

Differential approach to stroke aphasia and primary progressive aphasia using transcranial magnetic stimulation: A systematic review

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Language disorders can occur as a consequence of stroke or neurodegenerative disorders, among other causes. Post-stroke aphasia (PSA) and primary progressive aphasia (PPA) are syndromes that, despite having common features, differ in the brain mechanisms that cause their symptoms. These differences in the underlying functional neuroanatomical changes may influence the way they are addressed by different non-invasive brain stimulation techniques and, in particular, by repetitive transcranial magnetic stimulation (rTMS). The aim of this systematic review is to evaluate the efficacy of rTMS in the treatment of PSA and PPA, as well as the differences in the approach to these disorders using rTMS. To this end, a total of 36 articles were found in the Web of Science, Scopus, and PubMed. The results obtained suggest that whereas in PSA, the selection of the stimulation paradigm is based on bi-hemispheric functional reorganisation models with a tendency towards the application of inhibitory rTMS in the contralateral right hemisphere, in PPA, the application of excitatory rTMS in functionally compromised areas seems to show promising changes. It is concluded that rTMS is a potential treatment in the therapy of both disorders, although differences in the underlying brain mechanisms differentiate the rTMS approach in each case.

Key words: transcranial magnetic stimulation, aphasia, stroke, primary progressive aphasia

INTRODUCTION

Language is the main method of human communication, requiring the use of arbitrary signs and symbols (Mesulam et al., 2014). According to the Medical Subject Headings (MeSH) definition, aphasia is a cognitive disorder marked by an impaired ability to comprehend or express language, and it usually occurs as a result of damage in specific brain areas that are responsible for language (McNeil and Pratt, 2001; Brady et al., 2016).

Stroke is the main cause of aphasia (Brady et al., 2016). Typically, post-stroke aphasia (PSA) has

been classified into syndromes based on the Wernicke-Geschwind model (Fridriksson et al., 2018; Nasios et al., 2019). In the modular approach to this classical model, frontal lesions cause motor aphasias, temporal and temporo-parietal lesions cause sensory aphasias, lesions affecting the arcuate fasciculus cause conduction aphasia, and deeper cortical lesions cause disconnection syndromes (Nasios et al., 2019). However, the model is outdated (Nasios et al., 2019), and aphasia is now considered to be a network disorder (Hartwigsen and Saur, 2019; Lin et al., 2022) whose symptomatology involves other factors beyond the location of the lesion (Turkeltaub, 2019). The dual stream model (Hickok and Poeppel, 2007) proposed

a cortical brain organization of speech and language in which motor speech impairment is associated to the dorsal stream, whereas comprehension impairment involves ventral stream. This model also supports that many language processes rely on the two streams (Fridriksson et al., 2018).

The recovery of the linguistic function will depend on both the resolution of the acute injury and the reorganisation mechanisms that take place in the brain to compensate for the damage. In PSA, after the resolution of oedema, hypoperfusion and diaschisis, different processes of upregulation of brain activity start in the subacute phase (Hartwigsen and Saur, 2019; Meier, 2022). These changes in neural activity can last up to 6 months after the stroke, which is considered a chronic stage (Hartwigsen and Saur, 2019; Meier, 2022). Given the lateralisation of the linguistic domain, recovery is primarily associated with a return to premorbid left hemisphere activity (Heiss and Thiel, 2006; Hamilton et al., 2011; Meier, 2022). The role of the right hemisphere in language recovery is still being debated (Anglade et al., 2014; Turkeltaub, 2015). The reorganisation mechanism appears to be conditioned by the complex interdependence of multiple variables related to the characteristics of the lesion (e.g., location and size), stroke onset and patient-related factors such as the degree of language lateralisation (Heiss and Thiel, 2006; Hamilton et al., 2011; Anglade et al., 2014). Several models attempt to provide a simplified explanation of these dynamics by reducing them to the variability of a limited number of factors (Heiss and Thiel, 2006; Hamilton et al., 2011; Meier, 2022). In this line, Heiss and Thiel (2006) state that recovery of premorbid activity would only be possible in small lesions that do not affect important nodes of the language network. In contrast, in the case of severe damage, activation of homologous areas of the right hemisphere could be compensatory, although not as effective as intrahemispheric plasticity (Heiss and Thiel, 2006). Also, in relation to stroke onset, while in the right hemisphere a biphasic course takes place with a strong increase in activation of some brain areas in the subacute phase and a subsequent reduction, the onset in left hemisphere shows a continuous increase in activation during recovery (Saur et al., 2006).

On the other hand, aphasia may also occur as a consequence of neuronal degeneration which focally affects brain structures involved in language. This is known as primary progressive aphasia (PPA) (Mesulam, 2001; Tippett et al., 2020). This disorder may be linked to both frontotemporal lobar degeneration (FTLD) – Tau protein or transactive-response DNA-binding protein (TDP-43) – or Alzheimer disease

(AD) pathology (Mesulam et al., 2014; Montembeault et al., 2018; Roytman et al., 2022). PPA has an insidious onset and shows gradual deterioration of language due to the progressive atrophy of the language network (Mesulam et al., 2014; Tippett et al., 2020; Meier, 2022). This can give rise to compensatory mechanisms different from those that occur in PSA (Mesulam et al., 2014; Meier, 2022). The different brain functional reorganisation and damage implies that PPA requires its own taxonomy (Mesulam et al., 2014). Thus, PPA is classified into three variants: non-fluent or agrammatic PPA, semantic PPA and logopenic PPA (Gorno-Tempini et al., 2011). In the case of the non-fluent variant, the core of the lesion is the inferior frontal gyrus (IFG); in the semantic variant, the polar region of the temporal lobe; and in the logopenic variant, the regions of atrophy are the posterior part of the temporal lobe, the inferior part of the parietal lobe, and the temporo-parietal junction (Mesulam et al., 2014; Montembeault et al., 2018; Roytman et al., 2022). Although these anatomical changes occur in the dominant hemisphere, it is possible to find atrophy in some regions of the right hemisphere, more frequently in the semantic variant (Montembeault et al., 2018; Roytman et al., 2022).

As with PSA, the location of the structural lesion does not account for the totality of the subsequent symptomatology, with changes in the functional network caused by the lesion itself, and subsequent reorganisation processes accounting for much of the clinical profile (Wilson et al., 2016; Hardy et al., 2017; Bonakdarpour et al., 2019; Borghesani et al., 2021). While in the case of stroke, both grey and white matter are abruptly destroyed, in PPA neuronal damage is progressive. Thus, the remaining neurons in the atrophied regions seem to maintain the premorbid response (Sonty et al., 2003; Mesulam et al., 2014; Wilson et al., 2014). This results in a reorganisation process that is different than those found in PSA (Mesulam et al., 2014; Bonakdarpour et al., 2019). Studies analysing both task-related activity (Sonty et al., 2003; Nelissen et al., 2011; Wilson et al., 2016; Hardy et al., 2017; Borghesani et al., 2021) and functional connectivity (Whitwell et al., 2015; Bonakdarpour et al., 2017, 2019; Reyes et al., 2018; Battistella et al., 2019; Tao et al., 2020) in different variants of the PPA, have reported functional changes across the language network that expand beyond the boundaries of atrophy and may involve other cognitive networks. Overall, functional neuroimaging studies across PPA variants report reductions both in functional connectivity (Whitwell et al., 2015; Bonakdarpour et al., 2017, 2019) and activation (Wilson et al., 2016; Hardy et al., 2017) in different regions of the language network that correlate with impaired func-

tional performance. This decrease both in activity and functional connections, while occurring primarily in the left hemisphere, can also be found in right hemisphere regions that are involved in specific tasks in a premorbid state (Nelissen et al., 2011; Wilson et al., 2016; Hardy et al., 2017). Conversely, the recruitment of other previously uninvolved cortical regions could involve either compensatory change (Battistella et al., 2019; Borghesani et al., 2021) or aberrant changes (Sonty et al., 2003). As in the case of PSA, the quality of activation of the right hemisphere regions is unclear; while several studies that have examined its increased activation show that it correlates with poorer performance on different language tasks (Nelissen et al., 2011; Vandenbulcke et al., 2005), other studies have found that increased right hemisphere activity is associated with improvements in language following speech therapy (Dressel et al., 2010).

