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# Stimulations magnétiques transcrâniennes et aphasie chronique post-AVC : individualisation et modifications électrophysiologiques induites

Sophie Arheix-Parras

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POUR OBTENIR LE GRADE DE

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Par Sophie ARHEIX-PARRAS

**Stimulations magnétiques transcrâniennes  
et aphasie chronique post-AVC :  
individualisation et modifications électrophysiologiques induites**

Sous la direction de : Bertrand GLIZE

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## Liste des abréviations

AVC : Accident Vasculaire Cérébral

EBP : pratiques fondées sur les preuves / *Evidence-Based Practice*

EEG : Electroencéphalographie

Gev : variance globale expliquée / *Global explained variance*

GFP : puissance de champ global / *Global Field Power*

IFG : gyrus frontal inférieur / *Inferior Frontal Gyrus*

IRMf : Imagerie par Résonance Magnétique fonctionnelle

MEG : Magnétoencéphalographie

NIBS : Stimulations Cérébrales Non Invasives / *Non Invasive Brain Stimulation*

PEM : Potentiel Evoqué Moteur

RMT : seuil moteur de repos / *Resting Motor Threshold*

rTMS : stimulations magnétiques transcrâniennes répétées / *repetitive Transcranial Magnetic Stimulation*

SCED : études en cas uniques / *Single Case Experimental Design*

## Introduction

L'aphasie est un trouble du langage qui fait suite à une lésion cérébrale acquise, comme un Accident Vasculaire Cérébral (AVC) ou un traumatisme crânien. Elle impacte les versants de la production et/ou de la compréhension du langage, à l'oral et/ou à l'écrit. Ce trouble se caractérise ainsi par un continuum très large allant de l'impossibilité totale à parler et à comprendre, jusqu'à un discours fluent ponctué de quelques épisodes de manque du mot. En atteignant notre capacité à communiquer, l'aphasie pourra avoir un impact majeur sur la qualité de vie de la personne qui en est victime, en limitant ses activités et en restreignant sa participation au sein des sphères sociale, familiale et professionnelle (Lam & Wodchis, 2010; Lee et al., 2015). Les répercussions fonctionnelles dépendront de la sévérité du trouble, mais les aphasies dites « légères » pourront également induire un impact majeur au quotidien, notamment en fonction de l'utilisation prémorbide du langage (e.g., avocat en activité, parent d'enfant en bas âge). Les capacités langagières pourront évoluer avec la récupération, mais elles s'inscriront dans le temps pour une partie des personnes touchées (Pedersen et al., 2004). De par son impact important, parfois dévastateur, et sa prévalence, évaluée entre 7 et 77% en post-AVC (pour une revue, voir Frederick et al., 2022), l'aphasie constitue un enjeu de santé publique majeur.

Si le traitement de référence pour la récupération de l'aphasie post-AVC est l'orthophonie (Brady et al., 2022), les stimulations cérébrales non invasives, telles que les stimulations magnétiques transcrâniennes répétées (en anglais, repetitive Transcranial Magnetic Stimulation : rTMS), constituent de nouvelles pistes pour optimiser la récupération (Arheix-Parras et al., 2021; Biou et al., 2019). La Haute Autorité de Santé a en effet récemment reconnu l'utilisation de la rTMS comme niveau de preuve scientifique A pour le traitement de l'aphasie post-AVC en phase chronique, au même titre que la rééducation orthophonique à forte intensité (HAS, 2022).

Malgré cette recommandation pour une utilisation de ces stimulations en pratique courante par la HAS, de nombreuses interrogations demeurent au sein de la littérature scientifique, notamment à propos de leur efficacité concernant certains types de troubles phasiques (e.g., aphasies sévères, aphasies fluentes), et la possibilité d'individualiser les protocoles afin d'augmenter les bénéfices langagiers pour les personnes aphasiques (Arheix-Parras et al., 2021). De plus, les mécanismes neurobiologiques sous-tendus par ces stimulations sont encore très peu explorés, notamment par des méthodes d'imagerie à haute résolution temporelle comme l'électrophysiologie. L'électroencéphalographie (EEG) ou la magnétoencéphalographie (MEG), et en particulier l'étude de potentiels évoqués reliés (en

anglais, Event-Related Potential : ERP), sont pourtant les approches les plus pertinentes pour explorer les différents processus se déroulant lors de tâches langagières, grâce à leur grande précision temporelle (Im, 2018).

Nous nous sommes donc interrogés sur l'individualisation et les modifications électrophysiologiques afin de mieux maîtriser et comprendre l'utilisation et l'impact des stimulations magnétiques transcrâniennes dans l'aphasie post-AVC. Quelles sont les possibilités d'individualisation du traitement par rTMS pour la personne aphasique post-AVC, afin d'en améliorer l'impact langagier ? Quelles sont les modifications électrophysiologiques induites par ces stimulations au niveau des tracés de potentiels évoqués dans des tâches de dénomination d'image ?

La partie 1 de ce travail présentera le socle clinique et scientifique de cette thèse. Dans un premier temps, nous allons aborder la récupération de l'aphasie post-AVC, puis nous ferons un état de l'art de l'impact de la rTMS sur ces troubles langagiers acquis (article n°1). Dans un second temps, nous allons aborder l'intérêt de l'EEG et de la MEG dans la recherche sur le langage et ses troubles associés, mais également comme méthodes pouvant mettre en évidence des biomarqueurs prédictifs de la récupération de l'aphasie, voire de bonne réponse à un traitement, à travers une revue systématique d'études longitudinales (article n°2).

La partie 2 illustrera les aspects expérimentaux explorés pour l'individualisation de la rTMS et leur impact comportemental. Nous décrivons les trois études que nous avons menées, qui se sont intéressées à des personnes aphasiques post-AVC présentant des profils langagiers ou lésionnels spécifiques. La première étude traitera de l'impact de la rTMS pour des personnes présentant une aphasie sévère (article n°3). La seconde étude mettra en lumière la possibilité de choix de la cible corticale en fonction du profil clinique de la personne aphasique (article n°4). La troisième étude ciblera une personne au profil atypique présentant une aphasie sévère à la suite d'un AVC hémisphérique droit et les possibilités d'individualisation de son traitement par rTMS en fonction de composantes cliniques, lésionnelles et de latéralité (article n°5).

La partie 3 présentera les aspects électrophysiologiques expérimentaux de cette thèse, et l'impact de la rTMS sur les tracés d'ERPs en tâche de dénomination d'images. Nous évaluerons les différents changements retrouvés et les liens pouvant être fait entre évolution clinique et électrophysiologique.

Enfin, dans la dernière partie de ce travail, nous proposerons une discussion générale, ainsi que des perspectives cliniques et de recherche consécutives à cette thèse.

# **Partie 1. Contexte clinique et scientifique : la récupération de l'aphasie post-AVC**

## **1. Une récupération dynamique, spatiale et temporelle**

La récupération de l'aphasie post-AVC se découpe classiquement en étapes successives, sans limite stricte, comprenant les phases aiguë (première semaine), subaiguë (entre 1 semaine et 6 mois) et chronique (au-delà de 6 mois) (Hartwigsen & Saur, 2019; Stefaniak et al., 2020). Cette dernière phase va être caractérisée par une stagnation des processus de récupération spontanée. Cependant, plusieurs études démontrent l'intérêt de continuer à proposer une intervention lors de cette phase, car les améliorations langagières sont toujours possibles, parfois même à distance de l'événement lésionnel (Rehabilitation and Recovery of People With Aphasia After Stroke (RELEASE) Collaborators, 2021; Smania et al., 2010; Stark, 2010).

Dans les premiers stades aigu ou subaigu, des phénomènes de récupération par rétablissement vont se mettre en place, en vue d'un retour à des processus prémorbides. Les auteurs décrivent notamment la reperfusion des tissus cérébraux situés en périphérie de la lésion par la restauration du flux sanguin (Hillis et al., 2006), et la levée du diaschisis, correspondant à la reconnexion de zones situées à distance de la lésion cérébrale (Carrera & Tononi, 2014).

D'autres phénomènes de réorganisation langagière ou plasticité cérébrale vont permettre de recruter des zones périlésionnelles, voire des aires homologues situées dans l'hémisphère indemne (Hartwigsen & Saur, 2019). Ce recrutement compensatoire va varier et évoluer avec la récupération (Saur et al., 2006). Dans une tâche de jugement sémantique de phrases, Saur et al. (2006) ont observé via Imagerie par Résonance Magnétique fonctionnelle (IRMf), les différences de recrutement de zones cérébrales entre des personnes aphasiques post-AVC et un groupe contrôle: à la phase aiguë, les personnes aphasiques présentaient une diminution de l'activation corticale bihémisphérique ; puis, à la phase subaiguë, une suractivation de ces mêmes zones, avec notamment une forte activation de l'homologue de Broca à droite ; enfin, à la phase chronique, un pattern d'activation similaire aux personnes contrôles, en lien avec une bonne récupération langagière. Ces changements d'activation liés à la récupération langagière pourraient également dépendre du site lésionnel ; une atteinte de la capsule extrême gauche ou du lobe frontal pourraient prédire un recrutement plus important de zones homologues droites (Schneider et al., 2022; Stockert et al., 2020).

Bien que moins explorée, cette dynamique de récupération spatiale a également été retrouvée au niveau temporel dans des études en EEG. En effet, plusieurs études longitudinales de la



même équipe de recherche ont mis en évidence des changements électrophysiologiques en lien avec une amélioration langagière (Laganaro et al., 2008, 2011). Grâce à l'analyse d'ERP dans une tâche de dénomination d'images, Laganaro et al. (2008, 2011) retrouvent une évolution temporelle dynamique du tracé avec des divergences électrophysiologiques entre personnes aphasiques et personnes neurotypiques qui peuvent :

- Soit diminuer avec la récupération, en lien avec une normalisation du tracé ERP et des améliorations langagières ;
- Soit augmenter, voire laisser apparaître de nouvelles divergences, toujours en lien avec des améliorations langagières.

Ces éléments pourraient signer qu'un retour à une activation prémorbide du langage, tout comme une réorganisation des réseaux langagiers, pourraient être signe d'une récupération de l'aphasie.

Ces éléments de changements électrophysiologiques liés à la récupération seront développés plus en détail dans l'article n°2 de cette thèse (Partie 1, 2.2).

## 2. Les stimulations cérébrales non invasives

Les stimulations cérébrales non invasives (NIBS : Non Invasive Brain Stimulation) sont des techniques de neuromodulation qui vont impacter la plasticité cérébrale, dans le but d'améliorer la récupération des troubles du langage post-AVC.

### 2.1. La TMS et la tDCS : généralités

La stimulation magnétique transcrânienne (en anglais, Transcranial Magnetic Stimulation : TMS) est basée sur le principe de l'induction électromagnétique décrit par Faraday en 1831. Un courant électrique est envoyé au sein d'une bobine de cuivre, induisant un champ magnétique en son centre. Placée sur le scalp, ce champ magnétique induit va entraîner un champ électrique au niveau du cortex et une dépolarisation neuronale (Barker et al., 1985; Ridding & Rothwell, 2007). L'envoi d'un pulse électromagnétique au niveau du cortex moteur primaire va pouvoir déclencher un potentiel évoqué moteur (PEM) par l'activation des neurones pyramidaux, qui sera visible par une contraction involontaire du muscle controlatéral (Quartarone et al., 2006). Le seuil d'excitabilité corticale de repos (en anglais, Resting Motor Threshold : RMT) correspond à la puissance à partir de laquelle on déclenche ce PEM. Ce seuil est variable pour chaque personne, et sera notamment dépendant de l'épaisseur des tissus extra-cérébraux (i.e., cuir chevelu, boîte crânienne, méninges) et de l'orientation des neurones par rapport à celle de la bobine (Lefaucheur et al., 2014; Ridding & Rothwell, 2007).

