM	a-TMS	62.73 (55.94–69.52)	0.315	0.578	0.008
	s-TMS	59.32 (50.10–68.54)			
IDDD	a-TMS	43.54 (40.61–46.48)	4.10	0.048	0.073
	s-TMS	48.94 (44.91–52.96)			
NPI	a-TMS	6.99 (4.83–9.16)	4.30	0.043	0.074
	s-TMS	11.25 (7.98–14.53)			

Abbreviations: *a-TMS* = active transcranial magnetic stimulation; *s-TMS* = sham transcranial magnetic stimulation; *SUVR* = Standard Uptake Value Ratio; *MLSE* = Mini Linguistic State Examination; *WPM* = Words Per Minute; *IDDD* = Interview for Deterioration in Daily Living Activities in Dementia; *NPI* = Neuropsychiatric Inventory; *CI* = Confidence Interval; η^2 = eta squared (effect size).

Table 11. Summary of Secondary Outcomes at 3 Months by Treatment Group

Outcome	Group	Adjusted Mean (95% CI)	F	p	η²
MLSE	a-TMS	77.54 (74.22–80.87)	6.612	0.013	0.111
	s-TMS	69.92 (65.40–74.44)			
Naming	a-TMS	136.57 (130.71–142.44)	8.59	0.005	0.135
	s-TMS	121.77 (114.02–129.51)			
WPM	a-TMS	65.46 (60.19–70.74)	1.57	0.217	0.036
	s-TMS	59.57 (52.48–66.66)			
IDDD	a-TMS	45.81 (43.35–48.27)	0.701	0.406	0.013
	s-TMS	47.62 (44.39–50.85)			
NPI	a-TMS	7.38 (5.04–9.71)	3.51	0.066	0.059
	s-TMS	11.39 (8.05–14.73)			

Abbreviations: *a-TMS* = active transcranial magnetic stimulation; *s-TMS* = sham transcranial magnetic stimulation; *MLSE* = Mini Linguistic State Examination; *WPM* = Words Per Minute; *IDDD* = Interview for Deterioration in Daily Living Activities in Dementia; *NPI* = Neuropsychiatric Inventory; *CI* = Confidence Interval; η² = eta squared (effect size).

4.2.1. Primary Outcome: SUVR Change at 6 Months

The primary outcome measure was the change in standardised uptake value ratio (SUVR) over the 6-month treatment period. After adjusting for baseline SUVR, sex, and PPA variant, the adjusted mean SUVR at 6 months was 0.784 (95% CI: 0.774–0.794) in the active-TMS group and 0.766 (95% CI: 0.752–0.780) in the sham-TMS group. The difference between groups reached statistical significance ($F = 4.17$, $p = 0.046$, $\eta^2p = 0.077$), indicating a significantly less reduction in SUVR values in the active treatment group compared to the sham group.

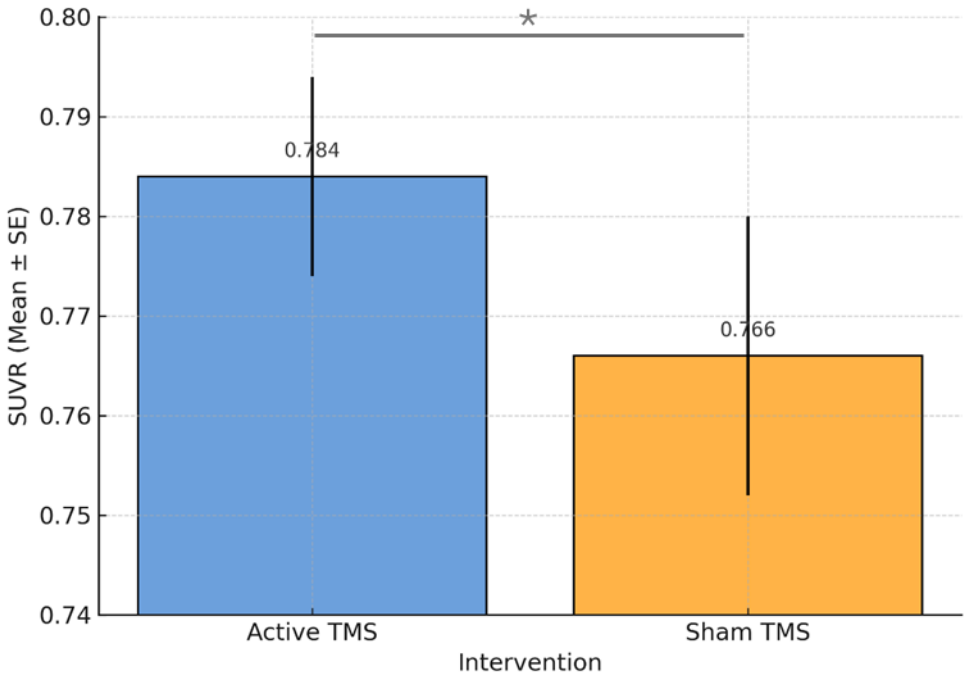

Figure 11. Mean Change in Primary Outcome by Treatment Group.

Adjusted mean SUVR values (± SE) at six months by treatment condition, adjusted for baseline SUVR, sex, and PPA variant. Active-TMS participants are shown in blue, and sham-TMS participants in orange. * = Significant differences.

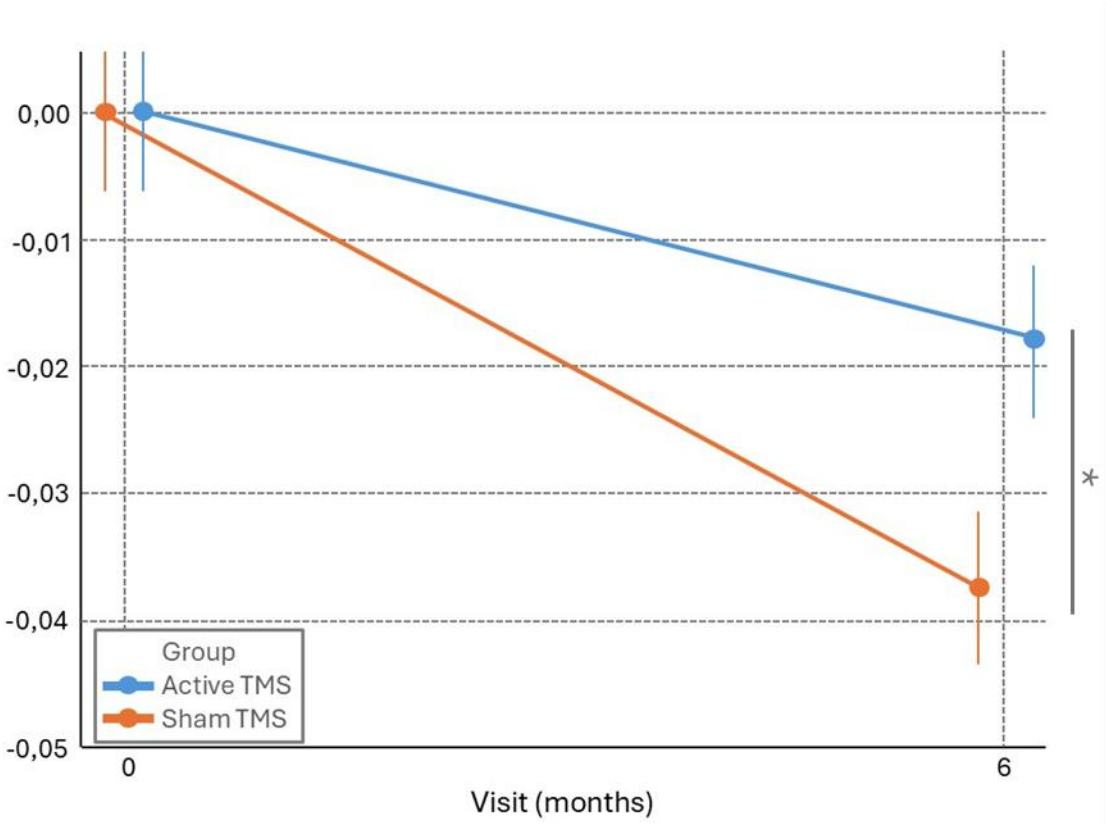

Figure 12. Primary outcome by Treatment group

Group-level changes in SUVR from baseline to six months. Active-TMS participants are shown in blue, and sham-TMS participants in orange. * = Significant differences.

4.2.2. Secondary outcomes

4.2.2.1. Secondary Outcome 1: Confrontation Naming of Trained Words

At 6 months, the active-TMS group showed significantly better naming performance of trained items compared to the sham group. The adjusted mean was 143.81 (95% CI: 137.26–150.35) in the active group and 119.99 (95% CI: 110.79–129.19) in the sham group ($F = 15.97$, $p < 0.001$, $\eta^2p = 0.238$). A similar effect was observed at 3 months ($F = 8.59$, $p = 0.005$, $\eta^2p = 0.135$), with adjusted means of 136.57 (95% CI: 130.71–142.44) for the active group and 121.77 (95% CI: 114.02–129.51) for the sham group.

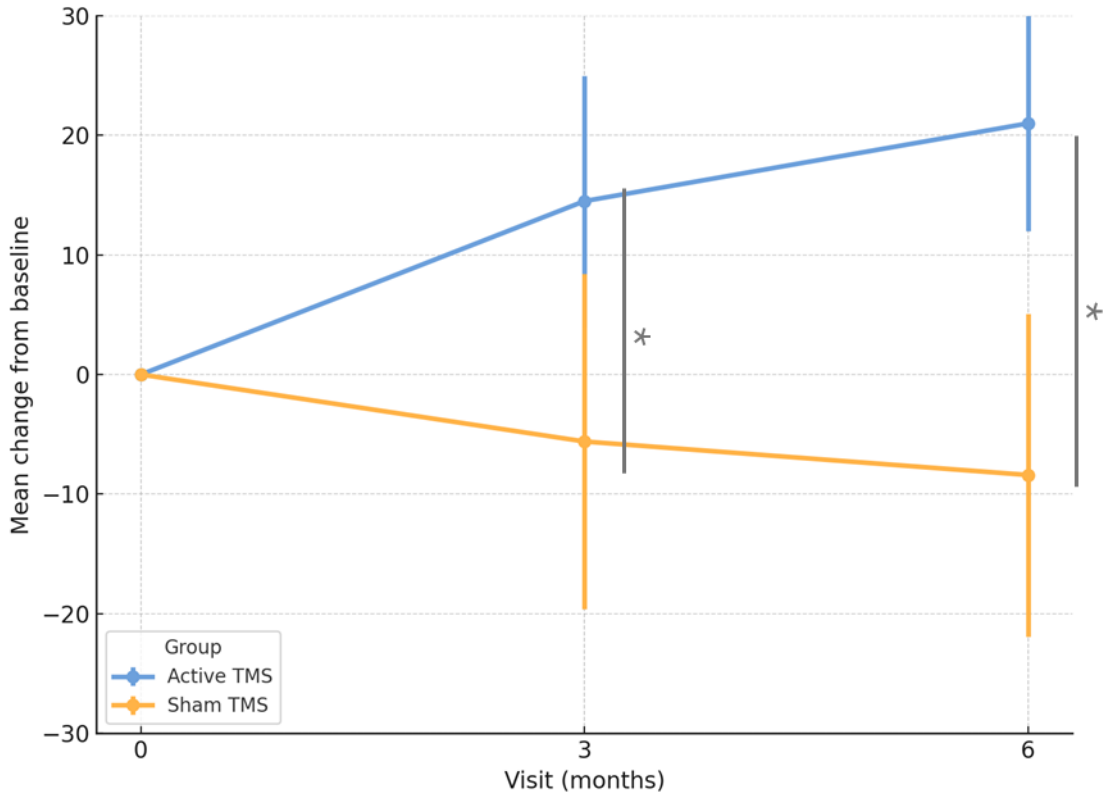

Figure 13. Mean Change on Naming by Treatment Group.

Plot representing changes (means with 95% confidence intervals). Active-TMS participants are shown in blue, and sham-TMS participants in orange. * = Significant differences.

4.2.2.2. Secondary Outcome 2: Language Function as Measured by MLSE

Significant group differences were also observed on the MLSE at both 3 and 6 months. At 6 months, the adjusted mean score was 79.06 (95% CI: 76.48–81.64) in the active-TMS

group, compared to 71.35 (95% CI: 67.76–74.94) in the sham group ($F = 11.07$, $p = 0.002$, $\eta^2p = 0.173$). At 3 months, the active group again performed significantly better, with an adjusted mean of 77.54 (95% CI: 74.22–80.87) versus 69.92 (95% CI: 65.40–74.44) in the sham group ($F = 6.612$, $p = 0.013$, $\eta^2p = 0.111$).