PSA and PPA are two clinical entities that present notable differences in terms of the underlying brain mechanisms. Scientific evidence indicates that non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS), could be beneficial in treating PSA and PPA (Norise and Hamilton, 2017; Breining and Sebastian, 2020; Nissim et al., 2020). TMS is a neurophysiological technique that allows the induction, in a safe and non-invasive manner, of a small electrical current in the brain (Pascual Leone and Tormos Muñoz, 2008). Its action mechanism involves the transformation of magnetic fields into an electrical current which can depolarise neuronal membranes and generate action potentials, leading to long-term after-effects in the brain's functioning (Klomjai et al., 2015). TMS can be used following different stimulation paradigms, which vary in a wide range of selected parameters of stimulation, such as intensity, frequency, number of patterns of pulses that are applied, among others (Brunoni et al., 2019). As for pulses, repetitive TMS (rTMS) is widely used for clinical purposes (Lefaucheur et al., 2020). rTMS is characterised by the emission of several pulses at a certain intensity, and this series of pulses produces changes that last beyond the stimulation period itself (Burke et al., 2019). There is some consensus about the differential effects based on the frequency selected: low-frequency rTMS (≤ 1 Hz) can generate an inhibitory effect on brain activity/excitability, whereas high-frequency rTMS (≥ 5 Hz) produces an excitatory effect (Rossini et al., 2015).

The objective of this work is to carry out a systematic review of the application of rTMS in PSA and PPA, analysing its efficacy, as well as comparing the differences in the stimulation protocols used on the basis of the functional restructuring theories followed.

SELECTION CRITERIA

To examine the available literature about the effect of rTMS in treating PSA and PPA, we performed this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021).

We searched the Web of Science (WoS), Scopus and PubMed databases until November 21, 2022. In order to focus on recent results, the search was restricted to those articles published in the last ten years. The search keywords we applied and combined were: “transcranial magnetic stimulation”, “aphasia” and “stroke”, to search for articles related to the application of rTMS in the treatment of PSA, and “transcranial magnetic stimulation”, “aphasia” and “progressive” for its use in PPA.

We limited the articles according to the following inclusion criteria: (1) experimental study where rTMS is an intervention tool and reports results, (2) use of rTMS alone or with language intervention, (3) stroke patients with aphasia, regardless of the stroke onset, (4) patients diagnosed with PPA, (5) adult patients, (6) English or Spanish language, (7) the study includes measures related to language performance both before and after applying rTMS, and (8) original studies. We did not consider articles that omitted the inclusion criteria and/or met the following exclusion criteria: (1) treatment with theta burst stimulation protocols, (2) use of rTMS in conjunction with other brain stimulation techniques, (3) use of rTMS not for treatment, (4) omission of any stimulation parameter, and (5) reports such as meta-analyses, reviews, letters to the editor or book chapters.

We detected and deleted duplicate articles. Then we screened the title and abstract of the remaining articles. Third, we analysed the selected articles exhaustively to exclude those not meeting the selection criteria.

For PSA, WoS, Scopus and Pubmed yielded 147, 114 and 28 articles, respectively. After discarding duplicates, we identified a total of 171 potentially relevant articles. After reading the title and abstract for eligibility, we removed 127. Through an in-depth reading, we assessed 44 articles for full eligibility. Of these articles, 11 did not match the selection criteria and were excluded. Therefore, a total of 33 articles were selected for this systematic review (Fig. 1).

For PPA, WoS, Scopus and PubMed yielded 31, 23 and 3 articles, respectively. After discarding duplicates, we identified a total of 44 potentially relevant articles. After reading the title and abstract for eligibility, 38 were removed. After an in-depth reading, we assessed 3 articles for full eligibility, which were selected for this systematic review (Fig 2).

Table 1 summarises the main characteristics of the studies.

Use of rTMS in the Treatment of PSA

A total of 33 articles were included in this section (Table 1). In the treatment of PSA, different stimulation approaches were registered to modulate the brain activity, with the aim of improving language performance. Three fundamental trends were found in the application of rTMS in PSA: (1) right hemisphere inhibition, (2) left hemisphere excitation and (3) right hemisphere excitation.

Most of the research on the use of rTMS in PSA (23 of the 33 included studies) assessed the effect of inhibiting the right hemisphere using low-frequency rTMS (Table 1). Based on preliminary studies in the area, the most frequently selected brain region was the right IFG – homotopic to Broca’s area (Table 1). These studies used 1 Hz inhibitory rTMS, with session duration varying between 10, 15, 20 or 30 minutes, and treatment duration varying between 6, 10, 15 or 20 sessions. The most common configuration was 1 Hz frequency, with a session duration of 20 minutes (1,200 pulses) and 10 treatment sessions (5 weekly sessions) (Table 1).

More specifically, many authors have stimulated a specific part of IFG, known as *pars triangularis* (Table 1). Moreover, the inhibition of this area has been applied in different types of PSA, both in the subacute and chronic phases. For example, in subacute apha-

sia, Heiss et al. (2013) reported improvements of the treated group, compared to sham-treated patients, in global scores in the Aachen aphasia test (AAT), with greater improvements in picture-naming performance. Thiel et al. (2013) also found an improvement in overall language performance in AAT scores when comparing treated and non-treated patients, with the highest ratings of improvement in naming, comprehension, writing and Token Test. They found no difference in treatment efficacy between the different types of aphasia – i.e., Broca, Wernicke, global or amnesic aphasia. Similarly, in fluent and non-fluent subacute aphasia, the study by Rubi-Fessen et al. (2015) showed benefits of TMS in combination with speech and language therapy in AAT profile score; Token Test, repetition, writing, comprehension, and naming AAT subtests; Everyday Language Test (ANELT) which measures functional verbal and nonverbal communication, and communicative behaviour measured by comprehension and expression items of the Functional Independence Measurement (FIM.35). Likewise, in a multilingual, multicenter aphasia trial, Zumbansen et al. (2020) found significant improvements in naming, when assessed using AAT, Montreal-Toulouse-86 and Western Aphasia Battery, 30 days after stimulation. Interestingly, this benefit was only observed in subacute PSA patients with preserved Broca’s area. Also, when these authors later compared the effects

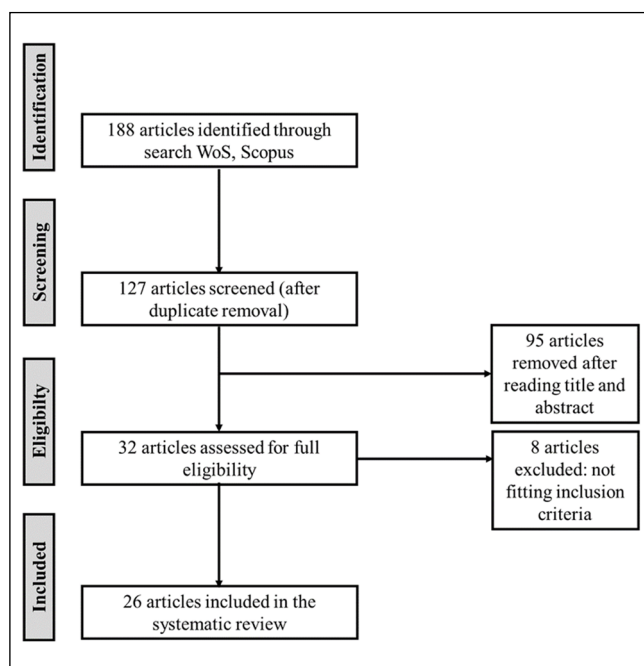


Fig. 1. Literature flow diagram of the selection process in the different phases of the systematic review, related to stroke-related aphasias and rTMS.

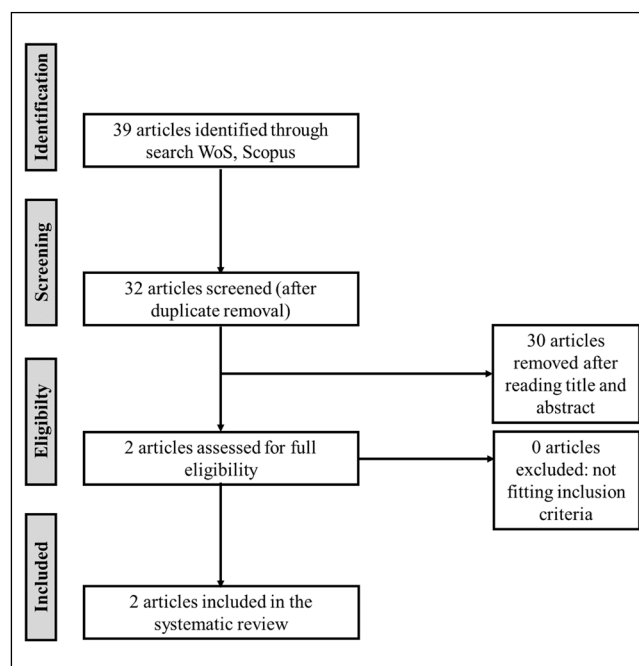


Fig. 2. Literature flow diagram of the selection process in the different phases of the systematic review, related to PPA and rTMS.