On parle de TMS répétitive (rTMS) lors de l'application d'un protocole de stimulation de plus de deux impulsions consécutives.

La stimulation transcrânienne par courant continu (en anglais, transcranial Direct Current Stimulation : tDCS) consiste à appliquer un courant électrique continu entre deux électrodes (cathode et anode) déposées sur le scalp, au-dessus de cibles corticales préalablement choisies (Nitsche et al., 2003). Cette méthode induit un changement dans le potentiel membranaire de repos, rendant les neurones plus ou moins prêts à déclencher un potentiel d'action (Lefaucheur et al., 2017; Nitsche et al., 2003).

Les mécanismes d'actions de ces deux méthodes sont donc différents. Si la rTMS induit directement une dépolarisation neuronale pouvant entraîner une contraction musculaire involontaire/automatique lorsque le cortex moteur est ciblé (Lefaucheur et al., 2014; Ridding & Rothwell, 2007), la tDCS induira uniquement une modification du seuil de repos membranaire des neurones, les rendant plus ou moins prêts à déclencher un potentiel d'action (Lefaucheur et al., 2017; Nitsche et al., 2003).

## **2.2. Inhibition ou facilitation : différents paramètres de stimulation**

L'utilisation répétée de la TMS ou l'application sur une plus longue période (> 5 min) de la tDCS va pouvoir induire des changements à plus long terme au niveau cérébral, c'est-à-dire une potentialisation ou une dépression à long terme (Quartarone et al., 2006).

Différents motifs fréquentiels peuvent être utilisés en rTMS afin d'induire une inhibition ou une facilitation de la région cérébrale ciblée et des réseaux corticaux, mais également sous-corticaux liés à cette cible corticale (Ridding & Rothwell, 2007). Ainsi, l'utilisation de stimulations de basse fréquence ( $\approx 1\text{Hz}$ ) ou de stimulation Theta Burst Continue (cTBS : continuous Theta Burst Stimulation) induirait une inhibition corticale (Figure 1). Au contraire, l'utilisation de stimulations à haute fréquence (>5Hz) ou de stimulation Theta Burst intermittentes (iTBS : intermittent Theta Burst Stimulation) induirait une facilitation du cortex sous-jacent (Figure 1). Les stimulations Theta Burst les plus couramment utilisées consistent en l'application de 3 pulses à haute fréquence (50Hz), de manière répétée 5 fois par seconde (= 5Hz, correspondant aux rythmes Theta en EEG) (Quartarone et al., 2006).

En tDCS, c'est l'emplacement de l'anode ou de la cathode qui va respectivement induire une facilitation ou une inhibition du cortex sous-jacent (Figure 1) (Lefaucheur et al., 2017; Quartarone et al., 2006).

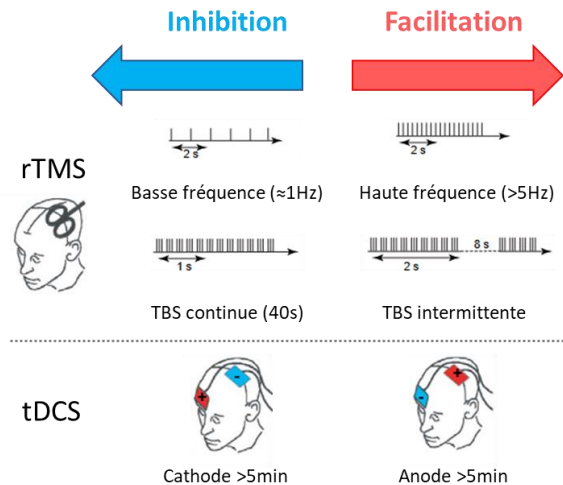


Figure 1 : Stimulations inhibitrices et facilitatrices en rTMS et en tDCS, traduit et adapté à partir de Quartanone et al., 2006

Ces effets inhibiteurs ou excitateurs induits par la rTMS ou la tDCS sont en réalité le résultat d'études sur le cortex moteur. Au sein de ces études, l'excitabilité du cortex moteur a été établie via la mesure de PEM par impulsion unique en TMS, avant et après l'utilisation de différents protocoles de neuromodulation. En fonction de l'augmentation ou de la diminution de l'excitabilité des PEM, les différents effets induits, inhibiteurs ou facilitateurs, ont été établis (Quartarone et al., 2006). Les résultats obtenus au sein de ces études sur le cortex moteur, en lien donc avec la réponse de neurones pyramidaux, ont ensuite été transposés dans différentes zones cérébrales en charge de différentes fonctions cognitives, dont le langage, questionnant d'ores et déjà la validité de cette transposition.

### 2.3. La balance interhémisphérique

Le principe de rééquilibrer la balance interhémisphérique constitue la théorie majoritairement utilisée dans les études en NIBS pour le traitement des troubles résultant d'une lésion cérébrale acquise (Carson, 2020; Stefaniak et al., 2020; Watila & Balarabe, 2015). En effet, on estime que la balance interhémisphérique est déséquilibrée suite à une lésion cérébrale, induisant une suractivation de l'hémisphère préservé induite et consolidée par une hypoactivation de l'hémisphère lésé (Hartwigsen & Saur, 2019). Cette théorie découle également d'études en TMS sur le cortex moteur.

Chez les personnes neurotypiques, l'envoi d'un pulse de TMS au niveau du cortex moteur d'un hémisphère induit une inhibition du PEM de l'hémisphère opposé (Ferber et al., 1992), via le corps calleux, structure liant les deux hémisphères. Lors de tâches utilisant un seul membre, comme la main droite par exemple, cette inhibition transcallosale permettrait de prévenir les mouvements involontaires en miroir de la main gauche (Hübner et al., 2008). En post-AVC, la

lésion cérébrale induirait une diminution de l'excitabilité du cortex moteur de l'hémisphère lésé, diminuant son action inhibitrice sur l'hémisphère indemne, et augmentant en parallèle l'action inhibitrice de l'hémisphère indemne sur l'hémisphère lésé (Carson, 2020; Gerges et al., 2022; Stefaniak et al., 2020). L'objectif dans les études en NIBS est donc de rétablir cette balance interhémisphérique, en utilisant des stimulations inhibitrices au niveau d'aires cérébrales situées dans l'hémisphère indemne, et facilitatrices visant des aires de l'hémisphère lésé (Stefaniak et al., 2020).

Cependant, selon Carson et al. (2020), les méta-analyses actuelles ne montrent pas d'efficacité clinique de l'inhibition de l'hémisphère indemne dans le cadre de la récupération motrice via rTMS ou tDCS. Une méta-analyse plus récente nuance légèrement ces éléments en rapportant des améliorations motrices induites par l'inhibition de l'hémisphère contralésionnel, uniquement retrouvée par tDCS (Veldema & Gharabaghi, 2022). De plus, une autre méta-analyse ne retrouve pas cette hyperexcitabilité supposée de l'hémisphère indemne, chez les personnes cérébrolésés comparativement à des personnes neurotypiques, et ce quel que soit leur stade de récupération (McDonnell & Stinear, 2017). Ces éléments questionnent ainsi la pertinence d'inhiber l'hémisphère indemne dans le cadre de la récupération motrice post-AVC. En outre, le postulat de déséquilibre interhémisphérique pourrait varier en fonction du stade de récupération (subaigu ou chronique) (Carson, 2020; Gerges et al., 2022), notamment si l'on prend en considération la variabilité de l'implication de l'hémisphère indemne au cours de la récupération (Saur et al., 2006). Ensuite, la localisation lésionnelle (sous-corticale notamment), les variations inter-individuelles et cliniques, peuvent aussi questionner ce principe (Carson, 2020; Gerges et al., 2022). Le dernier point de précaution concerne l'applicabilité de cette théorie basée sur le cortex moteur, dans le champ des troubles langagiers post-AVC (Siebner et al., 2022).

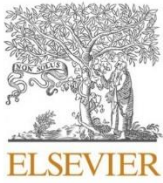
### 3. Aphasie post-AVC et rTMS

#### 3.1. Une revue systématique de littérature

Nous avons réalisé une revue systématique de littérature à propos de l'utilisation de la rTMS dans l'aphasie post-AVC, incluant tout type d'essai clinique, y compris les études en cas uniques, afin d'avoir une vision globale de tous les protocoles qui avaient pu être réalisés.

Cette revue a été publiée en 2021 dans le journal « Neuroscience and Biobehavioral Reviews ».

Article n°1: *A systematic review of repetitive transcranial magnetic stimulation in aphasia rehabilitation: Leads for future studies*



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Review article

## A systematic review of repetitive transcranial magnetic stimulation in aphasia rehabilitation: Leads for future studies

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## ABSTRACT

**Background:** Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive tool that induces neuro-modulation in the brain. Several studies have shown that rTMS improves language recovery in patients with post-stroke aphasia.

**Objective:** This systematic review summarizes the role of rTMS in aphasia rehabilitation.

**Methods:** We searched MEDLINE via PubMed and Scopus on 30 October, 2020, for English articles (1996–2020). Eligible studies involved post-stroke aphasia rehabilitation with rTMS. In some of these studies, rTMS was also combined with speech therapy.

**Results:** In total, seven meta-analyses and 59 studies (23 randomized clinical trials) were included in this systematic review. The methods used in these studies were heterogeneous. Only six studies did not find that rTMS had a significant effect on language performance.

**Conclusions:** The evidence from the peer-reviewed literature suggests that rTMS is an effective tool in post-stroke aphasia rehabilitation. However, the precise mechanisms that underlie the effects of rTMS and the reorganization of language networks in patients who have had a stroke remain unclear. We discuss these crucial challenges in the context of future studies.

### 1. Introduction

Approximately one-third of all patients who have a stroke subsequently experience language difficulties, which are collectively labeled aphasia (Dickey et al., 2010; Pedersen et al., 2004). Aphasia affects patients' functioning, mood, and quality of life, as well as restricting their participation in many activities and their ability to return to work (Carod-Artal and Egado, 2009; Ferro and Madureira, 1997; Mazaux et al., 2013).

This dramatic consequence of having a stroke is due to the disruption

of language networks, usually caused by a left-brain lesion. Recovery from aphasia is driven by spontaneous neuroplastic mechanisms (i.e., structural and functional changes in the brain) and reorganization of neural networks. Involvement of perilesional left hemisphere (LH) regions in linguistic tasks and/or the activation of the non-dominant hemisphere can have a positive or negative effect on neuroplasticity and thus affect recovery (for a review, see Hartwigsen and Saur, 2017). Indeed, lesions in the LH may lead to cortical disinhibition in perilesional structures, thereby increasing activity in the LH areas involved in language, and this perilesional activation may promote recovery

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(Cornelissen et al., 2003; Karbe et al., 1998). However, such lesions may also disrupt inter-hemispheric balance, resulting in neuromodulation (for more details, Biou et al., 2019)).

Patient recovery may be improved by modulating cortical activity in these areas of the brain, particularly the language areas in the LH (i.e., Broca's area, Wernicke's area, and the motor cortex), or decreasing activity in the homologous contralesional areas. Aphasia rehabilitation may be accelerated by non-invasive brain stimulation (NIBS) technologies, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Repetitive TMS (rTMS) has been used successfully to treat paresis, spasticity, pain, neglect, and dysphagia in patients who have had strokes (for a review, see Lefaucheur et al., 2011). tDCS has positive effects on aphasia rehabilitation and is probably the best tool for a routine approach because it is inexpensive, easy-to-use, and safe (for a review, see Biou et al., 2019). However, in addition to its benefits on patient rehabilitation and management, rTMS can stimulate focal modulations and provide accurate spatial resolution, which may also inform research into how language reorganization develops in patients who have had strokes. rTMS also has few contraindications and side effects (Cogné et al., 2017; Lefaucheur et al., 2011).