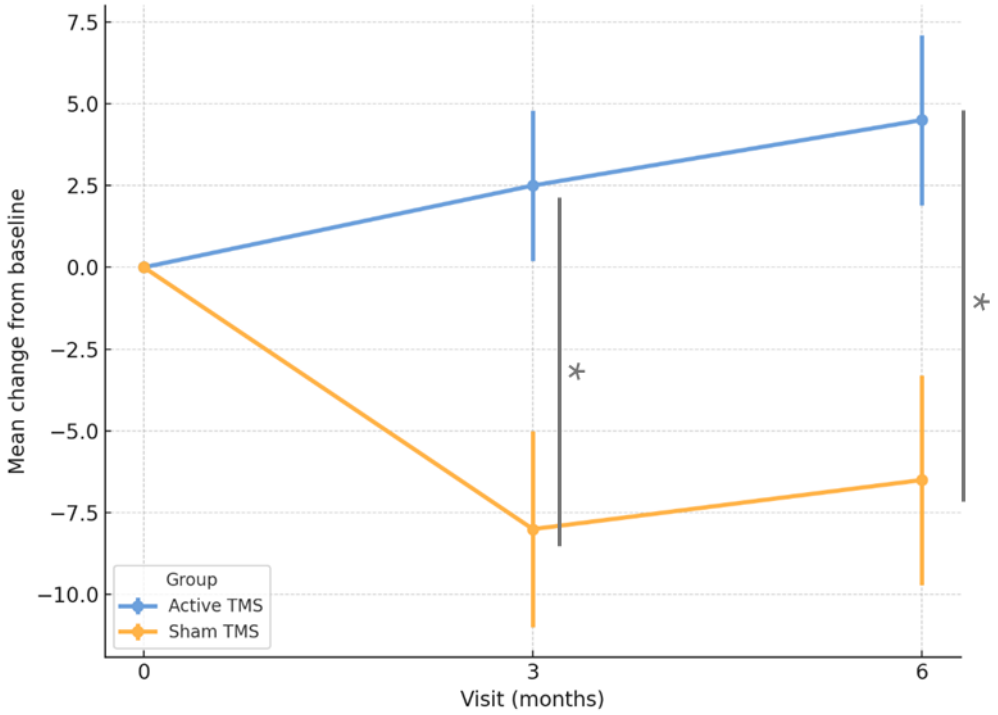

Figure 14. Mean Change on MLSE by Treatment Group.

Plot representing changes (means with 95% confidence intervals). Active-TMS participants are shown in blue, and sham-TMS participants in orange. * = Significant differences.

4.2.2.3. Secondary Outcome 3: Spontaneous Speech (Words per Minute)

No statistically significant effect of treatment was found for spontaneous speech rate, as measured by words per minute (WPM). At 6 months, the adjusted means were 62.73 (95% CI: 55.94–69.52) for the active group and 59.32 (95% CI: 50.10–68.54) for the sham group ($F = 0.315$, $p = 0.578$, $\eta^2p = 0.008$). Similarly, at 3 months, no significant difference was found ($F = 1.57$, $p = 0.217$, $\eta^2p = 0.036$), with means of 65.46 (95% CI: 60.19–70.74) in the active group and 59.57 (95% CI: 52.48–66.66) in the sham group. Although numerically higher in the active group, the results did not reach statistical significance.

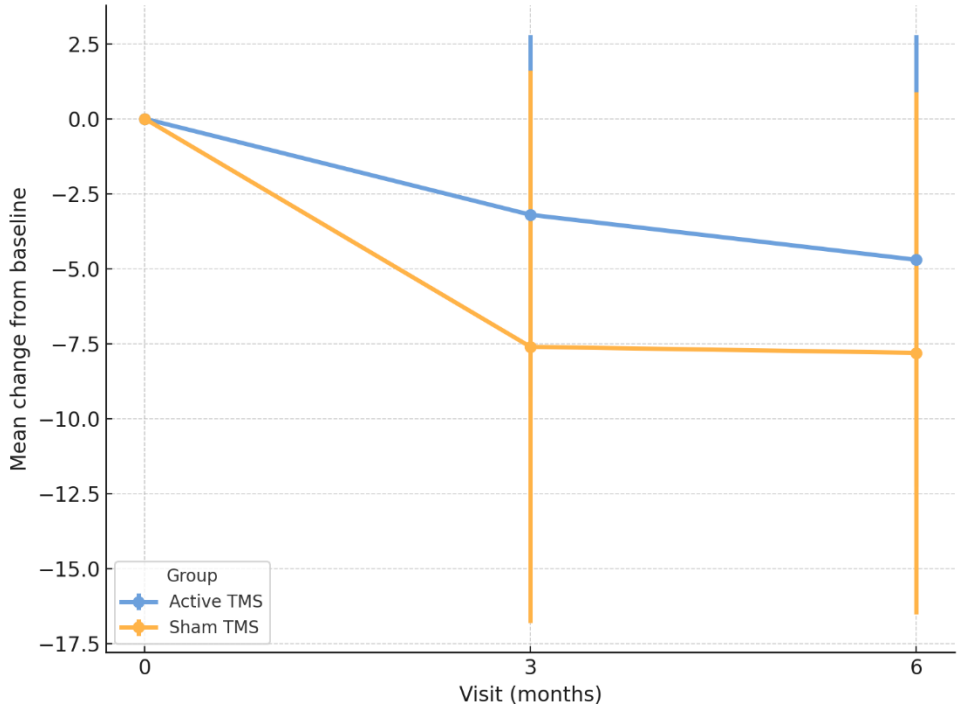

Figure 15. Mean Change on Words per Minute by Treatment Group.

Plot representing changes (means with 95% confidence intervals). Active-TMS participants are shown in blue, and sham-TMS participants in orange.

4.2.2.4. Secondary Outcome 4: Functional Activity in Daily Life (IDDD)

At 6 months, the active-TMS group had significantly lower IDDD scores, reflecting less impairment in daily functioning. The adjusted mean was 43.54 (95% CI: 40.61–46.48) for the active group and 48.94 (95% CI: 44.91–52.96) for the sham group ($F = 4.10$, $p = 0.048$, $\eta^2p = 0.073$). Although the difference at 3 months was not statistically significant ($F = 0.701$, $p = 0.406$, $\eta^2p = 0.013$), mean scores still favoured the active group (45.81 vs. 47.62).

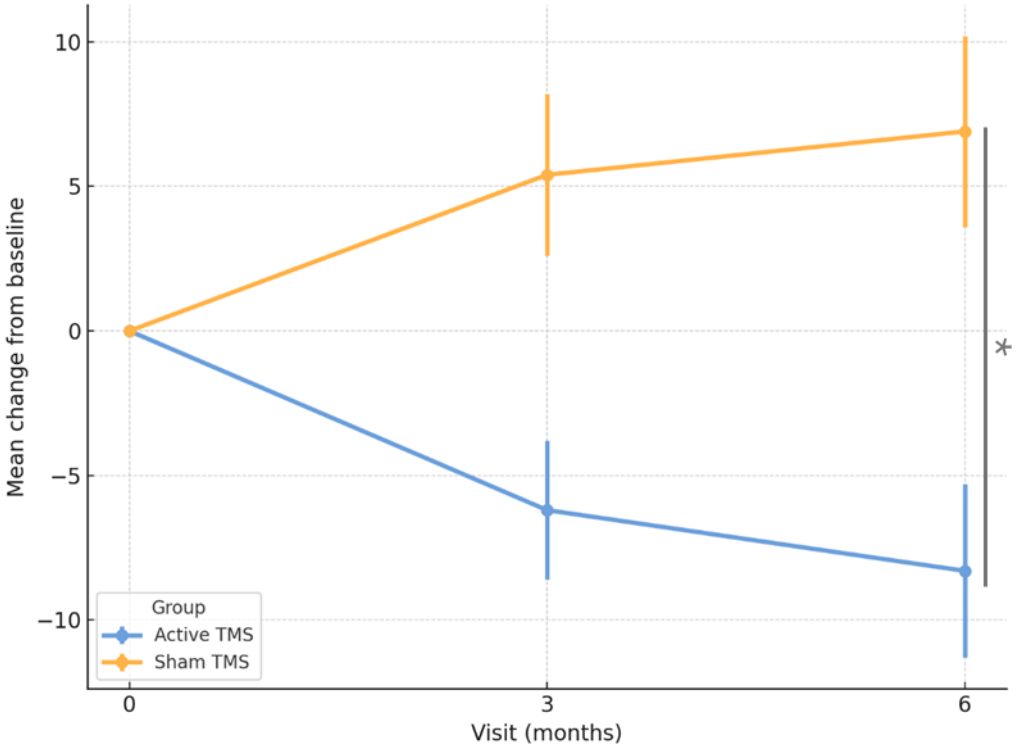

Figure 16. Mean change (SE) on IDDD by treatment group.

Plot representing changes (means with 95% confidence intervals). Active-TMS participants are shown in blue, and sham-TMS participants in orange. * = Significant differences.

To better understand the contribution of language to daily functioning, exploratory analyses were conducted on the six language-related items from the IDDD (items 24–29), which reflect the need for assistance with reading, writing, initiating conversation, verbal expression, conversational attention, and comprehension of spoken language. These items offer a more granular view of how the intervention may have impacted communicative independence. These specific items are described in Table 12.

Table 12. Language-related items from the IDDD

IDDD Item	Description
24.	Do you have to help him/her with reading?
25.	Do you have to help him/her write a letter, a postcard or fill in a form?
26.	Is he/she able to initiate a conversation with another person as frequently as before?
27.	Do you have to help him/her to express him/herself verbally?
28.	Is he/she able to maintain attention in a conversation with another person as frequently as before?
29.	Do you have to help him/her understand spoken language?

Abbreviations: *IDDD* = Interview for Deterioration in Daily Living Activities in Dementia

At 6 months, the a-TMS group consistently outperformed the sham group across all six language-related domains, with statistically significant differences observed in reading ($F = 15.546$, $p < 0.001$, $\eta^2 = 0.227$), writing ($F = 6.806$, $p = 0.012$, $\eta^2 = 0.114$), and comprehension of spoken language ($F = 10.910$, $p = 0.002$, $\eta^2 = 0.171$). A marginal trend was also observed for maintain attention in a conversation ($F = 3.753$, $p = 0.058$). At 3 months, similar patterns were present, with significant effects found in reading ($F = 9.397$, $p = 0.003$), and comprehension ($F = 6.884$, $p = 0.011$). Detailed statistical outcomes for the IDDD language-related items can be found in Table 13.

Table 13. Summary of Language-related Items from the IDDD at 3 and 6 Months

	Adjusted Mean		**F**	**p**	**η^2**
	(a-TMS)	(s-TMS)			
IDDD Language Total (6 months)	11.05	12.05	0.286	0.595	0.005
IDDD Language Total (3 months)	11.23	12.97	3.313	0.074	0.055
Item 24: Reading (6 months)	1.52	2.17	15.546	<0.001	0.227
Item 24: Reading (3 months)	1.62	2.17	9.397	0.003	0.146
Item 25: Writing (6 months)	2.00	2.61	6.806	0.012	0.114
Item 25: Writing (3 months)	2.11	2.27	0.668	0.417	0.012
Item 26: Conversation Initiation (6 months)	1.86	1.97	1.517	0.223	0.028
Item 26: Conversation Initiation (3 months)	1.92	2.21	1.947	0.168	0.034
Item 27: Verbal Expression (6 months)	2.17	2.44	0.180	0.673	0.003
Item 27: Verbal Expression (3 months)	2.21	2.38	1.504	0.225	0.027
Item 28: Conversational Attention (6 months)	1.76	1.89	3.753	0.058	0.066
Item 28: Conversational Attention (3 months)	1.91	2.14	1.017	0.318	0.018
Item 29: Comprehension of Spoken Language (6 months)	1.73	2.22	10.910	0.002	0.171
Item 29: Comprehension of Spoken Language (3 months)	1.82	2.28	6.884	0.011	0.111

Abbreviations: *a-TMS*: active transcranial magnetic stimulation; *s-TMS*: sham transcranial magnetic stimulation.

4.2.2.4. Secondary Outcome 5: Neuropsychiatric Symptoms (NPI)

The NPI scores showed a statistically significant group difference at 6 months. Participants in the active group had a lower symptom burden (M = 6.99, 95% CI: 4.83–9.16) compared to those in the sham group (M = 11.25, 95% CI: 7.98–14.53), with $F = 4.30$, $p = 0.043$, $\eta^2p = 0.074$. The difference at 3 months approached significance ($F = 3.51$, $p = 0.066$, $\eta^2p = 0.059$), with adjusted means of 7.38 (95% CI: 5.04–9.71) and 11.39 (95% CI: 8.05–14.73) for the active and sham groups, respectively. This suggests that active TMS may also help mitigate neuropsychiatric decline over time.

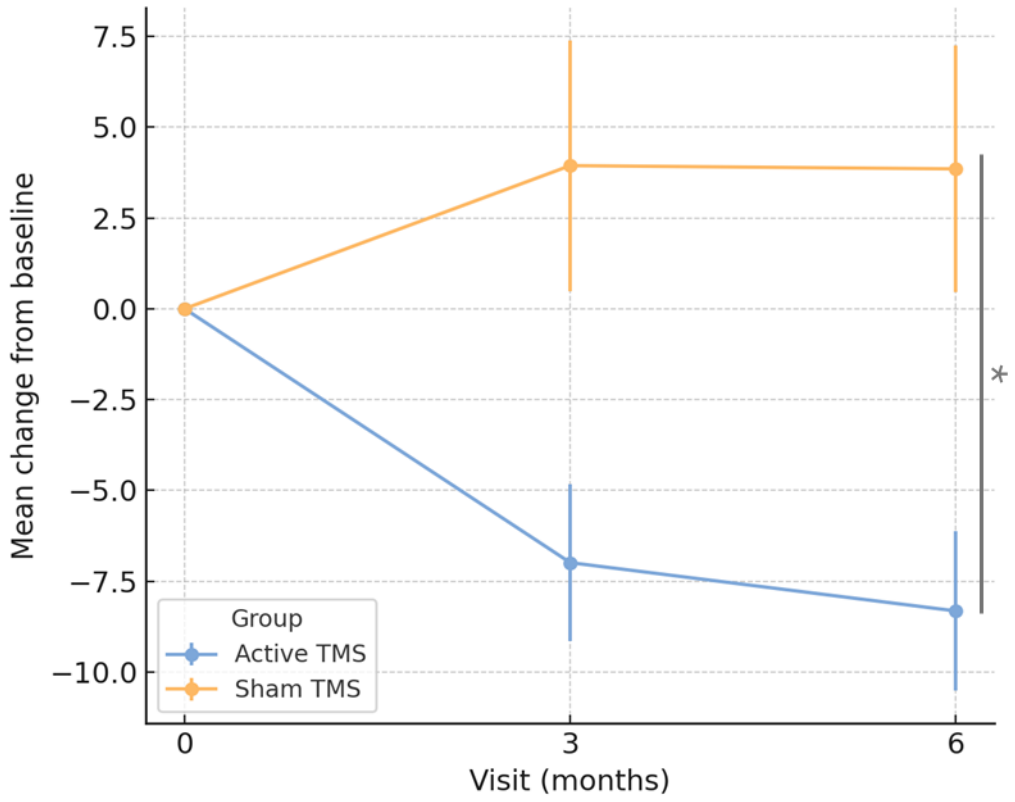

Figure 17. Mean Change on NPI by Treatment Group.