Table 1. rTMS effects in stroke aphasia and PPA.

Study	Type, sample	Type of aphasia, phase	rTMS parameters	Target area	Assessment	Main results
Bai et al., 2021	Randomized, sham-controlled, n=30	Non-fluent, subacute	Inhibitory rTMS, 1 Hz, 1000 p, 20 min, 20 sessions; same protocol applied 2 times a day (2rTMS)	Right posterior IFG	WAB	The rTMS and 2rTMS groups ↑ spontaneous speech, comprehension, repetition, and naming. Improvements were superior in the 2rTMS group
Bai et al., 2022	Randomized, sham-controlled, n=60	Non-fluent, subacute	Inhibitory rTMS, 1 Hz, 1000p, 20 sessions	Right posterior IFG	WAB, TT, rs-fMRI	rTMS group ↑ in all dimensions of the WAB and in the TT. Spontaneous language, naming, and aphasia quotient scores after treatment were significantly higher in the rTMS group than in the control
Barwood et al., 2013	Randomized, double-blind, sham-controlled, n=12	Non-fluent, chronic	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	<i>Pars triangularis</i> , in right IFG	BNT; subtests of BDAE; picture naming task	rTMS group ↑ naming, expressive language, and auditory comprehension, 12 months after stimulation
Bereau et al., 2016	Single case n=1	PPA logopenic variant	Excitatory rTMS, 10 Hz, 2000 p, 20 min, 10 sessions	DLPFC	Naming test; fluency test	The rTMS groups ↑ fluency and naming
Chang et al., 2022	Exploratory n=5	Non-fluent, chronic	Excitatory rTMS 10 Hz, 800p, 10 sessions	Optimal region for each subject, within the HI	WAB; fNIRS	↑ in aphasia quotient in WAB after treatment
Chou et al., 2022	Randomized, single-blind, sham-controlled, n=85	Non-fluent, chronic	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	<i>Pars triangularis</i> , in right IFG	CCAT	rTMS group ↑ CCAT total scores compared with their baseline. Compared with the sham-group, ↑ in expression, reading comprehension, and imitation writing subtests scores
Dammekens et al., 2014	Single case, n=1	Non-fluent, chronic	Excitatory rTMS 10 Hz, 2000 p, 15 sessions	Left IFG	AAT; EEG	rTMS group ↑ naming, repetition, and comprehension following treatment; naming and repetition were maintained 4 months later
Fahmy & Elshebawy, 2021	Exploratory n=20	Non-fluent, chronic	Excitatory rTMS, 10 Hz, 2000 p., 10 sessions.	<i>Pars opercularis</i> and <i>pars triangularis</i> , in left IFG	ASRS; KAAT	↑ ASRS and KAAT immediately and one month after treatment.
Georgiou & Kambanaros, 2022	Single-subject experimental design trial n=6 (only 3 received rTMS)	Anomic / global, chronic	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	<i>Pars triangularis</i> , in right IFG	BDAE (short version); PPVT-R; GOAT; MAIN; RCPMs	Different results for different subjects.
Haghighi et al., 2018	Randomized, sham-controlled, n=12	Broca, subacute	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	Right posterior IFG	WAB	rTMS group ↑ speech and linguistic ability, compared with its initial measure. rTMS group ↑ sentence content, repetition, and command comprehension compared with controls

Study	Type, sample	Type of aphasia, phase	rTMS parameters	Target area	Assessment	Main results
Hara et al., 2015	Experimental design trial, n=50	Non-fluent / fluent, chronic	Inhibitory rTMS 1 Hz, 40 min, 10 sessions	IFG for non-fluent, STG for fluent; hemisphere contralateral to compensatory hemisphere	SLTA; SPECT	rTMS ↑ SLTA in both groups
Hara et al., 2017	Experimental design trial, n=8	Non-fluent / fluent, chronic	To facilitate left hemisphere activation: Inhibitory rTMS 1 Hz, 40 min, 10 sessions To activate right hemisphere: Excitatory rTMS, 10 Hz, 12 min, 10 sessions	Right IFG	SLTA; fNIRS	rTMS ↑ SLTA in both groups
Harvey et al., 2017	Exploratory n=9	Non-fluent, chronic	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	Optimal region for each subject in RH	Naming in Categories subtest of BDAE; picture naming task, fMRI	↑ naming, maintained at 6 months
Heikkinen et al., 2019	Randomized, sham-controlled, n=17	Conduction / anomic / transcortical / Broca / Motor, chronic	Inhibitory rTMS 1 Hz, 20 min, 20 sessions	<i>Pars triangularis</i> , in right IFG	WAB; BNT; ANT	No significant differences
Heiss et al., 2013	Randomized, sham-controlled, n=31 (29 right-handers; 2 left-handers)	Broca / Wernicke / global / amnesic, subacute	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	<i>Pars triangularis</i> , in right IFG (right-handed) and left IFG (left-handed)	AAT; PET	Right-handed subjects: rTMS group ↑ AAT, picture naming. Left-handed subjects: only one subject obtained improvements within the expected range for treated right-handers
Hu et al., 2018	Randomized, sham-controlled, n=40	Non-fluent, chronic	Inhibitory rTMS 1 Hz, 10 min, 10 sessions Excitatory rTMS, 10 Hz, 10 min, 10 sessions	Right IFG	WAB	Inhibitory rTMS group in comparison with excitatory rTMS group in spontaneous speech, comprehension, and aphasic score following 2 months
Khedr et al., 2014	Randomized, double-blind, sham-controlled, n=30	Non-fluent / mixed, subacute	Inhibitory rTMS 1 Hz, 1000 p + Excitatory rTMS 20 Hz, 1000 p, 10 sessions	<i>Pars triangularis</i> and <i>pars opercularis</i> , in right IFG (inhibitory) and in left (excitatory)	HSS (language section), ASRS, SADQ-H, NIHSS	rTMS groups ↑ HSS, ASRS, SADQ-H which remain 2 months. No significant differences in 5 patients with mixed aphasia in HSS
Lee et al., 2022	Randomized, double-blinded, sham-controlled, n=26	Non-fluent, chronic or subacute	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	<i>Pars triangularis</i> , in right IFG	CCAT; rs-fMRI (fALFF)	rTMS group ↑ total CCAT scores and sub-scores of conversation, description and expression in comparison with sham-group
Lin et al., 2022	Randomized, double-blinded, sham-controlled, n=33	Non-fluent, chronic	Inhibitory rTMS 1 Hz, 15 min, 10 sessions	Right posterior <i>pars triangularis</i>	CCAT Rs-fMRI	rTMS group ↑ comprehension and expression abilities compared with sham-group
Liu et al., 2022	Single case, n=1	Sensory, Subacute	Inhibitory rTMS 1 Hz, 1200 p, 20 min, 6 sessions	Right anterior <i>pars triangularis</i>	BDAE; WAB	↑ auditory comprehension, naming and AQ immediately after treatment. ↑ spontaneous speech, auditory comprehension, naming and AQ at 7 months post-treatment