In 2004, the first studies on using rTMS in aphasia rehabilitation found that inhibitory stimulation (1 Hz) of Broca's homolog had a significant effect in patients with chronic aphasia (Martin et al., 2004; Naeser et al., 2005). Subsequently, many other studies investigated the effects of rTMS on aphasia rehabilitation. In this review, we summarize

the information from studies that have used rTMS to treat patients with aphasia, including randomized clinical trials, prospective studies, case reports, and conference papers. We also discuss some of the challenges for future research.

## 2. Methods

This systematic review followed the PRISMA guidelines ([www.prisma-statement.org](http://www.prisma-statement.org)). We searched MEDLINE via PubMed and Scopus on 30 October 2020, for English articles published from 1996 to 2020. The following words and phrases were used to search titles, abstracts, and keywords: "aphasia" AND "repetitive transcranial magnetic stimulation" OR "rTMS" OR "Non invasive brain stimulation" OR "NIBS". Eligible studies involved post-stroke aphasia rehabilitation using rTMS, with or without speech language therapy (SLT). We excluded articles describing primary progressive aphasia, tDCS, and other neuromodulation tools, as well as studies focusing only on the effects of rTMS in healthy subjects. We also excluded literature reviews, but studies within these reviews were assessed to complete our research. Meta-analyses were considered if they included sub-analyses investigating particular procedures (e.g., frequency, dose-dependent effects, or sub-acute versus chronic post-stroke phases). Restricting our review to randomized clinical trials may not have provided a complete summary of the use and efficacy of TMS in patients with aphasia, so we also included case reports, prospective studies, and conference papers. Two

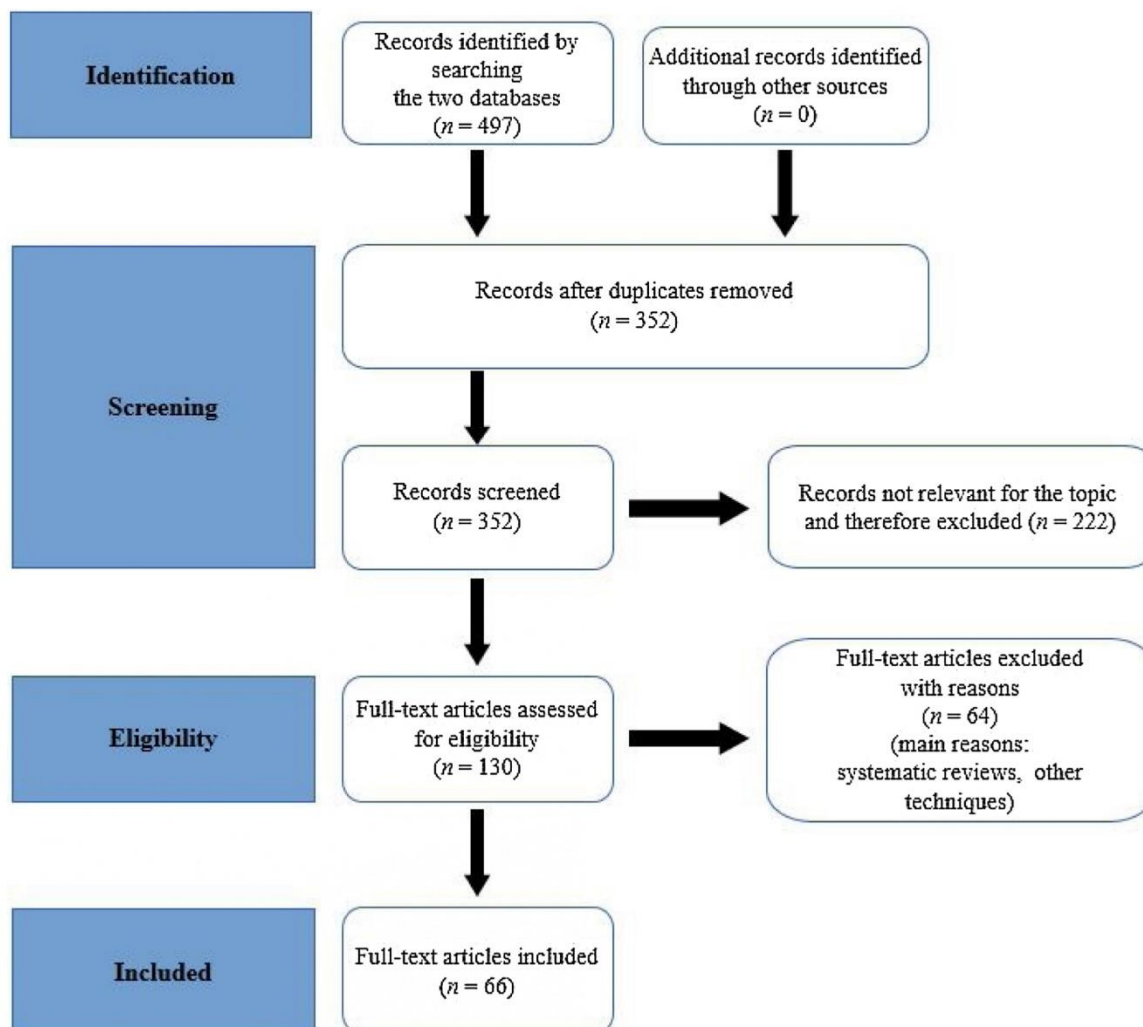


Fig. 1. Flow Diagram. (adapted from PRISMA 2009).

authors (CB and BG) assessed the eligibility of articles. Consensus was achieved by discussion or in consultation with a third author (GM).

### 3. Results

On 30 October 2020, we retrieved 352 articles from our literature search, after removing duplicates. A flow chart describing the articles identified in this study is shown in Fig. 1. We included seven meta-analyses and 59 studies describing the use of rTMS to treat patients with post-stroke aphasia. Among the 59 studies, there were 23 randomized clinical trials (526 patients), 18 prospective studies (213 patients), 17 case reports (28 patients), and one conference paper (11 stroke patients). Moreover, we briefly described one sub-analysis of a randomized clinical trial (Heikkinen et al., 2019). The tables shown in this systematic review summarize the methods and results of the articles listed.

#### 3.1. Randomized clinical trials

Table 1 summarizes the randomized clinical trials we identified and presents the main characteristics and results of these studies.

The methods used in the 23 randomized clinical trials were heterogeneous, with different target areas and various stimulation intensities, frequencies, and durations (Tables 1 and 3). No study found that rTMS had a negative effect on patients with aphasia. Among these 23 studies, four did not find that rTMS had a significant effect on language performance (Heikkinen et al., 2019; Santos et al., 2017; Seniów et al., 2013; Waldowski et al., 2012). All four of these studies used low frequency (LF) rTMS at an intensity of 90 % of the resting motor threshold. The target areas in these studies were the right pars triangularis (PT<sub>r</sub>) (Heikkinen et al., 2019; Santos et al., 2017; Seniów et al., 2013; Waldowski et al., 2012) and also the right pars opercularis (POp) for one study (Waldowski et al., 2012). One study involved a single session of rTMS stimulation, not combined with SLT (Santos et al., 2017). Two studies provided 45 min of SLT in the subacute phase (Seniów et al., 2013; Waldowski et al., 2012), and one study provided 3 h of intensive language-action therapy following the rTMS sessions (Heikkinen et al., 2019). The patients in these four studies had different types of aphasia: Broca's aphasia (21 patients), Wernicke's aphasia (21 patients), mixed aphasia (29 patients), transcortical mixed aphasia (four patients), conduction aphasia (five patients), anomic aphasia (15 patients), and transcortical motor aphasia (one patient).

#### 3.2. Prospective studies and case reports

The methods used in the 36 prospective studies and case reports were also heterogeneous, with different target areas and various stimulation intensities, frequencies, and durations. The 18 prospective studies, 17 case reports, and one conference paper are listed in Tables 2 and 4. No study found that rTMS had a negative effect on patients with aphasia. Among these 36 studies, two did not find that rTMS had a significant effect on language performance (Al-Janabi et al., 2014; Martin et al., 2009a,b). Martin et al., 2009a,b used 10 daily sessions of LF rTMS to target the PT<sub>r</sub>. This treatment was not combined with SLT. Al-Janabi et al. (2014) used excitatory intermittent theta burst stimulation (iTBS) to stimulate the right POp. The three sessions of iTBS were followed by melodic intonation therapy to activate the right hemisphere (RH) of the brain.

#### 3.3. Meta-analyses

All seven meta-analyses included in our systematic review used naming performance as an outcome measure (Table 3). Four of these meta-analyses (T. Li et al., 2020; Y. Li et al., 2015; Ren et al., 2014; Yao et al., 2020) used additional outcome measures, such as auditory comprehension and repetition.

The meta-analysis by Ren et al. (2014) showed that LF rTMS targeting the PT<sub>r</sub> of the right inferior frontal gyrus (rIFG) significantly improved overall language function and language features such as naming, repetition, writing, and comprehension. The following year, Otal et al. (2015) compared studies that investigated inhibition over the contralesional hemisphere using cathodal tDCS and LF rTMS. Analysis of studies that did not distinguish between subacute and chronic post-stroke patients found that rTMS was clinically effective, whereas tDCS was not. Another meta-analysis (Shah-Basak et al., 2016) that did distinguish between chronic and subacute patients found that only TMS was clinically effective in both patient populations. Bucur et al. (2019) analyzed studies that investigated the long-term effects of NIBS (i.e., tDCS and rTMS). These researchers found that NIBS had a significant medium- to long-term effect (from 1 to 6 months post-stimulation) on patients with post-stroke aphasia, and they found that rTMS was significantly more effective than tDCS. Li et al. (2020) analyzed 11 studies that investigated high frequency (HF) and LF rTMS, including one study that used only HF rTMS and one study that used both HF and LF rTMS. This meta-analysis found that rTMS had a significant effect on naming accuracy, but only for subacute patients. Moreover, there was no evidence that rTMS had an effect on repetition or auditory comprehension scores. However, the most recent meta-analysis, performed by Yao et al. (2020), concluded that LF rTMS improved language ability, including repetition and comprehension, in both chronic and subacute patients.

#### 3.4. rTMS procedure: low- vs high frequency stimulation of different brain areas

To restore the balance between the hemispheres and enhance language production, 34 studies inhibited the rIFG, corresponding to the homolog of Broca's area (Tables 1 and 2). Most of these studies used LF stimulation (1 Hz) to suppress the right PT<sub>r</sub>, although some studies also used continuous (c)TBS (Georgiou et al., 2019; Harvey et al., 2019; Kindler et al., 2012; Vuksanović et al., 2015). In addition, four studies (Dammekens et al., 2012; Griffis et al., 2016; Szaflarski et al., 2011, 2018) used HF iTBS to stimulate the left inferior frontal gyrus (lIFG), corresponding to Broca's area. One case report (Al-Janabi et al., 2014) used iTBS to activate the rIFG and stimulate the RH with melodic intonation therapy, with mixed results. A further three studies (Hara et al., 2017; Khedr et al., 2014; Vuksanović et al., 2015) used stimulation to affect both the right (inhibition) and left (excitation) hemispheres of the brain. Most studies reported improvements in spontaneous speech, auditory comprehension, repetition, and naming accuracy. Some studies reported a shift in activation to the ipsilesional hemisphere.

One randomized sham-controlled double-blind study (Ren et al., 2019) investigated changes in language performance after stimulating Broca's and Wernicke's homologs with LF rTMS. Both stimulated groups showed greater improvements in language scores than the sham groups, but inhibition of the right PT<sub>r</sub> improved performance in spontaneous speech and repetition, whereas inhibition of the right posterior superior temporal gyrus led to significantly higher auditory comprehension and repetition scores.