Plot representing changes (means with 95% confidence intervals). Active-TMS participants are shown in blue, and sham-TMS participants in orange. * = Significant differences.

4.3. Safety

Throughout the study, a total of 12 adverse events (AEs) were documented. In the sham-TMS group, two participants (9.52%) experienced serious AEs, specifically cancer diagnoses, which were determined to be unrelated to the study intervention. These cases led to their withdrawal from the trial upon initiation of chemotherapy.

In the active-TMS group, one participant (2.38%) reported treatment site discomfort, considered probably related to the intervention. To alleviate this adverse event, the stimulation intensity was reduced from 50 Hz to 40 Hz, followed by a progressive return to the planned stimulation level after session 12.

Mild, unrelated AEs were reported in both treatment arms. In the sham-TMS group, events included hypercholesterolemia (4.76%), asthma (4.76%), and depression (4.76%), with no other AE occurring more than once. In the active-TMS group, the following unrelated AEs were recorded in single participants (2.38% each): urinary tract infection, neuropathic pain, constipation, insomnia, gastroenteritis, and herpes zoster.

In total, six participants (14.28%) in the active-TMS group and three (14.28%) in the sham-TMS group reported at least one mild, unrelated AE. No statistically significant difference in the overall incidence of adverse events was observed between the two groups ($p = 0.157$), indicating a similar safety profile across treatment conditions.

Table 14. Adverse Events.

	Treatment, No. (%) of Participants	
Adverse event	a-TMS (N=42)	s-TMS (N=21)
	Probably related	
Treatment site discomfort	1 (2.38%)	0
	Unrelated	
Cancer	0	2 (9.52%)
Hypercholesterolemia	0	1 (4.76%)
Asthma	0	1 (4.76%)
Urinary Tract Infection	1 (2.38%)	0
Neuropathic Pain	1 (2.38%)	0
Constipation	1 (2.38%)	0
Insomnia	1 (2.38%)	0
Gastroenteritis	1 (2.38%)	0
Depression	0	1 (4.76%)
Herpes Zoster	1 (2.38%)	0

Abbreviations: *a-TMS:* active Transcranial Magnetic Stimulation; *s-TMS:* sham Transcranial Magnetic Stimulation.

4. 4. Treatment adherence

A high level of adherence to the intervention was observed across participants. Specifically, 92.06% of individuals completed the full treatment schedule, attending all 30 planned sessions. Only three participants (8%)—one in the active-TMS group and two in the sham-TMS group—did not complete the entire regimen. The reasons for non-completion included an ear surgery that prevented one participant from attending the final three sessions, the inability of a caregiver to accompany another participant to four sessions, and a third participant who, due to mobility difficulties, chose not to continue treatment after the third

month. Importantly, no major deviations from the established treatment protocol were identified throughout the study.

4.5. Prediction of clinical change

4.5.1. Correlations between clinical variables

Correlations between the change of the clinical variables from baseline to 6-months assessments were moderate between MLSE and naming (r=0.379, *p*=0.004), MLSE and IDDD (r= -0.359, *p*=0.007), and naming and IDDD (r= -0.440, *p*=0.001). The other correlations were not statistically significant. All the correlations are shown in Table 15.

Table 15. Correlations between clinical variables

	MLSE	Naming	WPM	IDDD	NPI
MLSE	-	0.379*	-0.011	-0.359*	-0.248
Naming	0.379*	-	-0.003	-0.440*	-0.065
WPM	-0.011	-0.003	-	-0.108	-0.148
IDDD	-0.359*	-0.440*	-0.108	-	0.212
NPI	-0.248	-0.065	-0.148	0.212	-

*Correlation is significant *(p* < 0.05)

4.5.2. Identification of predictors of change

In order to highlight the most influential predictors, only variables with absolute coefficients greater than 0.1 were specified in the text and Figures 18 – 22. Complete information about the predictors is included in Appendix Tables A2-A6.

4.5.2.1. Prediction of MLSE change

The LASSO model showed good performance in the whole cohort, with an R^2 of 0.52 and an RMSE of 4.94. The selected variables included treatment (with TMS), digit span backwards, Stroop color naming, VOSP (progressive silhouettes), repetition of syllables, and brain metabolism in the right cerebellum, the right posterior cingulate and the left

hippocampus. For the active TMS group, the model showed R^2=0.218 with an RMSE of 4.28. Regarding the TMS sham group, R^2 was 0.685 and RMSE was 5.61.

The Elastic Net model achieved an R^2 of 0.57 and an RMSE of 5.05 in the entire cohort. The selected variables included treatment, digit span backwards, Stroop color naming, VOSP (progressive silhouettes), repetition of syllables, and brain metabolism in the right cerebellum and right posterior cingulate. For the active TMS group, the model yielded an R^2 of 0.137 and RMSE of 4.38. The model for the sham group showed an R^2 of 0.64 and an RMSE of 5.94.

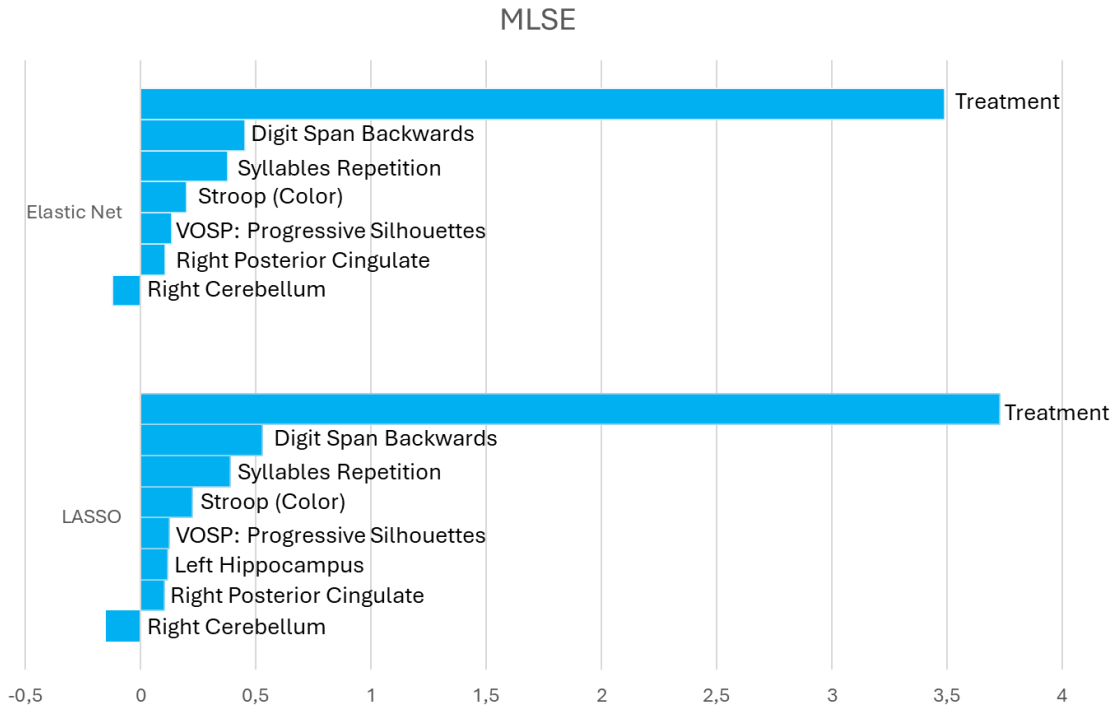

Figure 18. Predictors of Change in MLSE.

Bar plots represent standardized coefficients (absolute value > 0.1) from the best-performing models ($R^2 \geq 0.30$). Abbreviations: *MLSE* = Mini Linguistic State Examination

4.5.2.2. Prediction of Naming change

The LASSO regression model yielded an R^2=0.422 and an RMSE of 15.0 in the whole cohort. The selected variables included treatment, VOSP (number location) and the brain metabolism in the right cerebellum, left posterior cingulate, right superior orbital frontal cortex, and left hippocampus.

The predictive model built using Elastic Net regularization yielded an R^2 of 0.41 and an RMSE of 15.17 in the entire cohort. The selected variables included treatment, ROCF (time), VOSP (number location) and the brain metabolism in the left cerebellum, right cerebellum, left posterior cingulate, right superior orbital frontal cortex and left hippocampus.

The models in active and sham TMS showed no explanatory power (R^2=0) in both LASSO and Elastic Net.

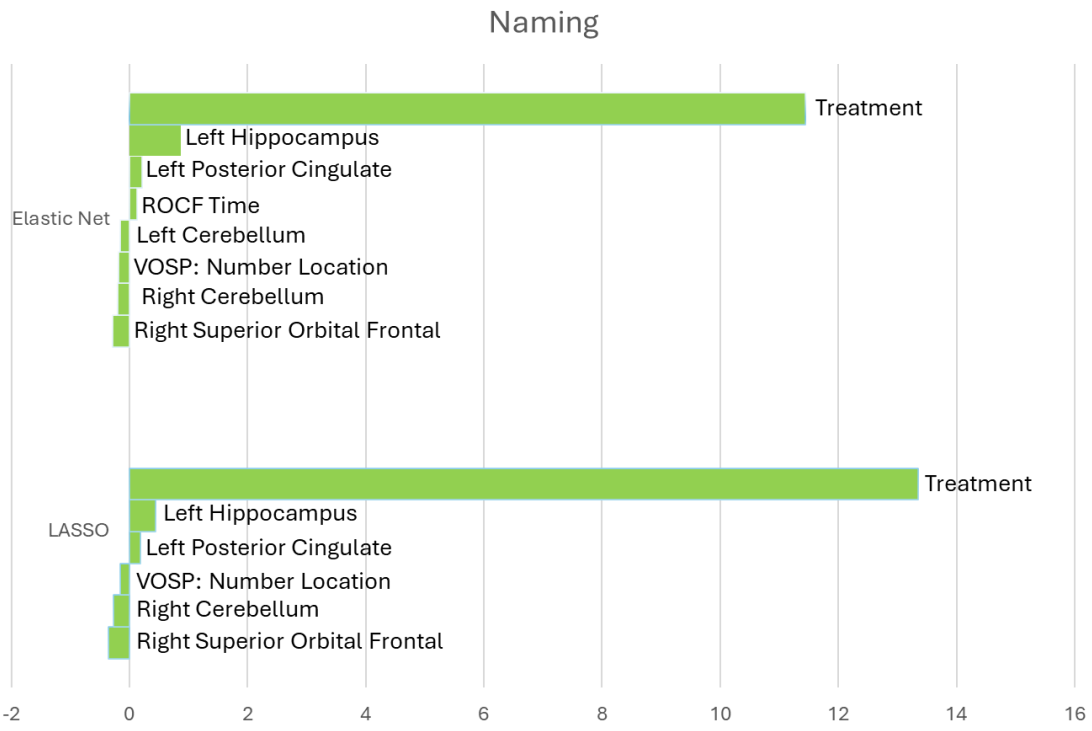

Figure 19. Predictors of Change in Naming.

Bar plots represent standardized coefficients (absolute value > 0.1) from the best-performing models ($R^2 \geq 0.30$).

4.5.2.3. Prediction of WPM change

In this case, both LASSO regression and Elastic Net models showed modest or no meaningful predictive capacity. For the total sample, the LASSO model yielded an R^2 of 0.19 and RMSE of 16.7. Elastic Net achieved R^2=0.19 and RMSE of 16.65. Models for active and sham groups showed R^2=0. The variables selected in the LASSO regression model included

sentences comprehension (passive sentences) and brain metabolism in the left superior occipital lobe. In the Elastic Net model, the variables were sentences comprehension (passive sentences) and brain metabolism in the right amygdala and the left superior occipital lobe.

4.5.2.4. Prediction of IDDD change

Model performance for the whole cohort was R^2=0.462 and RMSE= 6.12 using LASSO regression. The selected variables included treatment, IDDD Baseline score, ROCF (3 min recall and 30 min recall) and VOSP (object decision). For the active TMS group, the model showed R^2=0.156 with an RMSE of 7.20. Regarding the TMS sham group, R^2 was 0 and RMSE was 6.62.

The Elastic Net model provided an R^2 of 0.58 and an RMSE of 5.35 for the entire cohort. The variables included in the model were: treatment, IDDD Baseline score, Corsi span forward and backwards, ROCF (3 min recall, 30 min recall and recognition), VOSP (object decision), sentences comprehension (non-reversible distractors) and repetition of non-words. Performance of the model developed for the active group showed R^2=0.16 and RMSE=7.3. Conversely, for the sham group, the R^2 was 0.