Study	Type, sample	Type of aphasia, phase	rTMS parameters	Target area	Assessment	Main results
Lopez-Romero et al., 2019	Randomized, double-blind, sham-controlled, n=82	Non-fluent, chronic	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	<i>Pars triangularis</i> , in right IFG	BNT; Barcelona test; fluency test	No significant differences
Mirowska-Guzel et al., 2013	Randomized, double-blind, sham-controlled, n=20	Non-defined, subacute	Inhibitory rTMS 1 Hz, 30 min, 15 sessions	Right IFG	BDAE	rTMS application ↓ aphasia severity in a subgroup of patients. rTMS ↓ BDNF concentration, regardless r
Pytel et al., 2021	Randomized, double-blind, cross-over, n=20	PPA, Non-fluent / semantic variant	Excitatory rTMS 20 Hz, 1500 p, 15 sessions	Optimal region for each subject, left IFG, left STG, left DLPFC, left STG, right superior frontal gyrus and left anterior temporal lobe	Spontaneous speech, object naming test, story reading test, repetition test; ACE III, NPI, PET	rTMS group ↑ spontaneous speech, reading accuracy repetition of syllables and pairs of syllables, picture object naming, and NPI total score, and subscores for depression and apathy.
Ren et al., 2019	Randomized, double-blind, sham-controlled, n=45	Global, subacute	Inhibitory rTMS 1 Hz, 20 min, 15 sessions	<i>Pars triangularis</i> , in right IFG; right posterior STG	WAB	The effect of rTMS depends on the stimulation site. STG stimulated group ↑ auditory comprehension, repetition, and aphasia quotient. IFG stimulated group ↑ spontaneous speech, repetition, and aphasia quotient
Rossetti et al., 2019	Single case n=1	Anomic, chronic	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	Right IFG	BNT; semantic and phonological fluency test; Stroop task	The subject ↑ compared to the initial measurement in phonemic fluency, immediately and 2 months after treatment. Naming, semantic fluency, and Stroop performance did not show significant differences
Rubi-Fessen et al., 2015	Randomized, blinded, sham-controlled, n=30	Non-fluent / fluent, subacute	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	<i>Pars triangularis</i> , in right IFG	AAT, picture naming task, ANELT, subscales of FIM	rTMS group ↑ basic language abilities and functional communication
Seniów et al., 2013	Randomized, double-blind, sham-controlled, n=40	Broca / Wernicke / mixed / transcortical, subacute	Inhibitory rTMS, 1Hz, 30 min, 15 sessions	<i>Pars triangularis</i> , in right IFG	BDAE; ASRS	No significant differences compared to the control group
Thiel et al., 2013	Randomized, blind, sham-controlled, n=24	Broca / Wernicke / global / amnesic, subacute	Inhibitory rTMS 1 Hz, 20 min, 10 sessions	<i>Pars triangularis</i> , in right IFG	AAT; PET	rTMS groups ↑ AAT, naming, comprehension, Token Test, and writing. No differences between aphasia types.
Trebbastoni et al., 2013	Single case n=1	PPA, logopenic variant	Excitatory rTMS 20 Hz, 1500 p, 20 min, 10 sessions	DLPFC	Phonological fluency test; writing test	The rTMS groups ↑ linguistic ability, with no differences one week later
Tsai et al., 2014	Randomized, double-blind, parallel, sham-controlled, n=56	Non-fluent, chronic	Inhibitory rTMS 1 Hz, 10 min, 10 sessions	<i>Pars triangularis</i> , in right IFG	CCAT; picture naming task	rTMS group ↑ CCAT total score, conversation, description, expression and repetition subtests, object and action accuracy and reaction time. Changes maintained at 3 months

Study	Type, sample	Type of aphasia, phase	rTMS parameters	Target area	Assessment	Main results
Wang et al., 2014	Randomized, double-blind, sham-controlled, n=45	Broca / Transcortical motor / global, chronic	Inhibitory rTMS 1 Hz, 20 min, 10 sessions (with synchronous vs. asynchronous picture naming task)	<i>Pars triangularis</i> , in right IFG	Naming test; CCAT	rTMS synchronous group ↑ in CCAT score, description and expression subtests and object and action naming ability in comparison with rTMS asynchronous group and controlled group; superior results maintained at 3 months
Yoon et al., 2015	Randomized, controlled, n=20	Non-fluent, subacute	Inhibitory rTMS 1 Hz, 20 min, 20 sessions	Right IFG	WAB	rTMS group ↑ comprehension compared to the control group, and ↑ repetition and naming compared to the baseline
Zhang et al., 2017	Single case n=1	Conduction, subacute	Excitatory rTMS 5 Hz, 20 min, 10 sessions	Left IFG	WAB	↑ linguistic ability, spontaneous speech, auditory comprehension, repetition, and naming, 2.5 months later
Zumbansen et al., 2020	Randomized, blinded, sham-controlled, n=63	Non-defined, subacute	Inhibitory rTMS 1 Hz, 15 min, 10 sessions	<i>Pars triangularis</i> , in right IFG	BNT; semantic fluency test (SF1 min); Token Test; AAT; MTP; WAB	rTMS group ↑ BNT, one month later compared to control group. This effect is only found in the subgroup with preserved Broca's area
Zumbansen et al., 2022	Randomized, blinded, sham-controlled, n=67	Non-defined, subacute and chronic	Inhibitory rTMS, 1 Hz, 15 min, 10 sessions	<i>Pars triangularis</i> , in right IFG	BNT; semantic fluency test (SF1 min); Token Test; AAT; PMT; WAB	rTMS ↑ naming recovery only in subacute patients. There was no significant rTMS effect in the chronic aphasia group

AAT: Aachen Aphasia Test; ACE III: Addenbrooke's Cognitive Examination III; ANELT: Amsterdam-Nijmegen Everyday Language Test; ANT: Action Naming Test; ASRS: Aphasia Severity Rating Scale; BDAE: Boston Diagnostic Aphasia Examination; CCAT: Concise Chinese Aphasia Test; BNT: Boston Naming Test; CLQT: Cognitive Linguistic Quick Test DLPFC: dorsolateral prefrontal cortex; fALFF: fractional amplitude of low-frequency fluctuation; FIM: Functional Independence Measure; GOAT: Greef Object and Action Test; HSS: hemispheric stroke scale; IFG: inferior frontal gyrus; KAAT Kasr El-Eini Arabic Aphasia test; MAIN: Multilingual Assessment Instrument for Narratives; MTP: Montreal-Toulouse Protocol; NPI: Neuropsychiatric Inventory; PPVT-R: Peabody Picture Vocabulary Test-Revised; rs-fMRI: resting state fMRI; RCPMs: Raven's Coloured Progressive Matrices; rTMS: repetitive transcranial magnetic stimulation; SADQ-H: Stroke Aphasic Depression Questionnaire – Hospital version; SLTA: Standard Language Test of Aphasia; STG: superior temporal gyrus; TT: Token Test; WAB: Western Aphasia Battery.

of this paradigm in subacute and chronic PSA patients, they found that naming improvement was larger in subacute than chronic patients (Zumbansen et al., 2022). In chronic phase aphasia, Barwood et al. (2013) found significant improvements in subjects with non-fluent or global aphasia treated with rTMS when compared to the sham group 8-12 months post stimulation. These improvements were found in naming actions, tools and animals from the Boston Naming Test; complex ideational materials, repetition of sentences, repetition of non-words in the Boston Diagnostic Aphasia Examination (BDAE), picture description complexity and picture naming accuracy of the Cookie Theft picture of the BDAE; and Snodgrass and Vanderwart picture naming. Tsai et al. (2014) observed that subjects with non-fluent aphasia treated during 3 months improved in the Concise Chinese Aphasia Test (CCAT) when assessed their conversation and repetition, and object and actions naming accuracy and reaction time. These improvements were found when comparing with sham-treated patients and its

own baseline. Lin et al. (2022) also reported benefits of rTMS intervention compared to sham-treated in matching, auditory comprehension, and reading comprehension, simple response, expository speech, naming, and imitation writing of the CCAT. Lee et al. (2022) applied inhibitory rTMS over *pars triangularis* to subjects with non-fluent aphasia both in subacute and chronic phases and compare their performance after treatment with sham-group using also CCAT subtests. They only found gains in subtests of conversation, description, and expression immediately after treatment, with no improvements in comprehension. However, they made no differential analysis of the results between subacute and chronic phase subjects.

Studies to analyse the rTMS effects in both the chronic and the subacute phases show that the benefits obtained seem to be maintained in the long term, specifically, 1 (Zumbansen et al., 2020), 3 (Tsai et al., 2014), 6 (Harvey et al., 2017) or even 12 months (Barwood et al., 2013) after the conclusion of rTMS treatment.

It should be noted that not all the studies found benefits associated with inhibition of the *pars triangularis* of the right IFG. Thus, Heikkinen et al. (2019), who evaluated the efficacy of applying inhibitory rTMS in conjunction with Intensive Language-Action Therapy (ILAT) – a efficient behavioral therapy – in patients with different aphasia types in chronic phase, found no improvements related to the application of rTMS; although they detected advances with ILAT. Seniów et al. (2013) also found no differences between the experimental and control group in patients with different aphasia types in subacute phase, and López-Romero et al. (2019) found no significant improvements in chronic non-fluent aphasia when applying rTMS.