#### 3.5. SLT

Ten randomized clinical trials and 22 other studies used magnetic stimulation only. However, 27 studies combined magnetic stimulation with SLT, generally to activate the LH and improve naming, repetition, writing, and the expression and comprehension of spoken language. Some studies involved particular rehabilitation protocols such as melodic intonation therapy (Al-Janabi et al., 2014), intensive language-action therapy (Heikkinen et al., 2019), or constraint-induced language/aphasia therapy (Martin et al., 2014; Martin et al., 2009, 2018; Martin et al., 2009a,b; Naeser et al., 2012, 2010; Szaflarski et al., 2018). No study has yet compared the difference between benefits of rTMS with



**Table 1**  
Design and results of randomized clinical trials.

Study design	Number of patients, stage (time since stroke), type of aphasia, and lost to follow-up	Procedure: location, duration, and intensity	Number and frequency of sessions	Sham/control condition	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures, and follow-up	Results
Ren et al., 2019 (double blind)	45	rTMS-b group: right PTR			30 min per day.	WAB (spontaneous speech, auditory comprehension, repetition and naming)	Both stimulated groups showed greater improvements in language scores compared to the sham group.
	Subacute (4–12 weeks)	rTMS-w group: right pSTG			Interval from stimulation: immediately after stimulation.	Follow-up: at baseline and immediately after 3 weeks of stimulation.	rTMS-b group: inhibition of the right PTR increased scores for spontaneous speech and repetition.
	Global aphasia	1 Hz 20 min	15 sessions, five times a week for 3 weeks.	Sham stimulation + SLT			
	Lost to follow-up: rTMS-b group = 3 rTMS-w group = 0 sham group = 2 Discontinued intervention: rTMS-b group = 2 rTMS-w group = 0 sham group = 1	80 % RMT			Training: specific training of specific language features (semantic, phonological, syntactic or motor).		rTMS-w group: inhibition of the right pSTG led to significantly higher scores for auditory comprehension and repetition.
Heikkinen et al., 2019 (double blind)	17	Right PTR			3 h/day for a total of 10 days.	WAB, BNT, and ANT.	"ILAT was associated with significant improvement across groups."
	Chronic (> 11 months)	1 Hz	20 sessions, five times a week for 4 weeks, 10 without rehabilitation and 10 combined with ILAT.	Sham stimulation + same behavioral treatment i.e., naming (2 weeks) + ILAT (2 weeks).	Interval from stimulation: immediately after stimulation.	Follow-up: 1 (baseline), 4, and 7 weeks, as well as 3 months after therapy completion.	No significant effect of rTMS.
	Five conduction aphasia Eight anomic aphasia One transcortical motor aphasia Three Broca's aphasia Lost to follow-up: 0	20 min 90 % RMT Online: picture-naming task			Training: naming (2 weeks) + ILAT (2 weeks).		
Hu et al., 2018 (blindness not reported)	40	HF-rTMS 10 Hz (10 patients) or	10 sessions, once daily at a regular time.	Sham group (10 patients): sham stimulation + SLT	30 min per day.	WAB with Aphasia Quotient	LF-rTMS group exhibited a more marked improvement than the HF-rTMS group in spontaneous speech, auditory comprehension, and aphasia quotients (severity) immediately after treatment and at 2-month follow-up. Compared to the control group, the HF-rTMS cohort exhibited significant improvement at 2-months post-treatment in repetition and aphasia quotients (severity).
	Chronic (approximately 7 months)	LF-rTMS 1 Hz (10 patients) on right Broca's homolog		Control group (10 patients): SLT only	Interval from stimulation not reported.	Assessment (overall severity).	
	Non-fluent aphasia	10 min			Training: naming of objects, pictures and scenes.	Follow-up: before, and after treatment, as well as 2 months after treatment.	
Haghighi et al., 2018 (double blinded)	12	Posterior rIFG			45 min per day	WAB with Aphasia Quotient	Significant improvement in both groups for all subscores of the WAB and aphasia quotient.
	Subacute (1 month after stroke)	1 Hz	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation + SLT	Interval from stimulation: "Some minutes after rTMS or sham condition".	Assessment (overall severity).	Significant effect of rTMS on speech content only
	Broca's aphasia	20 min (contradictory)				Follow-up: at baseline and 2 weeks after the intervention.	

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Table 1 (continued)

Study design	Number of patients, stage (time since stroke), type of aphasia, and lost to follow-up	Procedure: location, duration, and intensity	Number and frequency of sessions	Sham/control condition	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures, and follow-up	Results
Santos et al., 2017 (double blind)	Lost to follow-up: 0	information, see Table 4) 100% RMT			Training: work on individual linguistic symptoms and linguistic deficits.		(contradictory information between figure and tables in the manuscript). Significant difference in the picture naming task after a single session of tDCS and this was also observed for the sham.
	13 Chronic (> 6 months)	All patients received tDCS, TMS and sham condition.	One single session.	Sham stimulation	No SLT, only TMS, tDCS and sham.	BNT	
	Seven anomic aphasia Six Broca's aphasia	TMS: right PTr (BA 45) 1 Hz 20 min				Follow-up: before and after each stimulation.	No statistical the 3 techniques.
	Lost to follow-up: not reported	90 % RMT					
	30	Right PTr (BA 45)			45 min	AAT, naming task based on Snodgrass and Vanderwart naming test: 60-item, Amsterdam Nijmegen Everyday Language Test, item of the Functional Independence Measure related to communication skill.	Both groups improved their language and communication skills.
	Subacute	1 Hz	10 sessions in 2 weeks.	Sham stimulation + SLT	Interval from stimulation: immediately after rTMS.  Training: oral naming, preactivation of word retrieval, application of increasing cues to support deliberate lexical retrieval, consolidation of successful verbal naming by additional written naming, variation of training stimuli progressing from single object to related action pictures as provided by everyday life activities, exclusion of holistic nonverbal facilitation methods, or both methods that primarily involve RH functions.	Stimulation group: significant improvements for all 10 measures.  Sham group: significant improvements for six of the 10 measures (AAT profile height, AAT repetition, AAT written language, AAT comprehension, naming screening, and Amsterdam-Nijmegen Everyday Language Test).	
Rubi-Fessen et al., 2015 (blinded)	19 fluent aphasia	20 min				Follow-up: the day before and the day after treatment.	The gain between baseline and post-treatment performance for almost all measures was higher in the real stimulation group.
	11 non-fluent aphasia						
	Lost to follow-up: 0	90 % RMT					
	20	rIFG			60 min, twice a week, for 4 weeks	WAB (Korean version, oral language domain was used).	Intra-group analysis only.
	Chronic (approximately 6 months)	1 Hz 20 min			Interval from stimulation: immediately after rTMS.		
Yoon et al., 2015 (not blinded)	Non-fluent aphasia		20 daily sessions, five times a week for 4 weeks.	SLT only	Training: conventional SLT, language-oriented treatment consisting of understanding the program via the visual and auditory senses, expression training for spoken language.	Follow up: before and after the treatment.	Significant improvements in repetition and naming in the case group, but no significant improvement was noted in the control group.
	Lost to follow-up: 0	90 % RMT					
Wang et al., 2014 (double blind)	45	Three groups:	10 daily sessions.	Sham stimulation + SLT	60 min, twice a week.	Object and action naming (Picture Naming Test from International Picture	TMSsyn group: significant improvements in all language tests

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Table 1 (continued)

Study design	Number of patients, stage (time since stroke), type of aphasia, and lost to follow-up	Procedure: location, duration, and intensity	Number and frequency of sessions	Sham/control condition	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures, and follow-up	Results			
	Chronic (> 6 months)	15: TMSsyn (real stimulation combined with a synchronous picture naming task: online model)	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation + SLT	Interval from stimulation: SLT shortly after rTMS in addition to picture naming activity.	Naming Database), CCAT (three subcategories: conversation, scene description, and object naming).	(greatest improvement). TMSsub group: significant improvement in CCAT score both at post 1 and post 2, as well as conversation at post 1.			
	Non-fluent aphasia	15: TMSsub (real stimulation followed by a picture naming activity: off-line model)			Training: verbal expressive skills (repetition, phonemic training, semantic training, naming, conservation, picture description tasks, and phrase generation tasks). Compensatory modalities were prohibited during training.					
	Lost to follow-up: TMSsyn = 0	15: TMSsham (sham stimulation combined with concurrent naming activity)			Right PTr (BA 45)	1 Hz	20 min	90 % RMT	Follow-up: before treatment, at the tenth session (post 1) and 3 months after the last intervention (post 2).	TMSsham group: improvement in action naming accuracy at post 1 and object naming accuracy at post 2 but not in CCAT score or subtests.
	TMSsub = 1									
Tsai et al., 2014 (double blind)	56	Right PTr (BA 45)			60 min	Object and action naming (Picture Naming Test from International Picture Naming Database), CCAT (four subcategories: conversation, scene description, naming objects, expression and repetition).	Experimental group showed significant improvement compared with sham group in overall CCAT scores, object and action naming accuracy and naming reaction times.			
	Chronic (> 3 months)	1 Hz			Interval from stimulation: within 30 min after rTMS.					
	Non-fluent aphasia	90 % RMT			Training: expression production (semantic and phonemic training, repetition, naming, conversation, picture description tasks, and phrase generation tasks).	Follow-up: before treatment, 1 day after the tenth session and 3 months after the last intervention.	Changes in the experimental group persisted at 3 months after the intervention.			
	Lost to follow-up:				Compensatory modalities were prohibited during training.		Patients with a lower RMT in the right motor system appeared to benefit the most from inhibitory rTMS (better improvement in action picture naming accuracy).			
Khedr et al., 2014 (double blind)	TMS = 2									
	Sham = 1									
	30	Right Broca's homolog	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation + SLT	30 min	Hemispheric Stroke Scale, ASRS, Stroke Aphasic Depression Questionnaire-Hospital version, the National Institutes of Health Stroke Scale.	Significant improvement in the Hemispheric Stroke Scale language score, in the Stroke Aphasic Depression Questionnaire-Hospital version and in the ASRS after real rTMS compared with sham.			
	Subacute (1–12 weeks)	1 Hz			Interval from stimulation: immediately after rTMS.					
	Non-fluent aphasia	110 % RMT			Training: stimulation of various aspects of the language system. Subtests of BDAE were used for training (naming, repetition, and auditory comprehension).	Follow-up: baseline, at the tenth session, 1, and 2 months after treatment.				
	Lost to follow-up: TMS = 1	500 pulses over PTr, 500 pulses over POP								
	Sham = 0	Left Broca's area								
		20 Hz								
Chieffo et al., 2014 (double blind)	TMS = 1	80 % RMT								
	Sham = 0	10 trains								
	5	rIFG	Three sessions for each patient separated by a 6-day washout period.	Sham stimulation + naming task	No SLT, only naming tasks (Snodgrass naming test) immediately before	AAT and Snodgrass naming test.	Only the excitatory stimulation (10 Hz) was associated with a significant improvement in			

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Table 1 (continued)