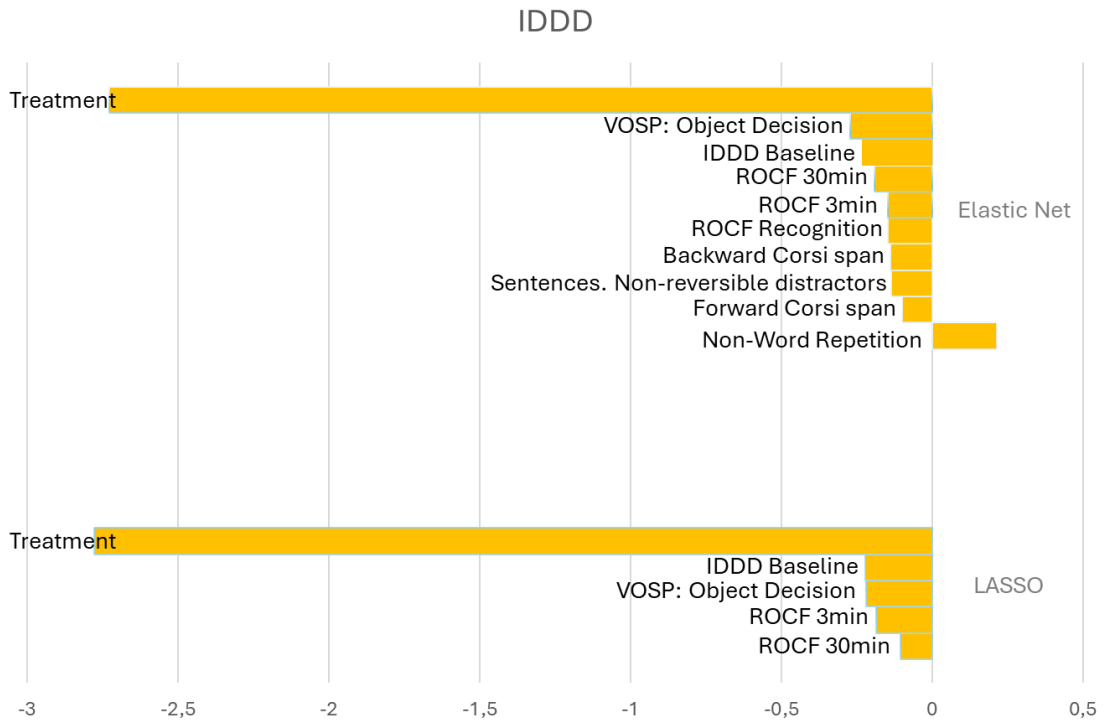

Figure 20. Predictors of Change in IDDD.

Predictors of clinical change in PPA according to LASSO and Elastic Net regression models. Bar plots represent standardized coefficients (absolute value > 0.1) from the best-performing models ($R^2 \geq 0.30$). *Abbreviations*: IDDD = Interview for Deterioration in Daily Living in Dementia.

4.5.2.5. Prediction of NPI change

The LASSO regression model yielded an R^2 of 0.807 and an RMSE of 3.47 in the whole cohort. The selected variables included treatment, PPA variant, NPI total score, VOSP (position discrimination), sentences comprehension (subject-focused sentence and non-reversible distractors), repetition of syllable pairs and words, and brain metabolism in the right caudate nucleus, right inferior temporal gyrus and left superior temporal gyrus. For the active TMS group, the model showed R^2=0.865 with an RMSE of 3.09, and selected the variables NPI total score, picture-word matching, sentences comprehension (subject-focused sentence), repetition of syllable pairs, and brain metabolism in the right caudate nucleus, right fusiform gyrus and left superior temporal gyrus. Regarding the TMS sham group, R^2 was 0.068 and RMSE was 5.04.

Using Elastic Net regularization, the R^2 for the total cohort was 0.769 with an RMSE of 3.79. The selected variables included treatment, PPA variant, NPI total score, VOSP (position discrimination), sentences comprehension (subject-focused sentence and non-reversible distractors), repetition of syllable pairs and words, and brain metabolism in the right caudate nucleus and left superior temporal gyrus. For the active group, the model showed R^2=0.96 with an RMSE of 1.46. For the sham group, R^2 was 0.94 and RMSE was 1.174.

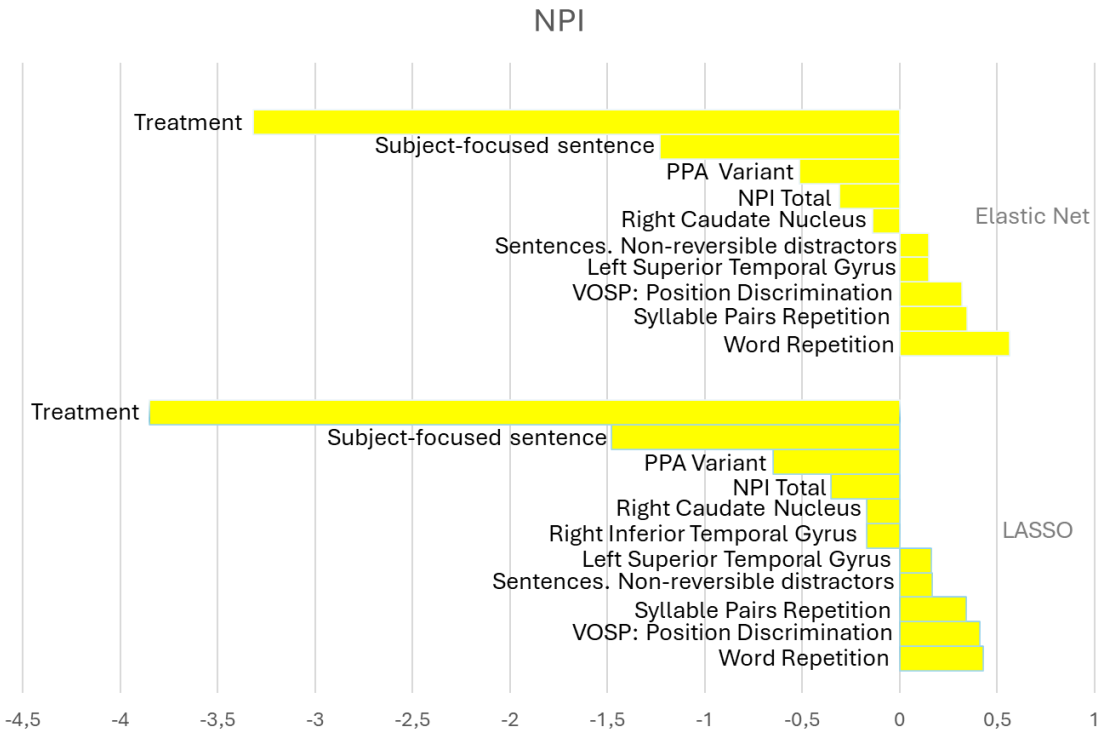

Figure 21. Predictors of Change in NPI.

Predictors of clinical change in PPA according to LASSO and Elastic Net regression models. Bar plots represent standardized coefficients (absolute value > 0.1) from the best-performing models ($R^2 \geq 0.30$). *Abbreviations*: NPI = Neuropsychiatric Inventory.

The R^2 values for the whole cohort in each outcome, for both the LASSO and Elastic Net models, are shown in Figure 22.

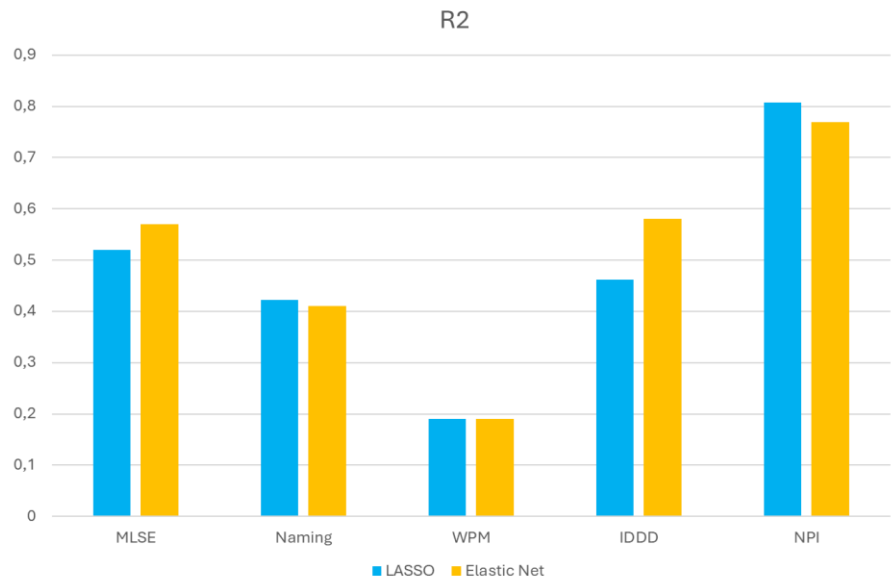

Figure 22. R^2 Values for LASSO and Elastic Net Models across all Outcomes in the Whole Cohort.

4.5.3 K-means clustering

The optimal clustering solution was k = 2, yielding two distinct groups: a non-responder group (cluster 1, n = 23) and a responder group (cluster 2, n = 34). A significantly higher proportion of patients who received active TMS were classified into the responder group (cluster 2: 31/40, 77.5%; cluster 1: 9/40, 22.5%), while the majority of patients who received sham TMS were part of the non-responder group (cluster 1: 14/17, 82.4%; cluster 2: 3/17, 17.6%) ($\chi^2 = 17.75$, $p < 0.001$) (Figure 23). No significant differences were observed in the distribution of PPA variants across clusters ($\chi^2 = 2.50$, $p = 0.284$).

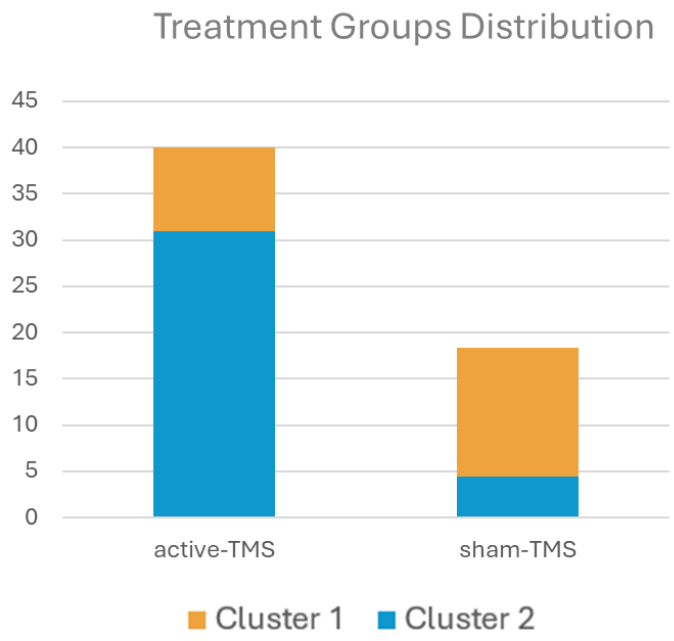

Figure 23. Treatment Group Distribution.

Proportion of participants classified as responders (Cluster 2) or non-responders (Cluster 1) within the active and sham TMS groups.

We then examined the clinical and demographic characteristics of patients who received active TMS, stratified by their membership in cluster 1 (non-responders) or cluster 2 (responders). There were differences in the distribution of PPA variants between clusters within the active group ($\chi^2 = 6.35$, $p = 0.042$). Specifically, cluster 1 included 2 patients with nfv-PPA,

0 with sv-PPA, and 7 with lv-PPA, whereas cluster 2 comprised 14 patients with nfv-PPA, 7 with sv-PPA, and 10 with lv-PPA (Figure 24).

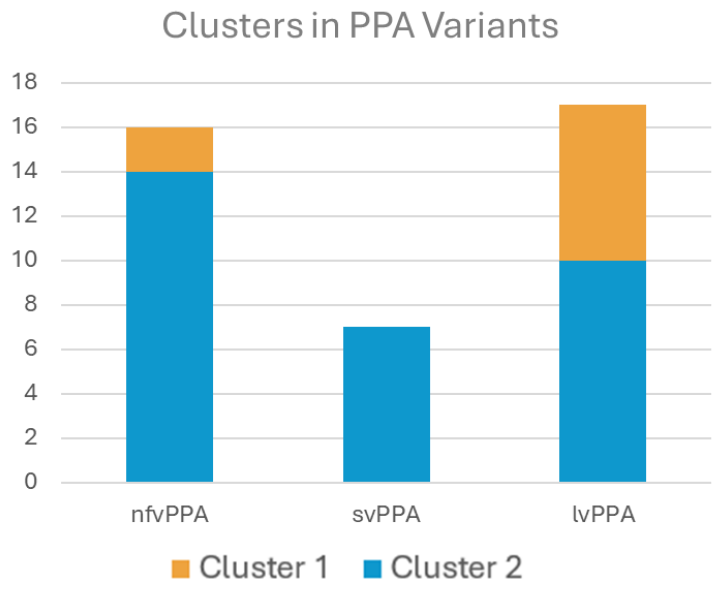

Figure 24. Distribution of PPA Variants by Cluster.

Abbreviations: *PPA* = Primary Progressive Aphasia; *nfv* = non-fluent variant; *sv* = semantic variant; *lv* = logopenic variant.

At baseline, patients in cluster 1 showed lower scores in the ACE-III memory domain, ACE-III visuospatial domain, and the ROCF delayed recall (3-minute) task (Figure 24).

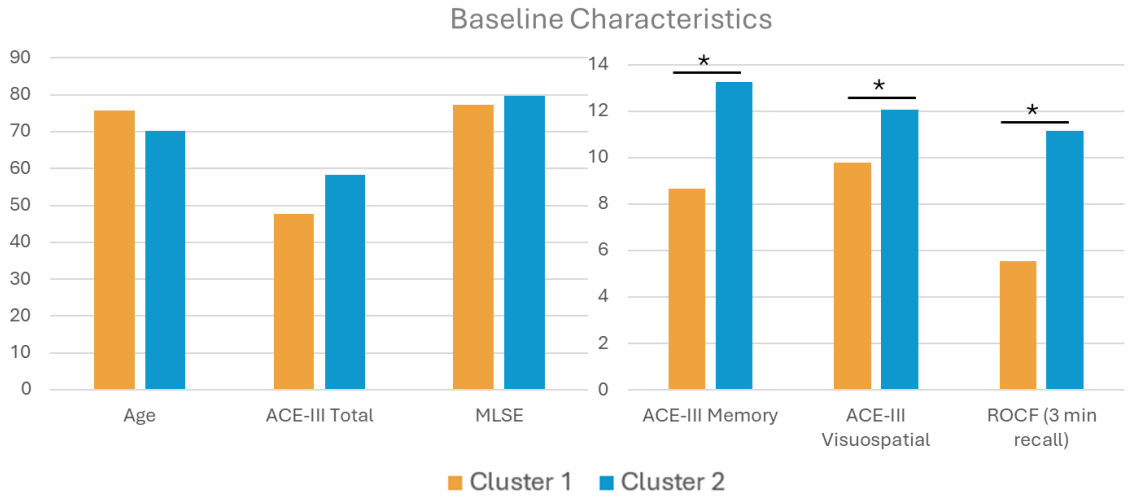

Figure 25. Characteristics of the Active TMS Group by Clusters.