Applying the above-mentioned stimulation paradigm, some authors have stimulated other regions within the right IFG. Interestingly, Harvey et al. (2017) carried out a pre-treatment phase whereby they selected the most appropriate stimulation area for each individual, based on a stimulation site-finding protocol previously described in Garcia et al. (2013). It consisted of an application of inhibitory rTMS to 5 different regions of the IFG or to the primary motor cortex – in the right hemisphere. Thus, 8 patients received inhibitory stimulation on the *pars triangularis*, and 1 of them on the *pars orbitalis*. The results showed an increase in naming, with the most substantial improvements 6 months after stimulation. However, some authors who reported positive results in different aspects of language did not mention the specific part of the IFG to which they applied the stimulation (Bai et al., 2021, 2022; Haghghi et al., 2018; Rossetti et al., 2019; Yoon et al., 2015).

In addition to IFG, the effect of rTMS in other areas of the right hemisphere has been assessed. For example, Ren et al. (2019), in a randomised sham-controlled study, assessed the differential effects of inhibiting IFG or the superior temporal gyrus (STG) – homotopic to Wernicke's area – in patients with subacute global aphasia. They applied a 1 Hz stimulation paradigm, with a session duration of 20 minutes and a total of 15 sessions. This study showed a differential effect depending on the area stimulated. While language improvements in the IFG-inhibited group seemed to focus on spontaneous speech and repetition, improvements in auditory comprehension and repetition were obtained in the STG-inhibited group.

Several of the studies mentioned above have used neuroimaging techniques to assess changes in brain activity after stimulation. Thus, some studies reported a change in the lateralisation index in favour of the left hemisphere in the group of subjects with subacute aphasia who had undergone rTMS treatment

(Heiss et al., 2013; Thiel et al., 2013). These changes in brain activity correlated with improvements in overall language test scores (Thiel et al., 2013). Likewise, Harvey et al. (2017) reported not only increased recruitment of left hemisphere regions after rTMS, but also a shift of activity from anterior regions of the right IFG (i.e., *pars triangularis*) to more posterior regions (i.e., *pars opercularis*). Analysing resting-state functional connectivity pre- and post-treatment, Lin et al. (2022) reported changes in the language network both in left and right hemispheres in patients with chronic aphasia. In the right hemisphere, the experimental group showed a decrease in coupling strength between *pars triangularis* and *pars opercularis*, whereas an increase in connectivity between these two areas was seen in the control group. These authors also found a strengthening in the connections between the right *pars opercularis* and the angular gyrus, as well as between the right superior temporal gyrus and the caudate nucleus. In the left hemisphere, they found an increase in the strength of coupling of Wernicke's area with the *pars orbitalis* and the angular gyrus. Improvements in various items of the language test correlated with changes in connectivity in these regions. Likewise, Lee et al. (2022) reported an increase in the spontaneous neuronal activity – measured by fractional amplitude of low-frequency fluctuations (fALFF) – in the right STG, right caudate nucleus, right insular cortex, and right dorsolateral prefrontal cortex (BA46) in the experimental group. In contrast, spontaneous neuronal activity decreased for the right thalamus and left superior parietal cortex. The clusters showing increased activity after rTMS stimulation were in the right frontotemporal cortex, the insular cortex and the caudate. As in the previous cases, these changes in brain activity correlated with improvements in language. In a similar vein, the study by Bai et al. (2022) found a decrease in fALFF in multiple regions of the right hemisphere, such as the dorsolateral superior frontal gyrus, the supplementary motor area, and the *pars opercularis* of the IFG, in the group subjected to rTMS treatment. Likewise, the measure of the degree of centrality increased in different regions such as the left parietal lobe, the left frontal lobe (area BA6, middle and superior frontal gyrus, supplementary motor area and paracentral lobe) and the bilateral limbic lobe (cingulate gyrus), indicating an increase of activity in these regions. Similarly, the authors found an increase in functional connectivity between the left frontal lobe (the supplementary motor area) and the right temporal lobe (medial temporal gyrus), suggesting that the connection between these regions became more robust after treatment.

Based on the assumptions explained about language reorganisation, 4 of the reviewed studies analysed the effects of directly exciting ipsilesional regions. Thus, Dammekens et al. (2014) used a high-frequency rTMS (10 Hz) paradigm, applied on the left IFG in a subject with chronic non-fluent aphasia. They found an improvement in repetition, naming, and comprehension immediately after applying rTMS. The improvements in repetition and naming were maintained 4 months post-treatment. Compared to the baseline condition, post-rTMS EEG revealed a reduction in the activation of the right IFG and normalisation of the left IFG, with an increase in functional connectivity between the two regions, both for the beta3-frequency band. An increase in activity was also shown in the right supplementary motor cortex for the same frequency band. Similarly, excitatory rTMS (5 Hz) was applied to the left IFG in a patient with conduction aphasia in the subacute phase, showing a significant improvement at 2 weeks post-treatment, which was increased at 2.5 months (Zhang et al., 2017). Furthermore, Zhang et al. (2017) found increased fractional anisotropy in the left STG, as well as higher post-treatment activation in perilesional areas, such as the IFG, precentral gyrus, postcentral gyrus, middle frontal gyrus, middle temporal gyrus and inferior parietal lobe, compared with the right hemisphere. Likewise, Fahmy and Elshebawy (2021) applied an excitatory stimulation (10 Hz) to Broca's area (*pars triangularis* and *pars opercularis*) of the left IFG in patients with chronic aphasia of diverse severity. They found a significant increase immediately and after one-month post-treatment in global language test scores, as well as in repetition, comprehension, spontaneous speech and writing components. Also, Chang et al. (2022) used an excitatory rTMS (10 Hz) over the left hemisphere in patients with non-fluent aphasia but, unlike the previous studies they selected the most appropriate area for each subject assessed by functional near-infrared spectroscopy (fNIRS) during the performance of a language task – i.e., the most activated ipsilesional area. They found significant improvements in language immediately after the 10 intervention sessions, but these improvements were not sustained at one month. In addition, analysis of pre- and post-intervention fNIRS data showed an increased strength of connectivity in the language areas as well as the clustering coefficient; but, again, only immediately after treatment.

Khedr et al. (2014) hypothesised that prior application of inhibitory rTMS to the right hemisphere might increase the effects of excitation on the ipsilateral hemisphere (the neural basis is explained below). Thus, they examined the benefits of a bi-hemispher-

ic stimulation paradigm in patients with fluent or mixed aphasia in the subacute phase. Low-frequency rTMS (1 Hz) was applied to the right IFG (500 pulses over the *pars triangularis* and 500 pulses over the *pars opercularis*), followed by high-frequency rTMS (20 Hz) to the left homonymous region (5 trains over the *pars triangularis* and 5 trains over the *pars opercularis*). This methodology led to a significant improvement in global language test scores, which were maintained 2 months after stimulation. These changes in language scores correlated with an increase in left hemisphere excitability, as measured by active motor threshold and resting motor threshold.

Although much of the research has focused on inhibiting right hemisphere activity – because the lesion was in the left hemisphere –, other studies have aimed to apply excitatory frequencies on regions homotopic to those of language. For example, Hu et al. (2018) carried out a study in which subjects with chronic non-fluent aphasia were randomly assigned to receive high-frequency rTMS (10 Hz), low-frequency rTMS (1 Hz), or sham stimulation (sham-group) on the right IFG for 10 sessions. Another group (control group) only received speech therapy. The results of the study showed a significant difference in language performance in favour of the inhibitory rTMS group, both immediately after and one month after treatment. The group receiving excitatory rTMS only showed improvement over the control group, with no significant difference compared to the sham group.