Study design	Number of patients, stage (time since stroke), type of aphasia, and lost to follow-up	Procedure: location, duration, and intensity	Number and frequency of sessions	Sham/control condition	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures, and follow-up	Results
					and after rTMS session.		naming performance and was significantly more effective than inhibitory stimulation.
	Chronic (> 18 months) Two anomic aphasia One conduction aphasia One Broca's aphasia One transcortical sensory aphasia Lost to follow-up: 0	Inhibitory (1 Hz) Excitatory (10 Hz, 15 min) 100 % RMT				Follow-up: administered twice separated by 1 week to ensure a baseline, immediately before and after each rTMS session.	The 'best responder' to HF-rTMS was "the patient with a large lesion involving the cortical frontal regions and more severe naming deficit".
Garcia et al., 2013 (blindness not reported)	Number of patients not reported Chronic (> 6 months), Non-fluent aphasia Lost to follow-up: not reported	Phase 1: locate "best response" RH cortical ROI: primary motor cortex (M1), POp (BA 44), anterior PTr (BA 45), dorsal posterior PTr (BA 45), ventral posterior PTr (BA 45), pars orbitalis (BA 47). 1 Hz 10 min 90 % RMT Phase 2: suppress best response RH ROI: right PTr (BA 45) for most patients 1 Hz 20 min 90 % RMT	Phase 1: six sessions, 5 consecutive days, with two sessions on the last day. Phase 2: 10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation alone	No SLT, only rTMS	BDAE (Cookie Theft picture description subtest, Word Comprehension and Commands), BNT, Snodgrass and Vanderwart, Cognitive Linguistic Quick Test. Follow-up: at baseline, after the tenth stimulation, 2 months and 6 months after the tenth stimulation.	"Patients' performance on picture naming is most consistently facilitated by stimulation of the ventral posterior pars triangularis." "Long-term improvement in performance on standardized language assessment." "The first 20 BNT item and BDAE "naming in categories" subsections demonstrate improvement over time." Significant improvement of the AAT score in the rTMS group. Increases more important for naming, comprehension, TT and writing.
Thiel et al., 2013 (double blind)	30 Subacute (approximately 40 days) Four Broca's aphasia 12 Wernicke's aphasia Four global aphasia Four amnesic aphasia Lost to follow-up: TMS = 2 Sham = 4	1 Hz 20 min 90 % RMT	10 sessions (no more detail).	Sham stimulation + SLT	45 min Interval from stimulation: immediately after rTMS. Training: deficit-specific aphasia therapy focused on individual linguistic symptoms.	AAT Follow-up: assessment between 16 and 18 days after the start of treatment.	More voxels activated in the LH after treatment.
Seniów et al., 2013 (double blind)	40 Subacute (2–12 weeks) Six Broca's aphasia 15 Wernicke's aphasia	1 Hz 30 min 90 % RMT	15 sessions, five times a week for 3 weeks.	Sham stimulation + SLT	45 min Interval from stimulation: immediately after each rTMS session.	BDAE (subtests of naming, repetition and comprehension).	Significant improvement, but no difference between the groups, either immediately after treatment or during the follow-up assessment in the BDAE-Comprehension test, or repetition. There was a trend

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Table 1 (continued)

Study design	Number of patients, stage (time since stroke), type of aphasia, and lost to follow-up	Procedure: location, duration, and intensity	Number and frequency of sessions	Sham/control condition	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures, and follow-up	Results
	17 mixed aphasia						toward significance in BDAE naming for the experimental group. Significant effect of rTMS in repetition at follow up for patients with severe aphasia at baseline.
	Two transcortical mixed aphasia						In sub-analysis including 20 patients with aphasia (Mirowska-Guzel et al., 2013), "serum BDNF (overall concentration, in patients who improved and in those who did not) was statistically higher in patients who did not undergo the rTMS procedure."
	Lost to follow-up: TMS = 1				Training: therapy focused on individual linguistic symptoms, expression and comprehension of spoken language.	Follow-up: at baseline, immediately after treatment, as well as 3 and 15 weeks after the completion of therapy.	"In men with aphasia, after the first 6 h of rTMS-supported rehabilitation, BDNF concentration was lower among rTMS-treated patients than placebo-treated patients. A similar difference was observed in women with aphasia after 3 weeks of rTMS-supported rehabilitation."
	Sham = 1						Significantly better recovery of language function in global aphasia test scores and naming picture performance for right-handed patients treated with rTMS than those who were treated with sham.
	29 (+ two left-handed patients not included in the group analysis).	Right-handed: right PTr (BA 45)	10 sessions (no more detail).	Sham stimulation + SLT	45 min	AAT	Shift of activation toward the ipsilesional hemisphere for treated right-handed patients (significant effect).
Heiss et al., 2013 (double blind)	Subacute (< 3 months) Seven Broca's aphasia 12 Wernicke's aphasia Eight amnesic aphasia Four global aphasia	Left-handed: left PTr (BA 45)					
	Lost to follow-up: not reported Discontinued intervention: 10	1 Hz			Interval from stimulation: immediately after rTMS.	Follow-up: at baseline and assessment between 16 and 18 days after the start of treatment.	
	12	20 min			Training: activated networks in the dominant hemisphere.		Both left-handed patients also improved.
	Chronic (> 24 months)	Right PTr (BA 45)				BNT, subsets of BDAE and Snodgrass and Vanderwart naming test.	Significant changes were observed up to 12 months post stimulation in naming performance, language expression and auditory comprehension
Barwood et al., 2013 (double blind)	Non-fluent aphasia Lost to follow-up: not reported	1 Hz	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation alone.	No SLT, only rTMS.	Follow-up: 1 week prior to stimulation and at intervals of 1 week, 2 months, 8	

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Table 1 (continued)

Study design	Number of patients, stage (time since stroke), type of aphasia, and lost to follow-up	Procedure: location, duration, and intensity	Number and frequency of sessions	Sham/control condition	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures, and follow-up	Results
	10 Chronic (> 6 months)	Phase 1: rIFG	Phase 1: Six sessions, over 5 consecutive days (two stimulations one the final day) toward different sites of the rIFG to identify the optimal target.			months and 12 months post treatment.	compared to the sham group.
	Non-fluent aphasia	Motor cortex corresponding to the mouth,	Phase 2: 10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation alone.	No SLT, only naming tasks before and after each stimulation of phase 1.	Cookie Theft Picture Description of the BDAE, and naming tasks.	Significant increase in multiple measures of discourse productivity for all patients who received real rTMS.
Medina et al., 2012 (double blind)	Lost to follow-up: not reported	POp (BA 44), 3 parts of the PTr (BA 45), pars orbitalis (BA 47)				Follow-up: three times at the start of the study and 2 months after the end of the study.	No significant increase in measures of sentence productivity or grammatical accuracy. No significant increase from baseline in patients who received the sham treatment.
	26 Subacute (< 3 months)	Right PTr (BA 45) (15 min)			45 min	CPNT, subtests of BDAE (naming, repetition, and auditory comprehension), ASRS.	No significant differences between the rTMS and sham stimulation groups in the CPNT.
	Six Broca's aphasia Six Wernicke's aphasia	Right POp (BA 44) (15 min)	15 sessions, five times a week for 3 consecutive weeks.	Sham stimulation + SLT	Interval from stimulation: immediately after rTMS. Training: expression and comprehension of spoken language, rehabilitation focused on specific training to stimulate various aspects of the language system.	Follow-up: at baseline, immediately after 3 weeks of experimental treatment, and 15 weeks after the end of therapy.	However, the rTMS subgroup with a lesion including the anterior part of the language area showed greater improvement in naming reaction time at follow-up and also showed improvement in functional communication abilities. The real stimulation group showed significantly greater improvements than the sham stimulation group in accuracy and latency in picture-naming.
Waldowski et al., 2012 (double blind)	12 mixed aphasia Two transcortical mixed aphasia	1 Hz 30 min					Better effects in the subacute phase.
	Lost to follow-up: 0	90 % RMT					Alertness: no difference between reaction times post TBS and post sham.
	18 Subacute and chronic (> 0.5 months)	Right Broca's homolog (BA 45) cTBS 30 Hz	Two sessions on 2 different days separated by 1 week.	Sham stimulation alone.	No SLT, only rTMS	Snodgrass and Vanderwart naming test and subtest of Test of Attentional Performance (assessment of alertness).	
Kindler et al., 2012 (double blind)	12 anomic aphasia Five Broca's aphasia One unclassified aphasia Lost to follow-up: not reported	90 % RMT				Follow-up: same day before and after the intervention, precise interval not reported.	
	12 Chronic (> 24 months)	Anterior portion of right PTr (BA 45)				ERP recorded in a two-stimulus: written word-picture semantic judgement task.	Active group N400 responses improved over 12 months, accompanied by improvements in the ERP task. Changes were more significant in the semantically incongruent than congruent condition.
Barwood et al., 2012b (single blind)	Non-fluent aphasia Lost to follow-up: not reported	1 Hz 20 min 90 % RMT	10 sessions, five times a week for 2 consecutive weeks	Sham stimulation alone.	No SLT, only rTMS	Follow-up: prior to stimulation (baseline), 1 week, 2 months, 8 months, and 12	

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Table 1 (continued)

Study design	Number of patients, stage (time since stroke), type of aphasia, and lost to follow-up	Procedure: location, duration, and intensity	Number and frequency of sessions	Sham/control condition	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures, and follow-up	Results
Barwood et al., 2011a (double blind)	12 Chronic (> 24 months) Non-fluent aphasia Lost to follow-up: not reported	Anterior portion of right PTR (BA 45) 1 Hz 20 min 90 % RMT	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation alone.	No SLT, only rTMS	months post stimulation. BNT, subtests of the BDAE and CNPT. Follow-up: 1 week prior to stimulation (baseline) and 1 week post stimulation.	Significant improvements in naming accuracy, latency and repetition for the real stimulation group compared with the sham stimulation group.
Barwood et al., 2011b (double blind)	12 Chronic (> 24 months) Mild to severe non-fluent aphasia Lost to follow-up: not reported	Anterior portion of right PTR (BA 45) 1 Hz 20 min 90 % RMT	10 sessions, one session per day for 10 days.	Sham stimulation alone.	No SLT, only rTMS	CPNT, BNT and subtests of the BDAE. Follow-up: 1 week prior to stimulation (baseline) and 2 months post stimulation.	Significant improvements in naming performance, language expression and auditory comprehension for the stimulation group at 2 months post stimulation.
Barwood et al., 2011c (double blind)	12 Chronic (> 24 months) Non-fluent aphasia Lost to follow-up: not reported	Anterior portion of right PTR (BA 45) 1 Hz 20 min 90 % RMT	10 sessions, five times a week for 2 consecutive weeks.	Sham stimulation alone.	No SLT, only rTMS	ERP recorded in a two-stimulus: written word-picture semantic judgement task. Follow-up: at baseline, 1 week and 2 months post stimulation.	Significant improvements were observed (peak amplitude, mean amplitude, and area under the curve of the N400) in the stimulation group compared with the placebo control group at 2 months post stimulation. However, "no changes were identified in the stimulation group compared to the sham group from baseline to 1 week post stimulation". No change in the latency of the N400.

HF: high frequency.

LF: low frequency.

LH: left hemisphere.

RH: right hemisphere.

BA: Brodmann area.

BDNF: brain-derived neurotrophic factor.

ROI: region of interest.

ASRS: Aphasia Severity Rating Scale.

ANT: action naming test PTR: pars triangularis.

POp: pars opercularis.

pSTG: posterior superior temporal gyrus.

rIFG: right inferior frontal gyrus.

CPNT: computerized picture naming test.

ERP: event-related potential.

TT: Token Test.

TMS: transcranial magnetic stimulation.

rTMS: repetitive transcranial magnetic stimulation ILAT: intensive language-action therapy.

WAB: Western Aphasia Battery.

AAT: Aachen aphasia test.

BNT: Boston naming test.

BDAE: Boston diagnostic aphasia examination.

CCAT: concise China aphasia test.

tDCS: transcranial direct current stimulation TBS: theta burst stimulation.

cTBS: continuous theta burst stimulation.

iTBS: intermittent theta burst stimulation.

SLT: speech language therapy.

RMT: resting motor threshold.