Significant differences are marked with * ($p < 0.05$). Abbreviations: *ACE-III* = Addenbrooke's Cognitive Examination III; *MLSE* = Mini Linguistic State Examination; *ROCF* = Rey–Osterrieth Complex Figure.

Figure 26 displays the six-month change in clinical and functional outcomes, comparing the responder and non-responder clusters within the sample.

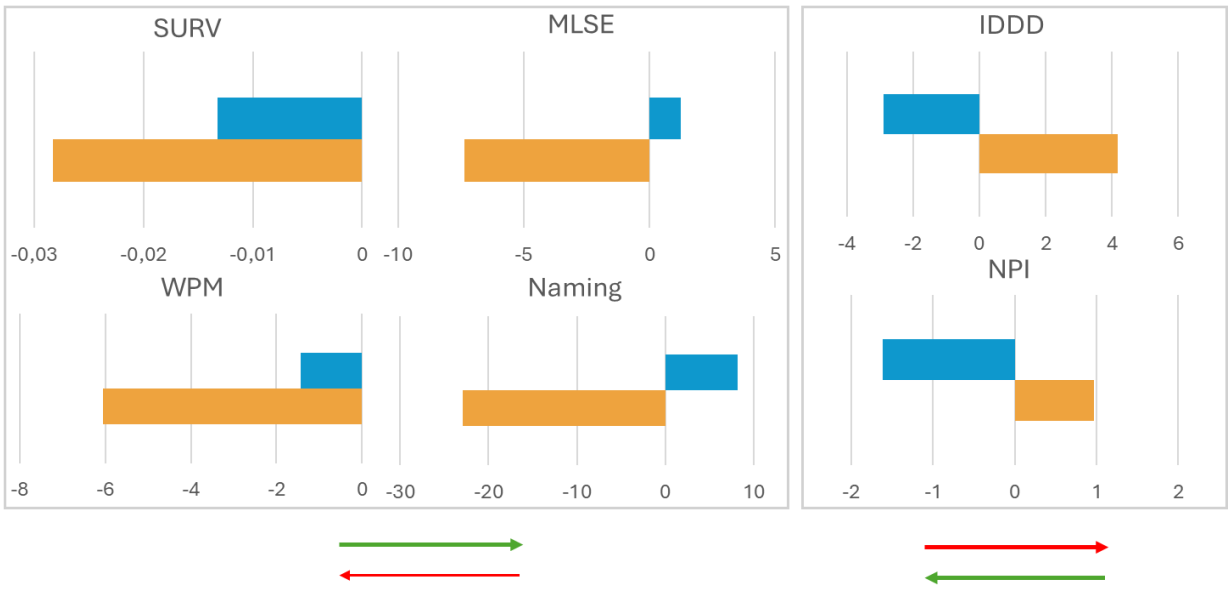

Figure 26. Change from Baseline to 6 Months in Outcome Measures.

Abbreviations: *TMS* = transcranial magnetic stimulation; *SUVR* = standardised uptake value ratio; *MLSE* = Mini Linguistic State Examination; *WPM* = words per minute; *IDDD* = Interview for Deterioration in Daily Living Activities in Dementia; *NPI* = Neuropsychiatric Inventory.

There were no other significant differences in demographic, cognitive or language characteristics (They are included in the Appendix Table A1). Cluster 1 showed lower metabolism in the left angular and supramarginal gyri, bilateral Heschl's gyri, left hippocampus, left inferior parietal lobule, and left inferior and middle temporal gyri, as well as higher cerebellar and right supplementary motor area metabolism compared to Cluster 2 (Figure 27).

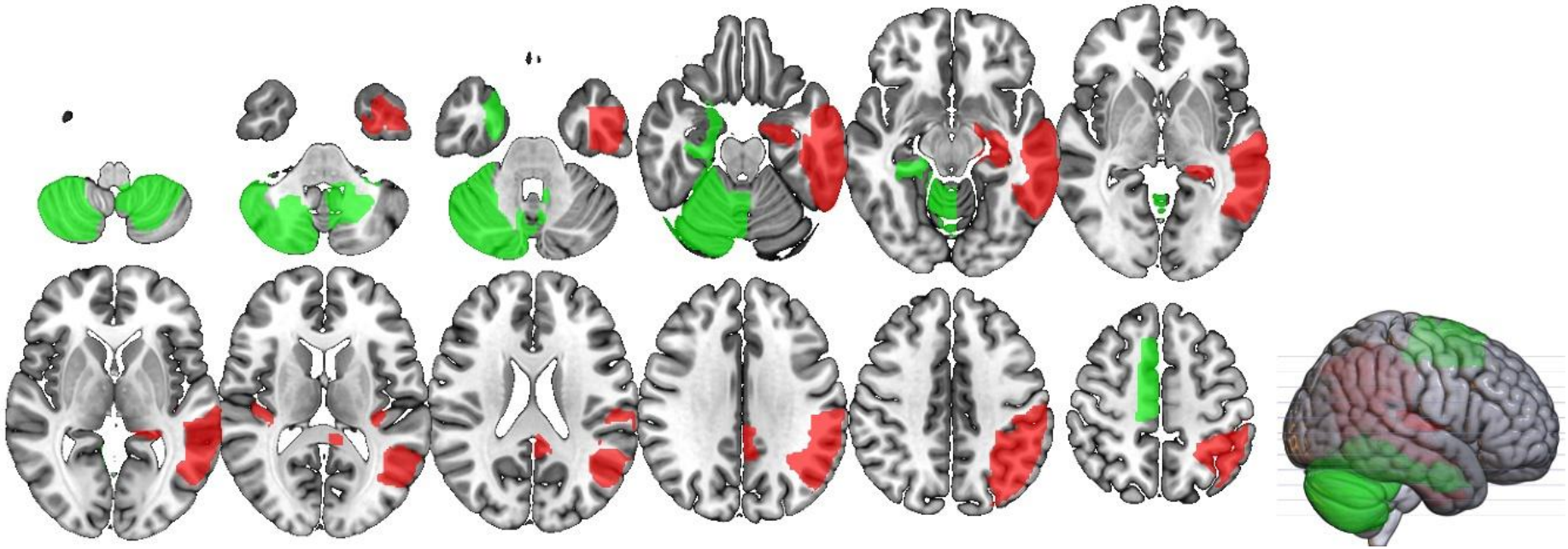

Figure 27. Brain Regions Associated with Clinical Response

Areas in green indicate regions where higher brain metabolism was associated with poorer treatment response. Areas in red indicate regions where lower baseline metabolism was associated with poorer treatment response.

5. DISCUSSION

PPA is a neurodegenerative condition that represents a leading cause of early-onset dementia. PPA initially manifests as a progressive deterioration of language, directly interfering with everyday communication, functional independence, and social participation. The gradual loss of language abilities severely limits personal and professional interactions and profoundly impacts patients' overall quality of life. Despite the considerable individual and societal burden associated with PPA, there are currently no approved treatments capable of halting or reversing its progression. As such, there is an urgent need to develop and evaluate therapeutic interventions that may help preserve linguistic function and delay further decline.

This randomized clinical trial examined the long-term effects of TMS applied to the left DLPFC over a six-month period, combined with a structured language intervention, in individuals with PPA. To our knowledge, this is the largest clinical trial in the field of PPA, and one of the first trials analysing the long-term effect of NIBS in neurodegenerative disorders. It is also the first study combining TMS and language therapy in PPA. The results suggest that TMS contributed to a reduction or mitigation of the expected decline in regional brain metabolism, as well as to improvements in trained language abilities, functional independence, and neuropsychiatric symptoms. These findings are particularly relevant in a population characterized by relentless neurodegenerative progression and limited therapeutic options.

5.1. Justification of stimulation protocol

The selection of the stimulation site and protocol was guided by prior findings supporting their clinical relevance and practicality. In a recent study by Moral-Rubio et al. (2025), different TMS protocols were tested in a preliminary phase, including both excitatory and inhibitory stimulation across multiple cortical targets. Excitatory protocols were associated with more favourable outcomes, and the most responsive regions were the left inferior frontal

gyrus and the left DLPFC (Pytel, 2021). This region, while not directly part of the core language network, is crucially involved in attention and executive functions such as planning, organization, working memory, and inhibitory control (Parris et al., 2021; Ware et al., 2021). Enhancing the neural circuits underlying these cognitive domains may help explain the beneficial impact observed on language performance. Moreover, stimulation of the left DLPFC has been associated with modulation of reward- and emotion-related dopamine and serotonin circuits (Sibon et al., 2007; Tik et al., 2017), which are known to be impaired in patients with nonfluent and semantic PPA (Premi et al., 2023). These mechanisms may contribute to improved engagement and motivation during therapy, amplifying the effects of language interventions. In a study by Klaus et al. (2018), the involvement of the left dorsolateral prefrontal cortex (DLPFC) in language processing was examined. The authors found that this region contributes to both language comprehension and production, as well as to broader cognitive functions, particularly working memory and motivational control. Importantly, modulating the activity of the left DLPFC can produce complex and non-linear effects, depending on the specific demands of the task and individual variability. Based on these results, the left DLPFC was selected as the optimal stimulation site. The stimulation target was applied uniformly across all participants, an approach that ensured methodological consistency and facilitated reliable comparisons across individuals.

We employed iTBS, a protocol shown to be as effective and safe as standard repetitive TMS, but considerably more efficient in terms of session duration (Ramos et al., 2025). This choice was further supported by a pivotal randomized clinical trial demonstrating the clinical equivalence of 3-minute intermittent TBS (iTBS) and 37.5-minute 10-Hz rTMS in improving depressive symptoms (Blumberger et al., 2018). Each iTBS session lasted only three minutes, which was particularly advantageous given the combination with 50-minute language therapy

sessions. This approach prioritised feasibility and participant comfort, enabling consistent delivery of the intervention throughout the six-month treatment period.

The selection of a lexical retrieval therapy (LRT) was primarily guided by the clinical presentation of the participants, whose main complaint was word-finding difficulty. All participants exhibited deficits in confrontation naming, as confirmed by baseline assessments, supporting the choice of an intervention targeting lexical access. LRT is one of the most empirically validated treatments for individuals with PPA, particularly effective in the semantic and logopenic variants (Henry et al., 2013; Henry et al., 2019; Grasso et al., 2021). In this study, the intervention followed a structured stepwise approach, modified to include semantic feature analysis to strengthen conceptual activation and promote spontaneous production. Crucially, each training item concluded with a sentence-generation task, allowing individuals with nfv-PPA to benefit not only from lexical support but also from syntactic practice. This integration of semantic, phonological, and orthographic processing, along with the use of self-cueing strategies, aligns with current evidence on maximising therapy outcomes in PPA and provided a strong foundation for pairing with neuromodulation.

5.2. Effects on brain metabolism

One of the most notable findings of this study was the relative preservation of brain metabolism in the left hemisphere following six months of active TMS combined with language therapy. This suggests that excitatory neuromodulation over the DLPFC may support synaptic activity and delay the typical hypometabolic progression observed in PPA. This could be interpreted as a direct stimulation of TMS, neuroplasticity or neuroprotection effects of TMS. FDG-PET, used here as the primary outcome measure, is widely recognised as a reliable indicator of synaptic function and neuronal integrity, given its close association with cognitive performance and clinical stage in neurodegenerative conditions (Staffaroni et al. 2019; Boxer

et al. 2020; Panza et al. 2020). Numerous studies have demonstrated that incorporating FDG-PET into the diagnostic process significantly improves sensitivity for detecting neurodegenerative diseases. For instance, a review by Silverman (2004) reported that the diagnostic sensitivity for pathologically confirmed Alzheimer's disease increased to approximately 91.5% when FDG-PET was included, compared to just 66% when based solely on clinical criteria. In addition to improving diagnostic accuracy, FDG-PET also appears useful for early detection and for identifying individuals with mild cognitive impairment who are at higher risk of progressing to dementia (Prestia et al., 2013).

FDG acts as a glucose analogue, becoming trapped within cells in proportion to their metabolic activity. The brain, even at rest, consumes a large part of the body's energy primarily due to the energy demands of synaptic activity, especially in the postsynaptic terminals (Attwell & Iadecola, 2002). Because neurons depend almost entirely on a continuous supply of glucose and oxygen (due to minimal glycogen or oxygen reserves), FDG uptake is a sensitive proxy for neuronal activity and synaptic function. Most of this activity is localised in the grey matter, making FDG-PET particularly valuable for visualising synaptic dysfunction. Consequently, hypometabolism observed in FDG-PET is considered a hallmark of neurodegeneration, with strong implications for the diagnosis and monitoring of dementia and related conditions (Silverman, 2009).

Our results align with existing evidence showing that non-invasive brain stimulation can modulate functional networks at the cortical level. For example, Pytel et al. (2021) reported increased FDG uptake following 15 sessions of rTMS in regions such as the left frontal and parieto-temporal lobes, as well as the precuneus and posterior cingulate cortex. Similarly, in our study, the active intervention appeared to enhance metabolic activity in targeted areas, supporting the hypothesis that neuromodulation can lead to functional reorganisation and increased excitability in language-related networks.