Hara and colleagues (2015, 2017) used functional magnetic resonance imaging (fMRI) or functional near-infrared spectroscopy (fNIRS) to select the most appropriate stimulation paradigm. Thus, in subjects with chronic aphasia, they analysed the effects of applying inhibitory stimulation (1 Hz) to the contralateral hemisphere to the one identified as the compensatory hemisphere for language in each individual. In subjects with non-fluent aphasia, the target area was IFG, whereas STG was stimulated in subjects with fluent aphasia. In cases in which either the left or right hemispheres were inhibited, significant improvements in linguistic performance were reported. Nevertheless, only for the group in which rTMS was applied to the left hemisphere, changes in total language scores correlated with changes in the lateralisation index in one of the regions of interest, the *pars opercularis* (Hara et al., 2015). Following the same methodology as in the previous study, inhibitory rTMS (1 Hz) applied over the right IFG in subjects with left-side language, or excitatory rTMS (10 Hz) over the same area in subjects with the right hemisphere identified as the compensatory hemisphere also showed significant improvements. In this case, pre- and post-intervention

fNIRS analysis showed a resolution in the imbalance of interhemispheric inhibition in the group receiving inhibitory stimulation as well as increased activation in the stimulated area in the group receiving excitatory rTMS (Hara et al., 2017).

Among the studies, other variables related to stimulation parameters and the methodology of rTMS application have been examined. For example, a relationship was found between the amount of stimulation –1 or 2 sessions per day – and the increase in linguistic competence. In their study, Bai et al. (2021) found better scores on language measures in subjects who received two daily sessions of rTMS compared to a group that only received one session a day. Similarly, whereas most studies apply speech and language therapy subsequently to rTMS, Wang et al. (2014) reported that performing synchronised naming tasks (on-line model) could increase the benefits of such stimulation.

Finally, the effect of rTMS on neurotrophins have also been addressed. Thus, Mirowska-Guzel et al. (2013) and Bai et al. (2021, 2022) investigated the changes in serum level of brain-derived neurotrophic factor (BDNF) – related to plasticity and neural repair functions – associated with the administration of rTMS and the improvement in language skills. While the former authors observed a decrease in serum BDNF levels associated with the application of rTMS and no difference between subjects who improved and those who did not, Bai and colleagues reported an increase in the BDNF associated with the treatment (Bai et al., 2021, 2022), and these levels correlated with the amount of stimulation applied (Bai et al., 2021).

Use of rTMS in the Treatment of PPA

Only 3 studies were found that analyse the effects of rTMS on PPA: 2 case studies and 1 clinical trial.

Both case studies evaluated the effects of rTMS on a logopenic variant of PPA. In the first one, Trebbastoni et al. (2013) applied high-frequency rTMS (20 Hz) on the left dorsolateral prefrontal cortex (DLPFC). The subject underwent 2 stimulation cycles of 20 minutes, for 5 days, with an inter-cycle interval of 14 days, administering 1500 pulses per session, and for a total duration of 69 days. The results revealed a significant improvement in language skills – phonemic verbal fluency and written language – 24 hours after stimulation. However, these benefits tended to disappear 7 days later. In the second case, to improve on the results of the previous one, Bereau et al. (2016) administered excitatory rTMS (10 Hz) by increasing the number of pulses delivered (2000 pulses per ses-

sion) and implementing concomitant speech therapy. The stimulated area was also the DLPFC. They found improvements in cognitive and language tasks immediately after the end of the treatment, including speed of processing and lexical access tests, the Mini-Mental State Examination (MMSE) and free memory recall. Some of these improvements were maintained 3 months after stimulation. Furthermore, analysis of SPECT data showed increased left cortical and basal perfusion one month after the rTMS.

The randomised clinical trial we found evaluated the effects of rTMS on the remaining two types of PPA – i.e., non-fluent and semantic variants (Pytel et al., 2021). In this study, participants received stimulation in the most appropriate region in each case. For this purpose, the study included a pre-treatment phase in which both inhibitory and excitatory rTMS were applied to different brain regions according to clinical variants of PPA and neuroimaging findings. The inhibitory protocol was tested only in right hemisphere regions. The target region selected for each patient was the one for which, when stimulated with rTMS, the best results were obtained in a series of language tasks. Finally, excitatory rTMS (20 Hz; 1500 pulses per session, 15 sessions) was chosen as treatment, and the regions targeted for its application were: left IFG (9 patients with non-fluent variant), left STG (3 patients with non-fluent variant), left DLPFC (1 patient with non-fluent variant and 5 with semantic variant), right superior frontal gyrus (1 patient with non-fluent variant) and left anterior temporal lobe (1 patient with semantic variant). The authors found higher improvements in spontaneous speech, reading accuracy, repetition of syllables and pairs of syllables and picture-object naming for the rTMS group immediately after treatment, as well as an amelioration in depression and apathy scores. Furthermore, no significant differences in treatment effects were found between the two types of PPA. For the rTMS group, positron emission tomography (PET) images showed increased metabolism after treatment in different cerebral regions, including the left middle and superior temporal gyrus, supramarginal gyrus, and superior and inferior parietal lobes; precuneus and posterior cingulate; left inferior frontal, medial frontal, and precentral gyrus; bilateral superior and medial frontal gyrus, and supplementary motor area; and left thalamus, insula, midbrain, and cerebellum (Pytel et al., 2021).

rTMS is a neurophysiological technique that allows the modulation of aberrant brain plasticity mechanisms that occur during a neurological condition (Burke et al., 2019). Therefore, it is essential to consider the brain substrate underlying a given disorder to select the most appropriate stimulation protocol.

Application of rTMS in PSA

Most of the research on the application of rTMS in PSA has focused on inhibiting the contralesional hemisphere and restoring left hemispheric activity, considering that right hemisphere activation is counterproductive for adequate language recovery and based on paradoxical functional facilitation and/or the interhemispheric inhibition theory. This theory, derived from the motor cortex literature (Turkeltaub, 2015), postulates that when the left hemisphere is injured, the inhibition it exerts on the right hemisphere is reduced or released, resulting in an ‘overactivation’ of the right hemisphere. In turn, the ‘overactivated’ right hemisphere may develop inhibition over the perilesional areas of the left hemisphere, preventing them from taking over language functions and, consequently, adequate language recovery (Anglade et al., 2014; Hamilton et al., 2011; Turkeltaub, 2015). Thus, it has been hypothesised that the application of inhibitory rTMS on the right hemisphere could not only reduce a possible detrimental overactivation in this hemisphere, but also indirectly facilitate the activity of the injured left hemisphere (Heiss et al., 2013; Ren et al., 2019; Bai et al., 2022; Lin et al., 2022).

Many of the studies included in this systematic review performed a treatment protocol used in the pioneering work of Naeser and collaborators (Martin et al., 2004; Naeser, Martin, Nicholas, Baker, Seekins, Helm-Estabrooks et al., 2005; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi et al., 2005), with the same (or similar) stimulation parameters – 1 Hz frequency, 20-minute sessions, and 2-week treatments with 5 weekly sessions – and applying stimulation to a specific part of the region homotopic to Broca’s area: the *pars triangularis* in the IFG (Table 1). Naeser’s group first established that this region received the greatest benefit when inhibited, as opposed to other regions of the right hemisphere, such as the *pars opercularis* in the IFG, STG and motor cortex (Martin et al., 2004). Although this paradigm was initially established to favour naming in subjects with non-fluent aphasia in chronic phase (Martin et al., 2004), the literature shows that it can be beneficial in other types of aphasia, both non-fluent and fluent (Heiss et al., 2013; Rubi-Fessen et al., 2015; Thiel et al., 2013), and in different phases after stroke, finding improvements that expand to multiple linguistic components beyond naming, such as repetition (Rubi-Fessen et al., 2015; Tsai et al., 2014), comprehension (Barwood et al., 2013; Lin et al., 2022; Rubi-Fessen et al., 2015; Thiel et al., 2013) or written language (Rubi-Fessen et al., 2015; Thiel et al., 2013).

While the *pars triangularis* of the IFG has been the predominant region selected among the paradigms

that inhibit the right hemisphere, good results have also been obtained from inhibiting other regions homotopic to those of language. In the study by Ren et al. (2019), the application of inhibitory rTMS in the STG has led to improvements in subacute global aphasia. Hara et al. (2015) also found benefits of inhibiting this region in subjects in chronic phase with fluent aphasia and with the left hemisphere compensating after the lesion. Similarly, inhibition of other regions of the right inferior frontal lobe, such as the *pars orbitalis*, may yield better results than suppression of the *pars triangularis*, in some cases (Harvey et al., 2017). These data suggest that inhibition of the region homotopic to Wernicke’s area and other regions within the IFG, could be beneficial. However, given the small number of studies that select these regions, no robust conclusions can be drawn about the benefits of applying inhibitory rTMS over STG or *pars orbitalis*.