**Table 2**  
Design and results of other studies and case reports.

Study design	Number of patients, stage (time since stroke), and type of aphasia	Stimulation parameters: location, intensity, frequencies, and duration	Number and frequency of sessions	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures and follow-up	Results
Versace et al., 2020 (pilot study)	13 Chronic (2–10 years) Fluent aphasia	Wernicke's area, the homologous temporal area of the right hemisphere and primary visual cortex iTBS 50 Hz 80 % AMT Right PTr (BA 45) cTBS 50 Hz	iTBS on the three different cortical regions on separate days.	No training	TT  Follow-up: baseline (T0), 5 min after iTBS (T1) and 40 min after iTBS (T2).  BDAE, Multilingual Assessment Instrument for Narratives, Quantitative Production Analysis Protocol, Stroke and Aphasia Quality of Life Scale 39.	"Transient facilitatory effect of a single session of iTBS over Wernicke's area on a simple auditory comprehension task", only at T1. At T2, there was no difference between the groups. Patient 1: improvement in auditory comprehension, significant improvement of language expression, naming ability remained stable post treatment and at follow-up. Improved quality of life but decreased psychosocial score. Patient 2: improvement in auditory comprehension, significant deterioration in language expression "but at follow-up showed a trend toward improvement". Slight decrease in naming scores post treatment and at follow-up. Significant decrease in psychosocial score.
	- Patient 1: Chronic (20 months post stroke)  Mild to moderate anomic aphasia					
Georgiou et al., 2019 (cases report)	- Patient 2: Chronic (25 months post stroke)  Severe global aphasia		10 sessions, 10 consecutive days.	No training	Follow-up: prior to treatment, post treatment and 3 months later.	
	11 Chronic (> 6 months) Six anomic aphasia	Right PTr (BA 45) and at the vertex (control site) in separate sessions			Naming accuracy from the International Picture Naming Project.	Improvement in naming for individuals with more severe baseline naming impairments.  Correlations between the severity of baseline phonological error production, naming improvements, and fewer phonological errors post cTBS.
Harvey et al., 2019 (prospective study)	Four Broca's aphasia  One conduction aphasia 12	cTBS 50 Hz  80 % RMT	Single session.	No training	Follow-up: two baselines and after stimulation.	No link between semantic error production and cTBS effects.
	Chronic (>12 months)	Residual left hemispheric language area (Broca)		45 min	WAB, BNT, Semantic Fluency Test, Controlled Oral Word Association Test, fMRI for language	"Preliminary safety, feasibility, and efficacy evidence for conducting fMRI guided iTBS therapy" associated with modified CIAT.
Szaflarski et al., 2018 (feasibility study)	Eight anomic aphasia One global aphasia	iTBS 50 Hz	10 sessions, one session per day for 10 consecutive weekdays.	Interval from stimulation: immediately after iTBS.	Follow-up: before the treatment (T1), immediately after the treatment (T2), and approximately 3 months later (T3).	"Significant effect of session on WAB aphasia quotient and spontaneously correct responses on BNT. Association between improvements in WAB aphasia quotient from T2 to T3 and decreased blood-oxygen-level dependent signal in left inferior parietal lobe. Improvements in BNT from T1 to T3 with decreased signal in rIFG."
	Two Broca's aphasia  One conduction aphasia	80 % of AMT obtained from the right hemisphere		Training: modified CIAT administered.		Significant improvement in verbal fluency immediately after rTMS (T3) and significant improvement 2 months after treatment (T4).
Rossetti et al., 2019 (case report)	Woman 64 years old	Right Broca's homolog 1 Hz 20 min	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	BNT, semantic and phonemic fluency tests. Stroop test to assess executive functions (and exclude nonspecific effect of stimulation).	

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Table 2 (continued)

Study design	Number of patients, stage (time since stroke), and type of aphasia	Stimulation parameters: location, intensity, frequencies, and duration	Number and frequency of sessions	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures and follow-up	Results
Harvey et al., 2017 (prospective study)	Chronic (23 months)					Not improvements in naming and semantic fluency.
	Anomic aphasia	90 % RMT			Follow up: 11 months after stroke (baseline, T1), before enrollment (23 months after stroke, T2), immediately after rTMS (T3), and 2 months after rTMS (T4).	Performance on the Stroop test did not show a trend toward improvement. Confirmation of the segregation of neural circuitries subtending phonemic and semantic fluency, suggesting selective benefits of rTMS treatment.
	9 Chronic (> 6 months) Non-fluent aphasia	8 in right PTR (BA 45) 1 in right pars orbitalis (BA 47) 1 Hz 20 min 90 % RMT	10 sessions, five sessions a week for 2 consecutive weeks.	No SLT, only naming tasks before and after rTMS in the optimal site-finding phase.	Naming task based on Snodgrass and Vanderwart naming test: 40 item, 20 items repeated across sessions and 20 novel items. Follow-up: before and immediately after rTMS, as well as at 2 and 6 months follow-up.	Significant improvement in naming accuracy immediately after rTMS and 6 months after rTMS. Posterior shift in the recruitment of the rIFG and increase in the number of left hemispheric areas recruited for naming in fMRI tasks.
Ilkhani et al., 2018 (blind study, no control group)	24	Right Broca's homolog	10 sessions, frequency not reported.	Not reported.	Naming: images of everyday objects that are not affected by cultural, ethnic, or educational differences. Persian version of the Wechsler test to assess vocabulary comprehension: accuracy score based on correct/incorrect answers.	Significant improvement in naming accuracy after rTMS.
	Chronic (> 1 year) Broca's aphasia	1 Hz 10 min Intensity not reported			Follow-up: before and after treatment.	Authors noted significant effect on dysarthria but did not report the precise assessment method used. Significant improvement in language function (SLTA total score) after intervention in both groups.
Hara et al., 2017 (single group intervention study)	8	Two groups:		60 min	SLTA	No difference in improvement between the groups.
	Chronic (> 29 months)	- LH activation:		Interval from stimulation: immediately after rTMS.		
	One mild-fluent aphasia One moderate-fluent aphasia One severe fluent aphasia One mild non-fluent aphasia One moderate non-fluent aphasia	rIFG inhibition 1 Hz 40 min 90 % RMT - RH activation: rIFG facilitation 10 Hz 12 min 90 % RMT LF-rTMS or HF-rTMS was chosen, depending on cerebral activation during a repetition task.	10 sessions, one session per day except on Sunday.	Training: three main tasks: - describe and answer questions about a photograph and recall the names of objects and scenes shown previously; - words and sentences repetition task;	Follow-up: baseline and 3 months after treatment.	Improvement associated with a decrease in interhemispheric imbalance.
	Three severe non-fluent aphasia			- dictate words and sentences presented by the therapist.		
Zhang et al., 2017 (case report)	Woman 39 years old Subacute (4 months after stroke)	Left Broca's area 5 Hz 20 min	10 sessions, five sessions a week for 2 consecutive weeks.	30 min Interval from stimulation: immediately after Rtms. Training: free talk, correction of mistakes in pronunciation and	WAB Follow-up: 1 month pre-rTMS, 1 week pre-rTMS, 2	Significant improvements in language ability at 2 weeks post-treatment. Constant increase in gains 2.5 months post-treatment. fMRI: more focused activation pattern and significant activation in the

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Table 2 (continued)

Study design	Number of patients, stage (time since stroke), and type of aphasia	Stimulation parameters: location, intensity, frequencies, and duration	Number and frequency of sessions	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures and follow-up	Results
Griffis et al., 2016 (prospective study)	Conduction aphasia	90 % RMT	10 sessions, five sessions a week for 2 consecutive weeks.	phonetic annotation of Chinese characters.	weeks post-rTMS, and 2.5 months post-rTMS.	left dominant hemisphere (perilesional areas) relative to the right hemisphere. Increased fractional anisotropy in the left STG, which is important in language processing.
	8 Chronic (> 5 years)	"residual language-responsive cortex in or near the IIFG" iTBS 50 Hz		No training.	BNT, Peabody Picture Vocabulary Test, Semantic Fluency Test,	Leftward shift in IFG activity, decrease in rIFG activation.
	Four anomic aphasia (2 with dysarthria and 1 with conduction aphasia). Four non-fluent Broca's aphasia (or 5 with anomic aphasia and 3 with Broca's aphasia: discrepancy between the table and text)	80 % RMT		Controlled Oral Word Association Test, complex ideation subtest of the BDAE.	Follow-up: before stimulation (maximum of 7 days before) and between 14 and 21 days after stimulation.	Significant improvement in the Semantic Fluency Test, non-significant improvements in the BNT, non-significant decrease in performance of the Controlled Oral Word Association Test.
	50	Two groups:		60 min	SLTA (including four subscales speaking, listening, reading, and writing).	No significant change in noun recognition performance pre and post iTBS.
Hara et al., 2015 (single group intervention study)	Chronic (> 6 months)	- RH-LF-rTMS group:	10 sessions, one session per day except Sunday.	Interval from stimulation: immediately after rTMS.	Follow-up: at the time of admission and at 3 months after treatment.	RH-LF-rTMS group: significant improvement in the total SLTA score correlated with the pre- and post-intervention change of laterality indices in BA 44 shown in single photon emission computed tomography. The changes in SLTA subscores were significantly correlated with changes in laterality indices (in BA 11, 20, and 21 for speaking subscores and in BA 6 and 39 for writing subscores).
	27 non fluent aphasia	29 patients: LF-rTMS 1 Hz on the right non-lesional hemisphere (left compensatory hemisphere for language at fMRI)		Training: Intensive SLT Three main tasks:  - describe and answer questions about a short comic		
	23 fluent aphasia	- LH-LF-rTMS group: 21 patients: LF-rTMS 1 Hz on the lesional left hemisphere (right compensatory hemisphere for language at fMRI). IFG for patients with non-fluent aphasia. STG for patients with fluent aphasia.		and recall the name of objects and scenes shown previously;  - word and sentence repetition task; - dictate words and sentences presented by the therapist Communication by gestures or drawing was prohibited.		
	Man	40 min 90 % RMT First: cTBS (inhibitory)				
Vuksanović et al., 2015 (case report)	63 years old	right PTR (BA 45)	15 daily sessions.	No training.	BNT, subtests of the BDAE, and the Rey Auditory Verbal Learning Test.	Improvements in several language functions (propositional speech, semantic fluency, naming, and auditory comprehension), and in short-term verbal memory and verbal learning.
	Chronic (> 17 months)	Immediately after cTBS: iTBS (facilitatory)		Follow-up: before (baseline, T0), 1 week after (T1), and 2 months (T2) after TMS treatment.		
	Severe non-fluent aphasia	Broca's area 50 Hz 80 % RMT - Patient 1: Right PTR (BA 45)		BNT, BDAE		

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Table 2 (continued)