A recent review further supports these interpretations by outlining the multiple neurobiological pathways through which rTMS exerts therapeutic effects (Antonioni et al., 2025). According to this synthesis of animal and human data, rTMS enhances synaptic function by upregulating structural proteins, promoting glutamate reuptake, inhibiting microglial activation, and increasing neurotransmitter synthesis. It also modulates neurotrophic signalling, particularly brain-derived neurotrophic factor and nerve growth factor pathways and contributes to reduced amyloid production and improved clearance of toxic aggregates. These changes are thought to underlie observed behavioral improvements and restored long-term potentiation–like mechanisms. Importantly, in patients, these cellular and molecular effects translate into increased cortical plasticity, strengthened functional and structural connectivity, and preservation of grey matter integrity. Together, these findings provide a compelling mechanistic framework supporting the use of rTMS as a disease-modifying intervention, although these mechanisms, in part hypothetical based on animal models, should be confirmed in patients with neurodegenerative disorders. In this regard, our findings on FDG-PET could suggest a neuroprotective effect, or the induction of neuroplasticity, and future studies should evaluate the pathophysiological mechanisms underlying this positive effect.

Importantly, these effects were achieved through a protocol of just one TMS session per week, highlighting its potential as a long-term maintenance strategy.

Taken together, these findings suggest that TMS may promote measurable neurobiological changes in PPA by stabilising or enhancing metabolic activity in affected cortical areas. This represents a promising mechanism of action, particularly in the context of neurodegenerative diseases where synaptic dysfunction is an early and critical contributor to cognitive decline.

5.3. Effects on language outcomes

The findings of this study suggest that TMS combined with language therapy enhances linguistic outcomes in individuals with PPA. Participants who received active stimulation showed significantly greater improvement in a structured language assessment, the MLSE (Patel et al., 2021; Matias-Guiu et al., 2021). The MLSE is a validated tool specifically designed to evaluate all core domains of language—such as motor speech, phonology, semantics, syntax, and working memory—making it a particularly robust and comprehensive instrument for capturing changes in linguistic performance across PPA subtypes. Notably, as it was specifically developed for use in PPA, the MLSE is well-balanced to detect deficits present across all three main variants. This is the first clinical trial to use the MLSE as a primary endpoint, demonstrating its potential as a valuable tool for future clinical trials in the PPA field. Its sensitivity to deficits in different language networks reinforces the clinical relevance of the improvements observed in the active TMS group.

Another finding of the study was the enhanced performance in naming trained items among participants receiving active TMS, relative to those in the sham group, whose naming ability remained stable. Given that language deterioration in PPA is progressive, this relative improvement is noteworthy and suggests that TMS may have an augmentative effect when paired with a language intervention specifically designed to target semantic, phonological, and orthographic components of language processing. The structured therapy employed in this study, which emphasized evidence-based self-cueing strategies, likely synergized with TMS-induced cortical plasticity to potentiate language outcomes.

Despite these positive results in naming performance, the study did not identify statistically significant differences between groups in the measure of words per minute in connected speech. This finding may reflect the inherent variability of this measure, both within and across participants, and highlights the limitations of WPM as a sensitive endpoint in this

population. Future studies should consider incorporating more refined analyses of discourse-level variables (e.g., syntactic complexity, informativeness, or pragmatic coherence) or include tasks more directly reflective of communicative functioning (Volkmer et al., 2025).

These results are broadly consistent with previous findings on non-invasive brain stimulation in PPA. Initial studies demonstrated that both tDCS and TMS can enhance naming and general language performance, particularly in the nonfluent and semantic variants (Cotelli et al., 2014; Pytel et al., 2021; Teichmann et al., 2016). More recently, larger controlled trials of tDCS combined with language therapy reported significant improvements in trained and untrained items, especially in the nonfluent and logopenic variants (Tsapkini et al., 2018; Zhao et al., 2021; Wang et al., 2022), while rTMS applied to the DLPFC was shown to improve language outcomes across all three variants and sustain benefits for up to six months (Huang et al., 2023). The current findings extend this evidence by demonstrating that active TMS combined with structured language therapy also produces significant benefits when measured with the MLSE, a standardized PPA-specific tool. Taken together, these converging results highlight that NiBS, whether tDCS or TMS, can potentiate language therapy in PPA, although heterogeneity in protocols and outcomes underscores the need for further research to clarify moderators of treatment response.

5.4. Effects on functional independence and neuropsychiatric symptoms.

Another important finding of this study was the observed improvement in functional abilities and neuropsychiatric symptoms among participants in the active-TMS group. Specifically, scores on the IDDD and the NPI revealed a maintenance or enhancement of daily functioning and a reduction in behavioral disturbances compared to the sham group. These effects suggest that the benefits of TMS combined with language therapy may extend beyond

language-specific gains, influencing participants' independence in daily living activities and neuropsychiatric symptoms (Murphy et al., 2023). This aligns with the results reported by Benussi et al. (2020), who found that 2 weeks of tDCS was associated with increased intracortical connectivity and improvements in both clinical scores and behavioral disturbances in patients with behavioral variant frontotemporal dementia.

In addition to the overall IDDD score, a focused analysis was conducted on the six language-related items within the scale to further explore the intervention's impact on functional language abilities in everyday contexts. Notably, participants in the active group showed significant improvements in items corresponding to reading comprehension, written expression, and comprehension of spoken language. These results support the hypothesis that combining TMS with language therapy contributes to the preservation and enhancement of functional communication in individuals with PPA. Similar findings were reported by Huang et al. (2023), who used the Communicative Activity Log (CAL)—a questionnaire designed to assess daily communication in people with aphasia—and observed improvements in language function after four weeks of rTMS. This convergence of evidence reinforces the notion that neuromodulation can positively influence real-life communicative abilities in this population.

5.5. Clinical Meaningfulness

Although there is currently no established threshold for defining clinically meaningful change in PPA, the effect sizes observed in our study suggest that the intervention produced relevant and tangible benefits. In particular, we found moderate to large effect sizes across several outcome domains directly linked to patients' daily functioning. For example, language competence showed robust improvements, with large effects on both the MLSE and confrontation naming tasks. Functional outcomes such as daily living activities (IDDD) and neuropsychiatric symptoms (NPI) also demonstrated moderate effect sizes, indicating that the

intervention may help preserve autonomy and reduce behavioral disturbances. Even in the primary outcome (FDG-PET), the effect size was in the moderate range, suggesting a measurable impact on cortical metabolic decline. Although the effect on speech rate was small and not significant, the consistent pattern across other measures supports the interpretation that the benefits observed are not only statistically significant but also clinically relevant for individuals with PPA.

5.6. Feasibility of the intervention

One of the most encouraging aspects of the present study is the high feasibility and tolerability of the proposed intervention, which combined once-weekly sessions of TMS with structured language therapy over a 6-month period. Adherence to the treatment protocol was notably high across both intervention groups, with an adherence rate of 92.06% indicating that most participants attending all scheduled sessions. This consistent participation underscores the practicality of implementing a stimulation protocol, which is less demanding than more intensive regimens and can be realistically integrated into the routines of patients.

Among the few participants who did not complete all sessions, the reasons for non-adherence were unrelated to the intervention itself. In one case, the participant required assistance to attend hospital sessions but was unable to secure a companion for several sessions; in another, the participant opted to discontinue visits due to mobility limitations. Importantly, even in these cases, participants completed at least half—or nearly all—of the planned sessions, further supporting the feasibility of the protocol in real-world conditions. The structure of the intervention, requiring only one visit per week, may have contributed substantially to this favourable adherence profile.

From a safety standpoint, the treatment proved to be well tolerated. No serious adverse events were reported in relation to the TMS procedure. The few adverse events that were

documented were either unrelated to the stimulation (e.g., unrelated medical diagnoses) or were mild. For instance, in cases where participants reported discomfort during the TMS application, the stimulation intensity was adjusted accordingly—from 50% to 40% —allowing for continued participation without compromising treatment. This adjustability highlights the adaptability of the protocol to individual tolerability while maintaining therapeutic continuity.

Taken together, these findings underscore the safety and feasibility of implementing a once-weekly TMS protocol in individuals with PPA over an extended period. The high adherence, minimal adverse effects, and participant retention suggest that this combined neuromodulation and language therapy approach is not only effective but also practical and acceptable for both patients and clinicians in routine clinical settings.

The neuromodulation technique has already been demonstrated as feasible in several studies in PPA and other neurodegenerative conditions (Benussi et al., 2020; Borrego-Écija et al., 2023; Koch et al., 2022). These studies have also reported good tolerability, which aligns with our findings. No serious adverse events were observed, and only mild, transient discomfort in the stimulated area was reported, with most participants completing the planned sessions. This consistency with our results further supports that neuromodulation is a safe and feasible technique in this condition.

5.7. Predictors of change

Regarding this analysis, we evaluated the ability of various demographic, clinical, and FDG-PET imaging measures to predict clinical change at 6 months in patients with PPA. The models for MLSE, Naming, IDDD, and NPI showed moderate to good fit according to R^2, and good to excellent precision following RSME.

One of the most striking findings of this analysis is the identification of the different variables more predictive of clinical change. Our results suggest that response to language

therapy in PPA is not uniform and is influenced by a combination of clinical, cognitive, and neurobiological factors. The fact that TMS treatment emerged as the strongest predictor in all the variables (MLSE, Naming, IDDD, NPI) underscores its potential as a therapeutic intervention in PPA, supporting the value of this technique to maximize language training and with language, functional, and neuropsychiatric effects. It is also noteworthy that the PPA variant was only predictive of change in the neuropsychiatric scale. On the one hand, this aligns with previous findings, as certain PPA subtypes (particularly the non-fluent and semantic variants) are known to exhibit more prominent behavioral and emotional changes over time (Foxe et al., 2022). On the other hand, the lack of predictive value of the PPA variant for the other outcome measures may reflect the broader and more balanced nature of these instruments, which assess changes across several language domains (e.g. MLSE) or functions affected in the three variants (naming, functional impairment) (Patel et al., 2021; Breining et al., 2023; Foxe et al., 2024).

Furthermore, we found that baseline cognitive performance was a significant predictor, probably allowing patients to better engage with language therapy. In this regard, higher performance in some attention and working memory tasks were predictive of improvement in MLSE, and a lower performance in episodic memory, attention, and visuospatial tests were related to increase in functional impairment over time. It was unexpected that variables related to language performance were not included in the predictive models. This suggests that the severity of language impairment may not predict therapeutic success, indicating that the language therapy used in our study should not be withheld from patients with more severe language deficits. However, it is important to note that all patients included in the clinical trial were in relatively early stages of PPA and were able to engage in the therapy.

Regarding behavior, the models showed good predictive performance, once again highlighting the effect of TMS treatment, which supports the use of this intervention in

symptoms such as apathy (Murphy et al., 2023). Additionally, associations were observed with various cognitive functions (both linguistic and non-linguistic) as well as with cortical and subcortical regions, consistent with the widespread structural and functional bases of neuropsychiatric disorders (Quang et al., 2021).

Unfortunately, the model for WPM change showed a poor performance. This is consistent with the high variability of this measure detected in the clinical trial, which suggests the need to examine other measures to reliably capture spontaneous speech in patients with PPA (Matias-Guiu et al., 2022). The lack of correlation with the other language outcomes also confirms that other variables to evaluate connected speech should be preferable in future studies.

On the unsupervised clustering analysis, two subgroups of patients were identified according to the changes at 6-months in language, functional, and behavioral outcomes. A large proportion of patients receiving active TMS were classified as responders, whereas most of the patients in the sham group were considered as non-responders. Interestingly, all patients with sv-PPA and 87.5% of the nfv-PPA were classified as responders. However, in the lv-PPA, the percentage of responders was 58.8%, and lower scores in non-language domains (memory and visuospatial) were associated with a suboptimal response. This could be interpreted considering the possibility that broader cognitive deficits beyond language, such as impairments in working memory, attention, and executive functions (de la Sablonnière et al., 2021), may limit the effectiveness of combined TMS and language therapy, as has been suggested for spelling therapy during transcranial direct current stimulation (de Aguiar et al., 2020). Alternatively, in cases with more pronounced memory impairments, other TMS targets (e.g. precuneus) could be more appropriate instead of DLPFC, as proposed in amnestic AD (Koch et al., 2022). In this regard, the analysis to select the optimal brain target after single-session stimulation was performed by our group in nfv-PPA and sv-PPA (Moral-Rubio et al., 2025), but not in lv-PPA.

Our analysis also identified several brain regions that were predictive of clinical change. Notably, areas such as the left hippocampus and the left posterior cingulate were associated with language improvement. In general, higher metabolism in these regions predicted more favourable clinical outcomes, suggesting that the integrity of certain key brain areas may be important for therapeutic success. Interestingly, the regions identified were not those typically most affected in PPA. In this regard, we also included a region of interest encompassing all areas commonly impaired in PPA (i.e., the same variable used as the endpoint in the clinical variant analysis), but this composite region did not predict clinical change. Overall, these findings suggest that the severity of language dysfunction or damage to core language regions may not be the primary driver of clinical change. Instead, clinical change may be more strongly related to the degree of preservation or impairment in brain areas supporting non-language functions. However, given the topographical heterogeneity across PPA variants, future studies focusing on variant-specific predictive patterns are necessary.

Interestingly, cerebellar hypermetabolism was associated with non-responders. This may reflect a compensatory mechanism in response to cortical dysfunction which, instead of supporting recovery, could be maladaptive. Notably, the cerebellum is functionally integrated, maintaining widespread connections with the cerebral cortex, including neocortical regions involved in higher-order cognitive processes (Yao et al., 2022). Cerebellar hyperactivity may interfere with synaptic plasticity and disrupt the functional balance of cerebro-cerebellar circuits, thereby limiting the efficacy of TMS and language therapy. Recent evidence has highlighted its role in the pathophysiology of neurodegenerative diseases such as frontotemporal dementia, PPA, and AD (Yao et al., 2022; Coemans et al., 2024; Antonioni et al., 2025). In this regard, some authors have proposed cerebellum as a potential target for brain stimulation in PPA (Runnqvist et al., 2016; Coemans et al., 2024).