With the same purpose of restoring premorbid activity, some studies have focused on stimulating the ipsilateral hemisphere by applying excitatory rTMS, also reporting positive results in language performance (Dammekens et al., 2014; Zhang et al., 2017; Fahmy and Elshebawy, 2021; Chang et al., 2022). However, there is considerably less research on the application of ipsilateral excitatory paradigms than protocols that inhibit the right hemisphere. The limited use of such paradigms could be due to several reasons. On the one hand, applying excitation to epileptogenic tissue may increase the risk of inducing seizures (Turkeltaub, 2015). Applying rTMS to the injured hemisphere requires not only localising the region where there is no encephalomalacia, but also detecting the region that has been recruited to perform a specific function (Thiel et al., 2013; Turkeltaub, 2015; Chang et al., 2022). Chang et al. (2022) employed functional neuroimage scans to select the target area to be stimulated (Broca’s, Wernicke’s, or adjacent regions). In contrast, Fahmy and Elshebawy (2021) applied rTMS over the left Broca area in a large sample of subjects. They observed that large-size infarctions were associated with poorer language performance than small-size infarctions, and consequently, a more significant improvement was found following rTMS application. Although they applied previous structural neuroimaging tests, it was not clear whether Broca’s area remained structurally preserved in all the individuals and with the capacity to reacquire its function or whether subjects in whom this region was damaged had recruited other perilesional regions to develop language functions. In this case, subjects with a lesion directly affecting Broca’s area might benefit more from activating other healthy ipsilesional regions. Given the limited number of studies using ex-

citatory protocols on the left hemisphere, more information is needed to ensure treatment benefits.

These protocols do not appear to be mutually exclusive, and authors such as Khedr et al. (2014) have tested the effects of applying an inhibitory protocol to the right hemisphere, followed by an excitatory protocol to the left hemisphere. Although, we cannot determine whether it is more effective than applying both protocols separately, this study opens up doors to the design of treatments in which more than one stimulation paradigm is used.

Although previous evidence suggests that the recruitment of homotopic regions of the right hemisphere favours language restoration in some instances, few studies have focused on analysing the benefits of stimulation facilitating the activity of this hemisphere. Studies such as that of Hu et al. (2018), in which excitatory rTMS was applied to the right IFC in subjects with chronic aphasia, did not observe language performance improvements compared to the inhibitory rTMS group and the sham group, while others reported good results when favouring the activity of this hemisphere in individuals who had adopted it as compensatory for language after the lesion (Hara et al., 2015, 2017). These data support the theory that the activation of certain regions homotopic to those of language is not counterproductive in all cases, and protocols that facilitate their activation could be a potential treatment.

Several of the studies included in this review incorporate complementary neuroimaging techniques to analyse the changes in activation and/or connectivity following rTMS administration and how this network restructuring may relate to linguistic improvements (Table 1). We can highlight different aspects of the neuroimaging data. First, the neurobiological explanation of the benefits of applying an inhibitory paradigm in homotopic regions is not limited to a decrease in activity in the stimulated hemisphere and a shift of activity to ipsilesional regions. Although studies choosing to inhibit right hemisphere regions report a re-lateralisation of language towards the language dominant left hemisphere (Heiss et al., 2013; Thiel et al., 2013; Hara et al., 2015, 2017; Harvey et al., 2017; Bai et al., 2022), supporting the theory of interhemispheric inhibition, the process of network restructuring that takes place after the application of rTMS is more complex. Thus, in some studies that applied inhibitory rTMS over the right IFG, the suppression of this region caused the reorganisation of the network recruited in this hemisphere, with the increased involvement of regions such as the *pars opercularis*, the superior temporal gyrus, the caudate nucleus, the insular cortex or the dorsolateral pre-

frontal cortex (Harvey et al., 2017; Lee et al., 2022; Lin et al., 2022). Studies that have directly applied excitatory rTMS to the left hemisphere have reported an increase in ipsilesional activity along with a decrease in right hemisphere involvement (Dammekens et al., 2014; Zhang et al., 2017; Chang et al., 2022). This is in line with the premises of language retrieval and the interhemispheric inhibition theory. However, studies such as that of Dammekens et al. (2014) have also found increased activation in right-hemisphere regions following treatment, in this case in the supplementary motor cortex, which may explain part of the improvements found. Therefore, further studies are needed that analyse in depth the network changes resulting from the focal application of rTMS (e.g., through functional connectivity measures) and how these changes affect language.

Also, these neuroimaging data, together with those reported for facilitating right hemisphere activity (Hara et al., 2015, 2017), add evidence suggesting that, while restoration of activity in the injured hemisphere is important for a good recovery, recruitment of the right hemisphere may be beneficial for the development of some language functions. Therefore, further studies are needed to analyse the benefits of rTMS in promoting activation in other regions of the right hemisphere, such as those mentioned above.

As discussed above, many individual variables influence brain reorganisation after stroke; consequently, the type of stimulation that will benefit each subject needs to be considered. While standard paradigms such as those previously mentioned have proven benefits at the group level (Seniów et al., 2013; Heikkinen et al., 2019; Lopez-Romero et al., 2019), at the individual level, all subjects may not have improved. For example, Khedr et al. (2014) found that 5 cases did not benefit from the left hemisphere activation recovery protocol. These authors suggest that patients with a complete middle cerebral artery occlusion may benefit more from a right hemisphere excitatory stimulation paradigm, given that Broca's area is severely damaged. Similarly, Zumbansen et al. (2020) found that *pars triangularis* inhibition was only effective in patients with intact Broca's area. Patients with this region compromised not only did not benefit from rTMS treatment but also showed a worse evolution than subjects with Broca's area lesion treated only with conventional speech therapy. These results seem to be in line with Heiss and Thiel's previously described model (Heiss and Thiel, 2006). In contrast, studies such as that of Fahmy and Elshebawy (2021) found that the subjects who benefit most from excitation in the left Broca area are those with a larger lesion in the left hemisphere (lesion > one lobe). The

authors attribute this higher percentage of change to the fact that subjects with a massive left infarct have lower initial scores on the applied scales than subjects with small infarcts, leading to a broader range of potential improvement than those with higher initial language performance. However, this contradicts previous literature suggesting that subjects with more extensive left hemisphere lesions tend to recruit the right hemisphere as compensatory (Heiss and Thiel, 2006) and might benefit more from excitatory treatments on the right hemisphere. Nevertheless, as previously mentioned, it was not specified whether Broca's area remained preserved in all subjects despite extensive left hemisphere lesion occupation.

Another factor to be considered is the phase in which rTMS is applied. Although, according to the study of Saur et al. (2006), the recruitment of the right IFG might be beneficial in the subacute phase of the PSA, the included studies inhibiting the *pars triangularis* of the IFG in this phase report improvements related to the application of rTMS (Table 1) and no study reports an effect of rTMS that works against the spontaneous recovery that occurs in this phase. Furthermore, Zumbansen et al. (2022) compare the effects of rTMS in the subacute versus chronic phase, finding only significant benefits associated with treatment in the subacute phase. The results of the latter study are in line with those reported in a recent meta-analysis, which states that the effect of rTMS is quantitatively greater in the subacute phase than in the chronic phase (Hong et al., 2021). Together with the results of the neuroimaging tests used in Heiss et al. (2013), Thiel et al. (2013), and Bai et al. (2022), where the changes in activation in favour of the left hemisphere are greater in the experimental group than in the control group, it could be hypothesised that applying rTMS in the subacute phase would accelerate this restoration of activity in the language areas and, consequently, the recovery of function. Nevertheless, it is important to note the period within the subacute phase in which stimulation is applied. A broad window of time from one week after the stroke to 6 months is considered (Hartwigsen and Saur, 2019). Thus, it is likely that the effects of rTMS are not the same in the earlier phases – where the mechanisms of injury are still in the process of resolving (Anglade et al., 2014) – as in the later phases. In the early phases, there may be a greater compensatory involvement of the right hemisphere (Turkeltaub, 2019). This would explain why the study of Saur et al. (2006), in which brain activity measurements were taken very early in the subacute phase, found activation of the right hemisphere to be beneficial, whereas studies using inhibitory rTMS in which the treatment start later (Bai et al., 2022; Zumbansen

et al., 2020), found improvements. In the case of the study by Zumbansen et al. (2020), in which the range of treatment initiation in subjects ranges from 5 to 45 days after stroke, it would be relevant to analyse whether subjects who started treatment earlier benefited from it, or, if not, to analyse how much time needs to elapse before starting treatment. In relation to excitatory paradigms, it should be considered that applying high-frequency rTMS to the ipsilesional hemisphere early after injury may produce overstimulation and excitotoxicity, resulting in counterproductive recovery (Fahmy and Elshebawy, 2021).