Study design	Number of patients, stage (time since stroke), and type of aphasia	Stimulation parameters: location, intensity, frequencies, and duration	Number and frequency of sessions	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures and follow-up	Results
Martin et al., 2014 (case report)	Chronic (> 6 months)	1 Hz		3 h of modified CIAT (with a break for lunch).		Significant improvement in naming pictures and propositional speech at 1–2 months post treatment.
	Mild to moderate non-fluent aphasia	20 min 90 % RMT	10 sessions, five sessions a week for 2 consecutive weeks.	Interval from stimulation: immediately after stimulation. Training: naming task with phonological and contextual cues if necessary, color picture card games. Gestures and drawing were prohibited.	Follow-up: for both patients, before the treatment, 1–2 months after stimulation. Patient 1: 16 months post stimulation. Patient 2: 6 months post stimulation.	Improvement in naming remained at 6 months post treatment for patient 2 but not at 16 months post treatment for patient 1.
	- Patient 2: Chronic (> 6 months) Severe non-fluent aphasia Man 54 years old	4 weeks for left homologous Wernicke's area	40 sessions, five sessions a week for 8 weeks.	No training.	WAB (including, fluency, auditory, comprehension, repetition, and naming subtests).	Significantly reduced structural and functional connectivity. Hypometabolism in RH and left cerebellum. "Stimulating left Wernicke area could improve auditory comprehension. Stimulating left Broca's area could enhance expression. Results outlasted 6 months by 1 Hz rTMS balancing the excitability inter-hemisphere". GOE improved significantly in verbal fluency and the repetition of phrases when treated with melodic intonation therapy and TMS.
Lu et al., 2014 (case report, with a control subject)	Subacute (2 months after stroke) Crossed aphasia	4 weeks for left homologous Broca's area 1 Hz 90 % RMT			Follow-up: before and after homologous Wernicke's area stimulation, before and after homologous Broca's area stimulation and 6 months after treatment.	
Al-Janabi et al., 2014 (two case reports, with sham treatment)	- Participant GOE: 65 years old Chronic (18 months)	GOE: Right PTr (BA 45) AMC: Right POp (BA 44)	Three sessions, separated by 3 days.	40 min	Automatic production of verbal sequence and repetition tasks, fMRI during two tasks (automatic speech task and naming/reading task).	
	Moderate non-fluent Broca's aphasia - Participant AMC: 49 years old	iTBS 50 Hz 80 % RMT		Interval from stimulation: immediately after stimulation.		No improvement for AMC.
	Chronic (20 months) Moderate to severe non-fluent Broca's aphasia Woman, 55 years old	IIFG		Training: melodic intonation therapy.		Follow-up: 1 week before treatment, immediately before the first treatment, after each treatment session and 1 week after completion of the study.
Danmekens et al., 2012 (case report)	Chronic (39 months) Non-fluent aphasia	10 Hz 80 % RMT	15 sessions, five sessions a week for 3 consecutive weeks.	No training.	AAT, continuous EEG during resting state. Follow-up: before, after and 4 months after treatment.	Long-term improvement in repetition tests, naming and comprehension. Increased functional connectivity between the IIFG and rIFG in response to theta and beta-3 frequency bands.
Barwood et al., 2012a (open protocol case series)	7 Chronic (2–6 years)	Right PTr (BA 45) 1 Hz	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	BNT, subtests of BDAE, and computerized naming task.	Significant improvements in picture naming accuracy and latency, spontaneous

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Table 2 (continued)

Study design	Number of patients, stage (time since stroke), and type of aphasia	Stimulation parameters: location, intensity, frequencies, and duration	Number and frequency of sessions	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures and follow-up	Results
	Non-fluent aphasia	20 min 90 % RMT			Follow-up: 1 week before stimulation, 1 week, 2 months, and 8 months post stimulation. Naming probe test, BNT, subtests of the BDAE, action naming picture from Druks and Masterson.	elicited speech and auditory comprehension. Improvements observed up to 8 months after TMS application. Improvement of more than 2 SD BDAE
Naeser et al., 2012 (case report)	1 Chronic (12.5 years) Non-fluent aphasia	1 Hz 20 min 90 % RMT	10 sessions, five sessions a week for 2 consecutive weeks.	3 h Interval from stimulation: immediately after stimulation. Training: CILT	Follow-up: before stimulation, 1 and 6 months after the tenth treatment.	action naming (only observed after the second TMS series, when CILT was included), as well as for naming tools/implements and single word repetition. "On Naming Probe Testing, the time series analysis showed significant improvement on BDAE action naming and tools/implements."
	24 Chronic (>15 months) 10 fluent aphasia	Application to the hemisphere contralateral to the activated areas on fMRI during a repetition task.	10 sessions, a single session per day except Sunday.	60 min Interval from stimulation: after stimulation (no more detail).	SLTA Follow-up: 1 week before admission and 4 weeks after discharge.	Patients with non-fluent aphasia: significant improvements in auditory comprehension, reading comprehension and repetition. Patients with fluent aphasia: significant improvements in spontaneous speech.
Abo et al., 2012 (pilot study)	14 non-fluent aphasia	rIFG: 11 patients with non-fluent aphasia lIFG: three patients with non-fluent aphasia rSTG: five patients with fluent aphasia lSTG: five patients with fluent aphasia 1 Hz 40 min 90 % RMT Four different RH cortical regions of interest (ROIs):		Training: improve expressive modality including word production, repetition, naming and writing. Other forms of communication were discouraged.	SLTA-ST and WAB Follow-up: 1 week before admission and 1 h after the final stimulation.	Note: there is discrepancy between the results shown in Table 2 and the text. The protocol (LF-rTMS combined with intensive ST) is safe may enhance recovery from aphasia.
Naeser et al., 2011 (prospective study)	8 Chronic (> 18 months) Non-fluent aphasia	- Right PTr (BA 45) - Right POP (BA 44) - Right motor cortex mouth area -Right STG 1 Hz 10 min 90 % RMT	Several single sessions with different brain targets.	No training	Naming performance and response time (base on Snodgrass and Vanderwart picture list). Follow-up: before and immediately after rTMS.	Suppression of right PTr: significant increase in picture naming performance and significant decrease in response time. Suppression of right POP: significant increase in response time, no change in number of pictures named.
Szaflarski et al., 2011 (prospective study)	8 Chronic (>12 months) Four anomic aphasia Four Broca's aphasia	Residual left Broca's area iTBS 50Hz 80 % RMT	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	BNT, Controlled Oral Word Association Test, Semantic Fluency Test, Complex Ideation subtests from the BDAE and Peabody Picture Vocabulary Test IV. Follow-up: before stimulation and during the week following stimulation.	Significant improvements in semantic fluency. Language improvement was associated with "significant shifts of fMRI signal to the affected hemisphere".
Weiduschat et al., 2011 (a randomized controlled blinded pilot study)	10 Subacute (18–97 days)	Right PTr (BA 45) 1 Hz	8–10 sessions, five sessions a week for 2 consecutive weeks (mean 9.2).	45 min	AAT and PET during a silent verb generation task.	Activation shift toward the RH in the control group.

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Table 2 (continued)

Study design	Number of patients, stage (time since stroke), and type of aphasia	Stimulation parameters: location, intensity, frequencies, and duration	Number and frequency of sessions	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures and follow-up	Results
Cotelli et al., 2011 (pilot study, randomized and sham treatment)	Two Broca's aphasia	20 min		Interval from stimulation: immediately after stimulation.	Follow-up: before stimulation and after a 2-week rehabilitation period.	Significant clinical improvements in the AAT for the rTMS group only.
	Five Wernicke's aphasia					
	Two global aphasia	90 % RMT		Training: attempt to activate LH language areas.		No clear linear relationship between the extent of lateral shift and clinical improvements.
	One amnesic aphasia		20 sessions, five sessions a week for 4 consecutive weeks:	25 min	Neuropsychological battery for reasoning and verbal fluency, AAT, the object and action naming subtests, comprehension and sentence comprehension subsets from the	Significant improvements in object naming.
Jung et al., 2010 (case report)	Chronic (> 12 months)	cortex		Interval from stimulation: immediately after stimulation.		Neuropsychological assessments, including formal language assessment (ATT and BADA), showed no changes. Significant effect on treated item post rTMS combined with behavioral therapy, with long-term effects.
	Non-fluent aphasia	20 Hz	1 patient received real rTMS and SLT for 4 weeks,		BADA.	
	Woman	25 min	2 patients received sham stimulation and SLT for 2 weeks, then real stimulation and SLT for the next 2 weeks.	Training: repetition and reading the target word to facilitate naming, articulatory suppression task.	Follow-up: before stimulation, after the first 2 weeks of treatment, after 4 weeks of therapy, and 12, 24, and 48 weeks after the start of stimulation.	At baseline, lack of activation in both hemispheres during fMRI tasks. After stimulation, significant activation in the rIFG (Broca's area), posterior temporal gyrus. (Wernicke's area), and parietal lobe during noun generation and sentence completion tasks. Activation of the sensorimotor area and posterior occipital lobe. Cognitive evaluation was not improved but speech evaluation was.
Hamilton et al., 2010 (case report) (including article corrigendum)	52 years old	Left lateral sulcus of the parietal lobe	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	WAB, MMSE, and Memory Assessment Scale, fMRI during noun generation and sentence completion tasks.	Improvement in picture naming, with significant improvement in the naming actions, animals and tools
	Chronic (3 years post stroke)	1 Hz			Follow-up: before stimulation and 3 days after the final stimulation.	Improvement in picture description at 2, 6, and 10 months after rTMS.
Hamilton et al., 2010 (case report) (including article corrigendum)	Conduction and crossed aphasia Man	20 min			Subtests of BDAE (Cookie Theft Picture description and picture naming), WAB (only over the 5 years preceding the patient's participation and also 10 months after stimulation).	
	61 years old	90 % RMT				
	Chronic (7 years post stroke)	Phase 1: identification of optimal site:	Phase 1:			
Hamilton et al., 2010 (case report) (including article corrigendum)		Six sites on the rIFG (motor cortex corresponding to the mouth, POP, dorsal posterior PTr, dorsal anterior PTr, anterior POp/ventral posterior PTr, and pars orbitalis).	Six sessions over 2 weeks.	No training	Follow-up: before the stimulation and 2, 6 and 10 months after the stimulation.	Improvement in picture description at 2, 6, and 10 months after rTMS.
	Non-fluent aphasia	1 Hz	Phase 2:			Significant improvement on the WAB subscale for spontaneous speech.
		10 min	10 sessions, five sessions a week for 2 consecutive weeks.			
		90 % RMT				
		Phase 2: administration of rTMS at the optimal site: right dorsal posterior PTr (BA 45,				

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Table 2 (continued)

Study design	Number of patients, stage (time since stroke), and type of aphasia	Stimulation parameters: location, intensity, frequencies, and duration	Number and frequency of sessions	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures and follow-up	Results
Kakuda et al., 2010 (case series pilot study)	4	greatest improvement in naming with Snodgrass and Vanderwart items). 1 Hz 90 % RMT				
	Chronic (> 5 months)	- Two patients: right frontal lobe	10 sessions, one or two sessions per day	60 min	WAB, SLTA and SLTA-ST.	In patients with moderate aphasia: improvement in language functions for all three tests (WAB, SLTA, and SLTA-ST).
	Mild to moderate motor-dominant aphasia	- Two patients: left frontal lobe Area homologous to the most active area during pretreatment fMRI in a word repetition task 1 Hz 20 min 90 % RMT	for 6 consecutive days: two sessions separated by a 7-h rest period on days 2–5, with a single session on the day of admission.	Interval from stimulation: the rest period of 7 h.  Training: not reported.	Follow-up: 1 week before admission, 1 h after the final rTMS session and 4 weeks after discharge.	The score increased in some categories of these scales in the patient with mild aphasia.  At 4 weeks after discharge, any decreases in improved scores were recorded.
	2	Phase 1: Target: locate "best response" (at least 2 SD above baseline for Snodgrass and Vanderwart naming test after 10 min rTMS).  RH cortical ROI among the M1, mouth, and four subregions within right Broca's area (PTr posterior, POp, PTr middle, and PTr anterior). 1 Hz  20 min	Phase 2:  10 sessions, five sessions a week for 2 consecutive weeks.	3 h	BNT, subtests of the BDAE.	Follow-up: approximately 2 and 6 months after stimulation (baseline not reported).
Naeser et al., 2010 (pilot study)				Training: CILT.		Improvement in BDAE verb action naming, tools/ implements, and single word repetition.
	Man 43 years old	90 % RMT of the first interosseous muscle. Phase 2: suppress best response RH ROI: usually right PTr (BA 45) 1 Hz 20 min 90 % RMT				Patient 2: significant improvement in the BNT and in naming tools/ implements.
Naeser et al., 2010 (case report)	Chronic (> 6 months)	Phase 1: locate "best response" RH cortical ROI: M1, mouth, and four subregions within right Broca's area 1 Hz 10 min 90 % RMT	Phase 2:	No training but treatment for apnea (continuous positive airway pressure) which also improves language (BNT and BDAE scores).	BNT, subtests of the BDAE.	Improvement in BDAE cookie theft picture description.  Significant increase in phrase length, auditory comprehension and BNT score.
	Non fluent aphasia	Phase 2: suppress best response RH ROI: Right PTr (BA 45) 1 Hz 20 min 90 % RMT	10 sessions, five sessions a week for 2 consecutive weeks.		Follow-up: 3 and 6 months after stimulation and 2.4 years later.	These improvements were retained 2.4 years after rTMS.
Kakuda et al., 2010 (case report)	2	Wernicke's area  1 Hz  20 min	10 sessions, one or two sessions per day for 6 consecutive days: two sessions separated by a 6–8 h rest period on	60 min  Six sessions (hospital) then 3 months of outpatient treatment.	TT and subcategories of the SLTA Follow-up: at the start and end of inpatient treatment and at the end of 3 months of outpatient treatment.	Increase in TT scores and subcategories of the SLTA after the inpatient treatment.