5.8. Limitations

This study has some limitations that should be acknowledged.

First, although active and sham groups were well balanced in the main demographic and clinical characteristics, there was some baseline imbalances in two specific variables (a higher proportion of women and elevated baseline SUVR values in the active group). For this reason, these variables were introduced as covariates in all the statistical analysis to limit their influence. Additionally, SUVR in the language region was not a significant predictor of change at 6 months in the entire cohort. Second, the single-center design and predominantly Spanish-speaking cohort, while addressing a gap in underrepresented linguistic groups in clinical research, limit the generalizability of findings to more diverse populations. Third, another methodological limitation concerns the selection of trained words for the naming task. Although items were individualized based on participant performance at baseline, participants did not select the words themselves. Incorporating personally relevant stimuli in future trials could increase ecological validity and possibly enhance engagement and motivation. Additionally, the positive effects observed in functional domains such as the IDDD were encouraging but should be complemented in future research with measures of communicative participation and caregiver burden to provide a more comprehensive evaluation of real-world impact. Forth, while FDG-PET results suggest a reduced decline in regional brain metabolism in the active TMS group, the clinical significance of these metabolic changes remains to be established. Longitudinal studies with neuropsychological follow-up beyond six months, as well as exploration of biomarkers of disease progression, will be crucial to determine the durability and depth of the observed effects. Fifth, an additional limitation of the present study is that we do not know whether the gains observed with the combined TMS and language therapy protocol would be maintained after the end of the intervention. Given that PPA is a progressive neurodegenerative condition, it is particularly relevant to assess whether

improvements in language, functional outcomes, and neuropsychiatric symptoms are sustained over time. Future studies should incorporate follow-up assessments to evaluate the long-term stability of TMS-induced changes and to determine the durability of combined neuromodulation and language therapy interventions in this population. Lastly, for the analysis of prediction of change, we used several machine learning algorithms. We performed LASSO regression, which produces simpler, more interpretable results because of the variable selection procedure. LASSO is especially useful in datasets with many variables compared to the sample size ($p>n$), because it performs automatic variable selection and minimizes the risk of overfitting. In addition, the use of cross-validation to determine the optimal lambda adds robustness to the model selection process. Feature selection in LASSO may be limited if there are several correlated predictors. For this reason, we also implemented Elastic Net, which in general confirmed the robustness of the models and the predictors identified with LASSO. While the results are consistent, further studies are needed to validate these predictors in independent samples. Due to the limited sample size, we did not include treatment as an interaction term in the regression model to evaluate specific predictors of response to TMS, as this could compromise model performance by increasing the risk of overfitting and reducing generalizability. Instead, we applied unsupervised clustering, which identified two subgroups based on clinical change. This approach allowed us to explore factors associated with response to TMS. Because the analysis characterizing the clusters was exploratory, we did not correct for multiple comparisons.

5.9. Future Perspectives

This study represents an important step in the treatment of PPA and in the use of non-invasive brain stimulation for long periods in neurodegenerative diseases, paving the way for future studies. In this regard, the positive findings and the identification of different predictors

suggest to continue studying more personalized and optimized interventions. Given the distinct neuroanatomical patterns across PPA variants, tailoring the stimulation target to individual atrophy profiles could help determine whether personalised targeting improves clinical outcomes. Similarly, language therapy protocols could also benefit from greater individualisation, for instance by allowing patients to select vocabulary and communicative contexts that are personally meaningful, in order to enhance engagement and generalisation to daily life.

Regarding the neuromodulation, despite the feasibility and high adherence to TMS, the practical application and generalization of TMS for PPA patients remains uncertain. In this sense, tDCS could be an alternative, but no studies using tDCS for several months have been conducted up to date. Similarly, the analysis of the effects of TMS therapy beyond 6 months should also be examined in future studies.

Finally, incorporating more specific outcome measures of real-life communicative functioning would allow for a more accurate capture of meaningful changes in patients' quality of life and social participation. These directions could guide the development of more effective and patient-centred interventions for PPA (Volkmer et al., 2025).

6. CONCLUSIONS

In accordance with the stated objectives, and based on the results obtained, the following general conclusions can be drawn:

Main Conclusion:

1) The intervention combining active TMS and language therapy was associated with significantly less metabolic decline in the left hemisphere compared to the sham group, as measured by FDG-PET at six months.

Secondary Conclusions:

1) The combination of active TMS and language therapy over six months showed greater improvement in naming trained items than in the sham group.

2) The combination of active TMS and language therapy over six months led to greater improvement in MLSE performance compared to the sham group.

3) The combination of active TMS and language therapy over six months did not result in significant differences between groups in the number of words per minute produced during spontaneous speech task.

4) The combination of active TMS and language therapy over six months resulted in improvement in functional abilities, as measured by the IDDD.

5) The combination of active TMS and language therapy over six months was associated with improvement in neuropsychiatric symptoms compared to the sham group.

Exploratory Conclusions

1) TMS therapy, better cognitive performance and more preserved brain metabolism in several key regions are associated with a more favourable clinical trajectory at 6-months in patients with PPA receiving language therapy

2) Non-fluent and semantic variants, more preserved memory and visuospatial function, and brain metabolism in different brain regions were predictive of clinical response to TMS.

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7. APPENDIX

CONSENTIMIENTO INFORMADO POR ESCRITO

TITULO DEL ESTUDIO:

"ENSAYO CLÍNICO RANDOMIZADO Y DOBLE CIEGO DE ESTIMULACIÓN MAGNÉTICA TRANSCRANEAL A LARGO PLAZO EN LA AFASIA PROGRESIVA PRIMARIA (RECONNECT -PPA)".

Yo, _____

He leído la hoja de información que se me ha entregado He podido hacer preguntas sobre el estudio He recibido suficiente información sobre el estudio.

He hablado con:._____

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

- cuando quiera
- sin tener que dar explicaciones
- sin que esto repercuta en mis cuidados médicos. Presto

libremente mi conformidad para participar en el estudio. Doy mi consentimiento para que los datos obtenidos en este estudio puedan ser utilizados en este o futuros estudios siempre que estén aprobados por el Comité Ético y se mantenga la protección de los datos necesaria para evitar la identificación personal.

Fecha:_____Firma:

Nombre y apellidos del participante:

Nota: "La fecha debe ser escrita por el propio paciente"

Nombre y firma del investigador que obtiene el consentimiento:

Registration of the naming list

	Inicial	Intermedia	Final
1. Gato			
2. Perro			
3. Vaca			
4. Cerdo			
5. Gallina			
6. Mono			
7. Cebra			
8. Pez			
9. Serpiente			
10. Cabra			
11. Elefante			
12. León			
13. Tortuga			
14. Tigre			
15. Gusano/Lombriz			
16. Delfín			
17. Caracol			
18. Loro			
19. Zorro			
20. Burro			
21. Caballo			
22. Águila			
23. Hipopótamo			
24. Pingüino			
25. Pato			
26. Cocodrilo			
27. Rata/Ratón			
28. Mariposa			
29. Búho			
30. Abeja			
31. Ardilla			
32. Jirafa			
33. Oso			
34. Foca			
35. Tiburón			
36. Rinoceronte			
37. Oveja			
38. Camello			
39. Rana			
40. Avión			

41. Coche			
42. Bici			
43. Moto			
44. Taxi			
45. Helicóptero			
46. Tren			
47. Barco			
48. Patinete			
49. Camión			
50. Autobús			
51. Caravana			
52. Furgón/Furgoneta			
53. Barco velero			
54. Brócoli			
55. Mora			
56. Tortilla			
57. Bellota			
58. Zumo			
59. Rábanos			
60. Infusión/ té			
61. Pera			
62. Limón			
63. Piña			
64. Sandía			
65. Melón			
66. Melocotón			
67. Almendras			
68. Zanahoria			
69. Lechuga			
70. Palomitas			
71. Aguacate			
72. Coco			
73. Chocolate			
74. Kiwi			
75. Sandwich			
76. Tomate			
77. Cereza			
78. Uvas			
79. Pepinillo			
80. Manzana			
81. Cebolla			
82. Sopa			
83. Berenjena			
84. Pimiento			
85. Esparrago			
86. Mandarina			

87. Fresa			
88. Alcachofa			
89. Calabacín			
90. Ciruela			
91. Pan			
92. Coliflor			
93. Café			
94. Agua			
95. Leche			
96. Vino			
97. Cerveza			
98. Huevo			
99. Queso			
100. Arroz			
101. Sal			
102. Pollo			
103. Ensalada			
104. Paella			
105. Langostinos			
106. Jamón			
107. Helado			
108. Pescado			
109. Chorizo			
110. Carne			
111. Espinacas			
112. Pizza			
113. Bocadillo			
114. Calamares			
115. Chuletas			
116. Espagueti			
117. Yogur			
118. Galleta			
119. Alubias			
120. Garbanzos			
121. Tarta			
122. Lentejas			
123. Ojo			
124. Nariz			
125. Boca/Dientes			
126. Oreja			
127. Brazo			
128. Mano			
129. Dedo			
130. Codo			
131. Hombros			
132. Espalda			

133. Cuello			
134. Pierna			
135. Rodilla			
136. Pies			
137. Uña			
138. Pelo			
139. Ceja			
140. Tobillo			
141. Tripa			
142. Cadera/Cintura			
143. Cabeza			
144. Vestido			
145. Camiseta			
146. Camisa			
147. Pantalones			
148. Calcetines			
149. Zapatos			
150. Falda			
151. Jersey			
152. Chaqueta			
153. Gorro			
154. Abrigo			
155. Chaleco			
156. Bufanda			
157. Bañador/calzoncillos			
158. Bañador			
159. Bolso			
160. Gafas			
161. Sombrero			
162. Gorra			
163. Collar			
164. Pulsera			
165. Anillo			
166. Pendientes			
167. Libro			
168. Teléfono			
169. Televisión			
170. Radio			
171. Botella			
172. Tenedor			
173. Vaso			
174. Copa			
175. Cuchillo			
176. Cuchara			
177. Plato			
178. Vela			

179. Llave			
180. Balón/Pelota			
181. Toalla			
182. Jabón			
183. Escoba / Cepillo			
184. Fregona			
185. Peine			
186. Bolígrafo			
187. Monedas			
188. Billetes			
189. Caja			
190. Plancha			
191. Calculadora			
192. Alicates			
193. Regla			
194. Hacha			
195. Enchufe			
196. Globo			
197. Cámara			
198. Tostadora			
199. Pala			
200. Cacerola/Olla			
201. Sartén			
202. Paraguas			
203. Silbato/Pito			
204. Sierra/ Serrucho			
205. Sacapuntas			
206. Cortauñas			
207. Martillo			
208. Tornillo			
209. Destornillador			
210. Clavo			
211. Tijeras			
212. Taladro			
213. Grapadora			
214. Linterna			
215. Sofá			
216. Sillón			
217. Silla			
218. Mesa			
219. Mesilla / Mesilla			
220. Puerta			
221. Ventana			
222. Escaleras			
223. Armario			
224. Microondas			

225. Estantería			
226. Lámpara			
227. Nevera / Frigorífico			
228. Cama			
229. Cojín			
230. Espejo			
231. Vitrocerámica			
232. Lavabo			
233. Horno			
234. Ducha			
235. Bañera			
236. Váter /Inodoro			
237. Cine			
238. Cocina			
239. Baño / Aseso			
240. Salón / Comedor			
241. Habitación			
242. Restaurante / Bar			
243. Pescadería			
244. Carnicería 245. Charcutería			
246. Papelería			
247. Librería			
248. Biblioteca			
249. Peluquería			
250. Panadería			
251. Farmacia			
252. Teatro			
253. Estanco			
254. Frutería			
255. Mar			
256. Cielo			
257. Playa			
258. Montaña			
259. Campo			
260. Parque			
261. Supermercado			

Table A1. Clinical and Demographic Characteristics of the Active TMS Group Across Clusters at Baseline.