Given the intricate complexity of the variables involved in reorganisation processes after stroke, the development and implementation of therapeutic protocols that consider the idiosyncrasies of each individual could represent an advantage over standardised paradigms. In this line, some studies have made attempts to adapt the stimulation paradigm to certain characteristics of the subjects, like the region that best responds to stimulation in terms of linguistic improvement (Harvey et al., 2017), the compensatory hemisphere for language (Hara et al., 2015, 2017), the regions within a hemisphere identified as compensatory (Chang et al., 2022) or the typology of aphasia – fluent or non-fluent (Hara et al., 2015). These studies have reported good results but, given the heterogeneity of the samples and the variability in clinical assessment tests, it is difficult to conclude whether these improvements are quantitatively greater than those found after applying a standard paradigm. It would also be necessary to analyse whether the differences of applying an individualised paradigm are significant enough compared to the application of a standardised protocol to compensate for the added cost of a complementary targeting procedure to the treatment, either a functional neuroimaging technique or using the stimulation itself. Similarly, more research is needed to analyse which pre-treatment techniques are best suited to select the ideal stimulation region.

Application of rTMS in PPA

The number of studies that use rTMS in PPA is limited. The case studies of Bereau et al. (2016) and Trebbastoni et al. (2013), both addressing the logopenic variant, selected the DLPFC as the stimulation target. While the DLPFC does not form the atrophy map characteristic of the logopenic variant (Montembeault et al., 2018; Roytman et al., 2022), it has been shown that functional connectivity in the lateral prefrontal cortex may be compromised in some cases (Whitwell et

al., 2015). The DLPFC is not considered a major nucleus in anatomofunctional models of language. However, it is involved in a broad variety of linguistic processes, presenting connections in the two pathways that make up the language network (i.e., dorsal and ventral) (Hertrich et al., 2021). This would explain the improvements observed in the included studies (Trebbastoni et al., 2013; Bereau et al., 2016). These two studies are in line with previous reviews about the use of non-invasive brain stimulation techniques in PPA (Nissim et al., 2020; Norise and Hamilton, 2017). That is, the treatment is based on the premise that patients continue to use pre-existing neural areas whose efficacy is progressively decreasing. Therefore, facilitating the activity of these weakened networks could be beneficial (Norise and Hamilton, 2017).

The recent study by Pytel et al. (2021) – focused on non-fluent and semantic variants – represents an advantage over previous research on the treatment of PPA, and it is the first to design a personalised rTMS protocol and integrate a PET scan that assesses changes in activation after treatment. Likewise, given that in the pre-treatment phase, it tests the efficacy of inhibitory protocols over right-hemisphere regions, the study considers a possible bi-hemispheric reorganisation of language. As in the case of PSA, the over-activation of contralateral regions could be ‘maladaptive’ in PPA, an issue previously suggested by some studies (Vandenbulcke et al., 2005; Nelissen et al., 2011). However, the ineffectiveness of applying inhibitory protocols in regions of the right hemisphere – glimpsed in the pre-treatment phase – compared to the observed efficacy of stimulating other regions, together with the increased activity in certain regions observed in the post-treatment PET, do not support such a premise. The over-activation of the right hemisphere would occur when damage to the left hemisphere is widespread, with the contralateral hemisphere being able to take over language tasks, although inappropriately (Heiss and Thiel, 2006). Thus, in contrast to the biphasic course of activation that takes place in the right hemisphere in stroke, a monophasic increasing course might occur in PPA, whereby patients could benefit more from excitatory paradigms in the right hemisphere.

These results suggest that, in contrast to PSA – where the use of inhibitory rTMS in the contralateral hemisphere has prevailed – the application of excitatory rTMS protocols in the ipsilateral hemisphere, seems to be more indicated in PPA.

Finally, given that the application of rTMS to treat PPA is an underexplored field, many questions still need further investigation. First, whereas in PSA the changes achieved with stimulation seem to be sustained over time after a relatively short period

of treatment (Barwood et al., 2013; Tsai et al., 2014; Harvey et al., 2017; Zumbansen et al., 2020), the data we have for PPA are inconclusive. Of the two studies using longitudinal language assessment (Bereau et al., 2016; Trebbastoni et al., 2013), only the study of Bereau et al. (2016) reported improvements that were maintained up to 3 months, whereas in the case of Trebbastoni et al. (2013), they disappeared 7 days after stimulation. In the case of PPA, it is not possible to achieve such long-lasting changes, and periodic rTMS treatments are required. For this reason, longitudinal studies are needed to analyse the persistence of the effects of stimulation, as well as the periodicity with which treatment would be required. In this line, regions that previously responded to stimulation may cease to do so when the structural damage becomes more severe. Therefore, it may be necessary to adapt the stimulation targets as the disorder progresses (Pytel et al., 2021). In contrast to PSA, where functional changes appear as a consequence of structural damage, in PPA, the disruption in functional connectivity may occur before the onset of atrophy (Bonakdarpour et al., 2017) and even before the manifestation of clinical symptomatology (Lee et al., 2019). The implementation of tools for early diagnosis, together with the use of neuroimaging techniques that allow glimpses of changes in functional connectivity, could allow PPA to be addressed from early stages.

Furthermore, in the case of PPA, the application of rTMS could have a dual function: on the one hand, to modulate the processes of neuronal plasticity and, on the other hand, to act on the progression of degeneration (Sanches et al., 2021). As it has been suggested that disruptions in connectivity in intact regions of the functional network could predict the progression of the atrophy (Tao et al., 2020), it could be interesting to deepen knowledge on the directionality of the interdependence between functional connectivity and atrophy (Wilson et al., 2016) and to explore the possibility of modifying the progression of atrophy through changes in functional connectivity achieved with rTMS.

Finally, from a molecular perspective, another variable that is relevant in the case of PPA is the different pathology underlying each syndrome, as altered proteins may have a different pattern of deposition in brain tissue. For example, the Tau protein is the pathology most characteristic of non-fluent PPA and appears to affect the white matter more than the grey matter (Bonakdarpour et al., 2019). This may influence not only the mechanisms of plasticity but also modify how the rTMS-induced current is distributed throughout the brain and, therefore, the effects achieved by the treatment. In a similar vein, another point to consider is the possibility of increased deposition of

the underlying proteinopathy by increasing neuronal activity, something that has been questioned in other pathologies such as Alzheimer's disease (Weiler et al., 2020). In this respect, longitudinal clinical trials with a control group in which molecular neuroimaging techniques are implemented would be of relevance.

CONCLUSIONS

In PSA, the selection of a stimulation paradigm has been based on bi-hemispheric functional reorganisation models, with a clear tendency towards right-hemisphere inhibition. In PPA, research is focused on re-establishing activation and connectivity in the affected areas by applying excitatory stimulation paradigms.

In this review, we focus on analysing those neuro-anatomical and neurofunctional aspects that differentiate the PSA and PPA and how this influences the application of an rTMS stimulation protocol. However, clinical aspects, such as improvements in the different language processes and sub-processes, the assessment tests used, the type of concomitant speech therapy, etc., are not detailed. For a more exhaustive review on these subjects, the the systematic review of Kidwai et al. (2022) for rTMS in PSA may be of interest to the reader.

We believe that the future of rTMS as a treatment for PSA and PPA relies on its better assessment rather than on the standardisation of treatment. Given the large number of factors that influence neuronal plasticity, the implementation of personalised protocols both in PSA and PPA that bridge existing inter-individual differences could be an advantage over standardised treatments.

Similarly, it is worth noting the extent of the effect of applying focal stimulation across neural networks. The effects of applying rTMS exceed the focal activation/inhibition heuristic of the stimulated region (Beysel et al., 2020), and changes can be found along the networks that are not consistent with the directionality of the type of stimulation used (i.e., facilitation or suppression). Therefore, increasing our knowledge of how rTMS acts on the neural substrate and brain networks would be helpful to select the appropriate paradigm.

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