	Cluster 1	Cluster 2	U	p
Sex (Female)	6 (66.7%)	30 (75%)	0.430	0.512
Age	75.77	70.29	85.000	0.077
IDDD Total	47.33	47.32	139.500	1.000
MLSE Total	77.22	79.68	115.500	0.437
SUVR Baseline	0.79	0.84	88.000	0.095
Naming	123.56	69.63	91.500	0.120
WPM	71.23	70.14	116.000	0.970
NPI Total	13.33	10.57	122.500	0.580
ACE-III Total	47.67	19.52	93.000	0.132
ACE-III Attention	11.44	13.45	84.500	0.073
ACE-III Memory	8.67	13.26	77.000	**0.043**
ACE-III Fluency	4.56	4.77	135.000	0.883
ACE-III Language	13.22	14.84	116.500	0.455
ACE-III Visuospatial	9.78	12.06	74.500	**0.034**
Digit Span (Forward)	4.33	4.52	120.500	0.524
Digit Span (Backward)	2.33	2.81	106.500	0.264
Corsi Blocks (Forward)	4.11	4.42	108.500	0.302
Corsi Blocks (Backward)	2.44	3.35	87.000	0.080
TMT-A	142.78	114.00	108.500	0.315
TMT-B	702.56	504.06	99.000	0.165
SDMT	11.67	19.74	86.500	0.086
ROCF Copy	20.17	25.000	102.500	0.230
ROCF 3-min Recall	5.556	11.177	76.500	**0.041**
ROCF 30-min Recall	5.278	9.806	85.500	0.080
ROCF Recognition	16.67	17.65	91.000	0.110
Stroop Word	40.22	47.71	117.000	0.466
Stroop Colour	21.33	27.29	100.500	0.206
Stroop Interference	8.67	13.10	104.500	0.253
ToL Total Correct	1.22	1.71	117.500	0.440
ToL Total Moves	4.67	5.97	111.000	0.324
VOSP Object Decision	14.33	15.55	90.500	0.110
VOSP Progressive Silhouettes	14.44	12.74	104.500	0.255
VOSP Position Discrimination	18.00	18.71	106.000	0.252
VOSP Number Location	7.56	7.29	126.000	0.656
Semantic Fluency (Animals)	5.33	7.03	115.000	0.425
Formal Fluency (P)	7.67	6.45	104.500	0.254
JLO	13.11	16.68	107.500	0.298
Reading Words	21.56	21.45	139.000	0.986
Reading Capital Letters	20.56	18.58	110.000	0.335
Reading Foreign Words	10.22	13.68	105.000	0.262
Reading Non-Words	18.78	18.35	130.000	0.756
Initial Phoneme Omission	7.00	6.52	131.000	0.781
Word Spelling	3.00	4.00	123.000	0.587

Repetition of Non-Words	6.78	5.61	116.000	0.444
Semantic Association	19.11	18.65	129.000	0.711
Object Naming	7.11	11.03	89.000	0.101
Word–Picture Matching	19.22	19.55	105.500	0.147
Synonym Judgement	18.44	14.90	88.000	0.092
Action Naming	13.11	15.87	83.500	0.065
Picture–Action Matching	18.22	18.68	130.500	0.746
Complex Sentence Comprehension (Total)	11.33	13.13	112.000	0.372
Verb Tense Agreement Total	37.22	49.39	121.500	0.555
Action Fluency	7.67	7.71	134.500	0.871
Repetition of Syllable	7.33	6.90	126.000	0.640
Repetition of Syllable Pair	6.78	6.23	119.500	0.494
Repetition of Non-Word	5.11	5.16	124.500	0.620
Repetition of Minimal Pairs	5.67	5.19	132.500	0.818
Repetition of Word	8.89	9.23	120.500	0.469
Repetition of Sentence	45.56	46.13	125.500	0.649

Note: Bold values indicate statistically significant differences between clusters ($p < 0.05$). Abbreviations: IDDD= Interview for Deterioration in Daily Living Activities in Dementia; MLSE= Mini Lingüistic State Examination; SDMT= Symbol Digit Modalities Test; NPI= Neuropsychiatric Inventory; ROCF= Rey–Osterrieth Complex Figure; VOSP= Visual Object and Space Perception Battery; ToL= Tower of London; ACE-III= Addenbrooke's Cognitive Examination – Third Edition; TMT= Trail Making Test; WPM= Word per Minute. JLO: Benton Judgment of Line Orientation test.

Table A2. Coefficients of LASSO and Elastic Net analysis for MLSE

	LASSO	Elastic Net
Total R^2(RMSE)	0.52 (4.94)	0.57 (5.05)
Treatment	**3.73**	**3.49**
MLSE Total	-0.042	-0.0206
Digit Span Backward	**0.53**	**0.454**
Stroop Word	0.012	0.058
Stroop Colour	**0.22**	**0.197**
VOSP Progressive silhouettes	**0.13**	**0.134**
VOSP Position discrimination	$-2.306e^{-4}$	0.0258
Reading of Foreign Words	$4.009e^{-4}$	-
CSC (Relative)	0.0017	0.058
Repetition of Syllables	**0.39**	**0.376**
Repetition of Sentences	0.09	0.077
Right Cerebellum	**0.15**	**0.121**
Right Posterior Cingulate	**0.103**	**0.107**
Left Hippocampus	**0.115**	0.092
Right Insula	0.034	0.042
Left Superior Temporal Pole	$9.189e^{-4}$	0.004
Right Hippocampus	-	0.007
Naming Words	-	$5.412e^{-4}$
Left Cerebellum	-	0.008
Right Cerebellum	-	-0.019
Active group R^2(RMSE)	0.218 (4.28)	0.137 (4.38)
Stroop Colour Baseline	**0.235**	**0.238**
CSC (Reversible distractors)	0.016	0.051
Left Inferior Occipital Gyrus	0.019	0.027
Digit Span Backward	-	0.043
Left Superior Medial Frontal Gyrus	-	$-7.74e^{-4}$
Left Fusiform Gyrus	-	0.002
Right Fusiform Gyrus	-	0.016
Sham group R^2(RMSE)	0.685 (5.61)	0.137 (4.38)
Digit Span Forward Baseline	**1.327**	**0.986**
CSC (Object focused)	**0.136**	**0.283**
Repetition of Words	**3.282**	**2.25**
Repetition of Sentences	0.033	0.045
Right Heschl's Gyrus	0.049	0.039
Digit Span Backward	-	0.035
Repetition of minimal pairs	-	0.179
Right Superior Temporal Pole	-	0.017

Note: Variables in bold are those with absolute coefficients greater than 0.1. Abbreviations: MLSE= Mini Lingüistic State Examination; VOSP= Visual Object and Space Perception Battery; CSC= Complex Sentence Comprehension.

Table A3. Coefficients of LASSO and Elastic Net analysis for Naming

	LASSO	Elastic Net
Total R^2(RMSE)	0.422 (15.0)	0.41 (15.17)
Treatment	**13.351**	**11.444**
ROCF (Time)	0.046	**0.123**
VOSP (Number location)	**-0.158**	**-0.198**
Left Cerebellum	-0.072	**-0.151**
Right Cerebellum	**-0.272**	**-0.190**
Left Posterior Cingulate,	**0.180**	**0.208**
Right Superior Orbital Frontal Gyrus	**0.352**	**-0.279**
Left Hippocampus	**0.445**	**0.387**
Left Inferior Occipital Gyrus	0.098	0.088
Vermis	-0.008	-0.052
Reading of Foreign Words	-	$-6.054e^{-4}$
Right Inferior Frontal Gyrus (Triangular Part)	-	-0.0489
Active group R^2(RMSE)		
Left Cerebellum	$-9.885e^{-16}$	

Note: Variables in bold are those with absolute coefficients greater than 0.1. Abbreviations: ROCF= Rey–Osterrieth Complex Figure; VOSP= Visual Object and Space Perception Battery.

Table A4 Coefficients of LASSO and Elastic Net analysis for IDDD

	LASSO	Elastic Net
Total R^2(RMSE)	0.462 (6.12)	0.58 (5.35)
Treatment	**-2.779**	**-2.727**
IDDD Baseline	**-0.221**	**-0.233**
Corsi Span Forward	-0.014	**-0.101**
Corsi Span Backward	-0.006	**-0.138**
ROCF (3min recall)	**-0.185**	**-0.148**
ROCF (30min recall)	**-0.104**	**-0.191**
ROCF (Recognition)	-0.096	**-0.147**
VOSP (Object decision)	**-0.219**	**-0.272**
VTA (High-frequency 1st conjugation regular verbs)	**0.102**	-0.081
Left Rolandic Operculum	0.0261	-0.039
NPI Total	-	-0.019
Education (years)	-	0.066
ROCF (Recognition)	-	-0.014
ToL (Total correct items)	-	0.086
CSC (non-reversible distractors)	-	**-0.135**
VTA (Low-frequency 1st conjugation regular verbs)	-	-0.005
Repetition of Non-Words	-	**0.214**
Repetition of minimal pairs	-	0.098
Left Heschl's Gyrus	-	-0.0302
Right Heschl's Gyrus	-	-0.0065
Active group R^2(RMSE)	*0.156 (7.20)*	*0.16 (7.3)*

IDDD Baseline	-0.068	**-0.102**
ROCF (3min recall)	**-0.204**	-
Repetition of Non-Words	0.0746	0.0461
Sham group R^2(RMSE)	0 (6.62)	0
Repetition of Syllables	$3.396e^{-16}$	

Note: Variables in bold are those with absolute coefficients greater than 0.1. Abbreviations: IDDD= Interview for Deterioration in Daily Living Activities in Dementia; NPI= Neuropsychiatric Inventory; ROCF= Rey–Osterrieth Complex Figure; VOSP= Visual Object and Space Perception Battery; VTA: Verb Tense Agreement; ToL= Tower of London; CSC= Complex Sentence Comprehension.

Table A5. Coefficients of LASSO and Elastic Net analysis for NPI

	LASSO	Elastic Net
Total R^2(RMSE)	0.807 (3.47)	0.769 (3.79)
Treatment	**-3.851**	**-3.318**
PPA Variant	**-0.652**	**-0.513**
NPI Total	**-0.352**	**-0.311**
Stroop Word	0.019	0.015
Stroop Interference	0.067	0.042
VOSP (Object decision)	-0.021	-0.005
VOSP Position discrimination	**0.409**	**0.321**
CSC (Subject focused)	**-1.479**	**-1.229**
CSC (Relative)	-0.006	-0.095
CSC (Non-reversible distractors)	**0.168**	**0.151**
Repetition of pairs of syllables	**0.341**	**0.344**
Repetition of Words	**0.429**	**0.564**
Age	-0.025	-0.022
Right Caudate	**-0.171**	**-0.142**
Right Cerebellum	0.052	0.048
Left Paracentral Lobule	0.057	0.041
Right Superior Parietal Lobule	-0.014	-0.034
Right Supramarginal Gyrus	0.062	-0.075
Right Inferior Temporal Gyrus	-0.168	-0.076
Left Middle Temporal Gyrus	0.078	0.067
Left Superior Temporal Gyrus	**0.162**	**0.151**
Vermis Lobules I–II	0.038	0.037
Vermis Lobules VIII	$-5.362e^{-4}$	-
ROCF (Time)	-	$6.376e^{-4}$
Right Middle Temporal Pole	-	-0.022
Active group R^2(RMSE)	0.865 (3.09)	0.96 (1.46)
NPI Total	**-0.417**	**-0.488**
IDDD Baseline	0.005	0.035
ACE-III Language	0.037	0.086
ROCF (Recognition)	-0.009	**-0.240**
Stroop Word	0.022	0.035
Stroop Interference	0.041	**0.232**
Word-Picture Matching	**-0.215**	**-0.185**
CSC (Subject focused)	**-1.298**	**-1.092**
CSC (Non-reversible distractors)	**0.068**	**0.251**

Repetition of pairs of syllables	**0.255**	**0.549**
Repetition of Words	0.013	0.051
Repetition of Sentences	0.051	0.039
Age	-0.084	**-0.161**
Right Angular Gyrus	-0.057	-
Right Caudate	**-0.145**	**-0.160**
Right Inferior Frontal Gyrus (Triangular Part)	-0.012	-
Right Fusiform Gyrus	**-0.176**	-
Left Heschl's Gyrus	0.084	**0.109**
Left Superior Temporal Gyrus	**0.232**	**0.181**
Vermis Lobules I–II	0.084	0.004
Synonym Judgement	-	**0.178**
Initial phoneme omission	-	0.029
Right Cuneus	-	-0.0905
Left Amygdala	-	0.0779
Left Calcarine Cortex	-	0.023
Left Cerebellar Lobules IV–V	-	,-0.004
Right Cerebellar Lobule IX	-	0.039
Right Fusiform Gyrus	-	**-0.198**
Right Paracentral Lobule	-	-0.005
Right Parahippocampal Gyrus	-	0.027
Right Inferior Temporal Gyrus	-	-0.002
Vermis Lobules VIII	-	-0.085
Digit Span Backward	-	**-0.247**
Corsi Span Forward	-	-0.08
TMT (B)	-	0.002
ROCF (Copy)	-	0.082
Sham group R^2(RMSE)	0.068 (5.04)	0.94 (1.174)
ROCF (Time)	0.001	0.007
NPI Total	-	**-0.104**
ROCF (Recognition)	-	**0.452**
VOSP Number location	-	**-0.174**
CSC (Present Continuous)	-	**-0.493**
Repetition of Words	-	**-0.149**
Right Cerebellar Crus I	-	0.067
Right Cerebellar Crus II	-	0.081
Left Posterior Cingulate	-	0.015
Right Gyrus Rectus	-	**-0.137**
Right Middle Temporal Pole,-	-	-0.037
Left Thalamus	-	**0.232**

Note: Variables in bold are those with absolute coefficients greater than 0.1. Abbreviations: PPA= Primary Progressive Aphasia; IDDD= Interview for Deterioration in Daily Living Activities in Dementia; NPI= Neuropsychiatric Inventory; ROCF= Rey–Osterrieth Complex Figure; VOSP= Visual Object and Space Perception Battery; VTA: Verb Tense Agreement; ToL= Tower of London; CSC= Complex Sentence Comprehension; ACE-III= Addenbrooke's Cognitive Examination – Third Edition; TMT= Trail Making Test.

Table A6. Coefficients of LASSO and Elastic Net analysis for WPM

	LASSO	Elastic Net
Total R^2(RMSE)	0.19 (16.7)	0.19 (16.65)
CSC (Passive)	**-1.880**	**-1.638**
Right Amygdala	0.004	**0.118**
Left Superior Occipital Gyrus	**-0.285**	**-0.241**
Stroop Word	-	-0.004
Left Superior Parietal Gyrus	-	-0.036
Active group R^2(RMSE)	0	0
Left Superior Occipital Gyrus	$-1.67e^{-16}$	-
Sham group R^2(RMSE)	0	0
WPM	$-2.594e^{-4}$	-
Right Anterior Cingulate Gyrus	**0.462**	-
Left Middle Temporal Gyrus	**-0.714**	-

Note: Variables in bold are those with absolute coefficients greater than 0.1. Abbreviations: CSC= Complex Sentence Comprehension; WPM= Word per Minute.

THESIS PUBLICATIONS

Fernandez-Romero L, Cabrera-Martin MN, Delgado-Alonso C, Suárez-Coalla P, Grasso SM, Portolés A, Pérez-Macías N, Carreras MT, Díez-Cirarda M, Gil-Moreno MJ, Olazarán J, Vieira A, Oliver-Mas S, Gómez-Pinedo U, Matías-Guiu J, Matías-Guiu JA. Long-term therapy with transcranial magnetic stimulation in Primary Progressive Aphasia. A randomized clinical trial. *JAMA Network Open* 2025;8:e2526129. doi:10.1001/jamanetworkopen.2025.26129

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