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Table 2 (continued)

Study design	Number of patients, stage (time since stroke), and type of aphasia	Stimulation parameters: location, intensity, frequencies, and duration	Number and frequency of sessions	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures and follow-up	Results
Martin et al., 2009a (pilot study)	Sensory dominant aphasia	90 % RMT	days 2–5, with a single session on the day of admission Then, once per week for 3 months (outpatient treatment).	Interval from stimulation: after stimulation (no more details). Training: auditory comprehension, spoken word-picture matching and spoken printed word matching.	3 h	No decreases during the period of outpatient rTMS treatment.
	Woman (age not reported) Significant improvement in BDAE, action naming, tools/ implements and single word repetition. - Patient 1: Chronic (> 2 years) Mild moderate non-fluent aphasia. - Patient 2: Chronic (> 2 years)	Chronic (12.5 years post stroke)	Right PTR (BA 45) 1 Hz 20 min	10 sessions, five sessions a week for 2 consecutive weeks.	Interval from stimulation: immediately after rTMS.	BDAE, BNT
Severe non-fluent aphasia	- Patient 1: Chronic (> 2 years) Mild moderate non-fluent aphasia. - Patient 2: Chronic (> 2 years)	90 % RMT	Training: CILT	No training	BNT, substets of the BDAE.	Patient 1: improvement in naming and phrase length persisting for almost 4 years post stimulation.
		Phase 1: locate "best response" RH cortical ROI: M1, mouth, PTR anterior, PTR posterior, or POP, 1 Hz	Phase 1: four separate sessions.  Phase 2: 10 sessions, fiveSevere non-fluent aphasia90% RMTsessions a week for 2 consecutive weeks. sessions a week for 2 consecutive weeks.		Follow-up:  Patient 1: before stimulation and at 2, 3, 6, 8, 16, 43 and 46 months after stimulation.	Significant activity in the LH perilesional sensorimotor cortex activation at 16, and 46 months post rTMS.
Martin et al., 2009a,b (case report)	Severe non-fluent aphasia	10 min				Patient 2: no change in naming or propositional speech post treatment. No new persisting perilesional LH activation across the sessions.
		90 % RMT	Phase 2: suppress best response RH ROI: Patient 1: right PTR posterior (BA 45) Patient 2: right PTR anterior (BA 45) 1 Hz 20 min 90 % RMT IIFG and rIFG		Patient 2: before stimulation and at 2, and 6 months after stimulation.	Activation persisted in the rIFG, right sensorimotor cortex and mouth at 2 and 6 months post-rTMS.
Heiss et al., 2007 (conference paper, prospective study)	Three groups: - eight male volunteers. - eleven patients with non-fluent aphasia, subacute (2 weeks after left-sided middle cerebral artery infarction). - seventeen patients with mild to moderate aphasia (due to gliomas in the LH).	4 Hz			Positron Emission Tomography (PET) and verbal fluency task.	"Three stroke patients activated rCBF in the left inferior frontal gyrus, eight activated both sides during verb generation. rTMS resulted in increased reaction time latency or error rate with right IFG stimulation in five patients indicating essential language function. In the verbal fluency task these patients had a lower performance than patients with effects of rTMS only over the left IFG, suggesting a less effective compensatory potential of right sided network areas."
		At RMT	Not reported.	No training.	Follow-up: not reported.	Significant increase of latency during stimulation over the IIFG but not over the rIFG, compared with no stimulation.
Winhuisen et al., 2005 (prospective study)	11					Significant increase of latency during stimulation over the IIFG but not over the rIFG, compared with no stimulation.
	Subacute (within 2 weeks)  One mild verbal amnesia	Right and left IFG at maximal activation on PET during a semantic task.  In case of no right inferior frontal activation:	Not reported.	No training.	Verbal fluency: "Over each stimulation site, rTMS stimulation was started after 10 words. After the end of the 10-s pulse train, the generation task was continued for another five nouns."	All patients exhibiting increasing reaction time latency or error rate in the

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Table 2 (continued)

Study design	Number of patients, stage (time since stroke), and type of aphasia	Stimulation parameters: location, intensity, frequencies, and duration	Number and frequency of sessions	Speech training: duration of sessions, interval between stimulation, and training	Outcome measures and follow-up	Results
Naeser et al., 2005 (open protocol pilot study)	Three moderate and one severe sensoric aphasia	right PTr (BA 45).				semantic task following right rTMS stimulation also exhibited significant activation in the rIFG in PET scans.
	Three mild and one moderate global aphasia	4 Hz				"The patients with TMS effect only over the left IFG demonstrated a significantly better performance in the verb generation task than those with TMS effect over the right IFG."
	Two mild sensoric aphasia and also severe expressive aphasia	20 % of maximum output (2.1 T) Online stimulation: verbal generation task Right PTr (BA 45)				
	4 Chronic (> 5 years) One anomic/conduction aphasia (recovered Broca) One mild non-fluent aphasia One moderate non-fluent aphasia One severe non-fluent global aphasia	1 Hz  20 min  90 % RMT	10 sessions, five sessions a week for 2 consecutive weeks.	No training.	Snodgrass and Vanderwart picture naming task, BNT, subtests of the BDAE.  Follow-up: pre- and post-stimulation, 2 and 8 months after the tenth stimulation.	"Significant improvement in picture naming at 2 months post rTMS with lasting benefit at 8 months for 3 patients."  Improvements in the number of words per phrase for two of the three non-fluent patients at 2 months post-rTMS. However, no persisting effects at 8 months.
Naeser et al., 2005 (case report)	Woman 57 years old Chronic (6.5 years after stroke)	Phase 1: locate "best response" RH cortical ROI: right PTr, right POP, right posterior superior temporal gyrus and right motor cortex. 1 Hz 10 min 90 % RMT	Phase 2:  10 sessions, five sessions a week for 2 consecutive weeks.	No training.	BNT, subtests of the BDAE.  Follow-up: within 2 weeks prior to the first stimulation, as well as 2 and 8 months after the tenth session.	Improvements in picture naming on BNT and BDAE subtests at 2 and 8 months after rTMS.
	Severe non-fluent/global aphasia	Phase 2: suppress best response RH ROI: right PTr (BA 45) 1 Hz 20 min 90 % RMT				
Martin et al., 2004 (crossover, double blind, sham controlled)	4 Chronic (> 5 years) Broca's anomic	Phase 1: locate "best response" RH cortical ROI: rPTr, right POP, right posterior superior temporal gyrus and right motor cortex mouth area	Phase 2:  10 sessions, five sessions a week for 2 consecutive weeks.		BNT, subtests of the BDAE.	
	Mild non-fluent	1 Hz 10 min 90 % RMT		No training.	Follow-up: before stimulation and 2 months after stimulation.	Significant improvement in naming pictures.
	Moderate non-fluent	Phase 2: suppress best response RH ROI: right PTr (BA 45) 1 Hz 20 min 90 % RMT				
	Severe non-fluent					

RH: right hemisphere.  
 LH: left hemisphere.  
 IFG: inferior frontal gyrus.  
 lIFG: left inferior frontal gyrus.  
 rIFG: right inferior frontal gyrus.  
 PTr: pars triangularis.  
 POP: pars opercularis.  
 STG: superior temporal gyrus.  
 rTMS: repetitive transcranial magnetic stimulation  
 BA: Brodmann area.



SLT: speech language therapy.  
 ROI: region of interest.  
 PET: positron emission tomography.  
 fMRI: functional magnetic resonance imaging.  
 EEG: electroencephalography.  
 HF: high frequency.  
 LF: low frequency.  
 CILT: constraint-induced language therapy.  
 CIAT: constraint-induced aphasia therapy.  
 BDAE: Boston diagnostic aphasia examination.  
 BNT: Boston naming test.  
 AAT: Aachen aphasia test.  
 WAB: Western Aphasia Battery.  
 SLTA: Standard Language Test of Aphasia.  
 MMSE: Mini-Mental State Examination.  
 TT: Token Test.  
 iTBS: intermittent theta burst stimulation.  
 cTBS: continuous theta burst stimulation.  
 rCBF: right cerebral blood flow.  
 SD: standard deviation.  
 AMT: active motor threshold.  
 RMT: resting motor threshold.  
 BADA: battery for the analysis of aphasic disorders.

or without SLT.

### 3.6. Targeting

In total, 14 studies used the standard international 10–20 electrode positioning system to locate the coil over the target area. One study tried to identify a “hot spot” over the left primary motor cortex using TMS, and stimulated this area (Naeser et al., 2011). A total of 33 studies used neuronavigational methods based on magnetic resonance imaging (MRI) or functional (f)MRI. Tables 4 and 5 summarize the locations and rTMS procedures used in these studies. Some studies (Abo et al., 2012; Hara et al., 2015; Kakuda et al., 2010; Martin et al., 2009a,b; Winhuisen et al., 2005) also used functional imaging during linguistic tasks (e.g., repetition, naming, or semantic tasks) to identify the best hemisphere and area to target.

### 3.7. Subacute vs. Chronic phase

Most of the studies described in this review focused on patients who had chronic disease (i.e., more than 6 months after a stroke). Only 14 studies investigated the effects of rTMS on patients with subacute disease (Haghighi et al., 2018; Heiss et al., 2013; Khedr et al., 2014; Lu et al., 2014; Ren et al., 2019; Rubi-Fessen et al., 2015; Seniów et al., 2013; Heiss et al., 2007; Thiel et al., 2013; Waldowski et al., 2012; Weiduschat et al., 2011; Winhuisen Lutz et al., 2005; Zhang et al., 2017), including eight randomized clinical trials and one study with both chronic and subacute patients (Kindler et al., 2012). Among these 14 studies, four did not use SLT (Kindler et al., 2012; Lu et al., 2014; Heiss et al., 2007; Winhuisen et al., 2005). Two studies did not find that rTMS had a significant effect (Seniów et al., 2013; Waldowski et al., 2012), and the study with both patient groups found that rTMS was more effective in treating patients who had subacute disease (Kindler et al., 2012).

### 3.8. Outcome measures

In most of the studies described in this review, the outcome measure was an assessment of language performance such as naming tasks, fluency, reading, or auditory verbal comprehension. Interestingly, most studies reported a significant improvement in naming performance. Only one study (Georgiou et al., 2019) investigated quality of life.

### 3.9. Short- vs. long-term effects

In most studies, language performance was assessed before, immediately after, and up to 3 months after treatment. In 27 studies, language performance was assessed after more than 3 months. The maximum interval between treatment and language performance assessment was 46 months (Martin et al., 2009a,b). Significant effects were usually found immediately after treatment. Among those studies that found an improvement in language performance immediately after treatment and also performed long-term assessments (i.e., more than 3 months), only one study did not report that the effects of rTMS persisted (Naeser et al., 2005).

### 3.10. Risks of bias

In most of the studies reviewed, patients included suffered from non-fluent aphasia. Only 7 randomized controlled trials (205 patients) versus 12 (321 patients) included patients who suffered from other subtypes of aphasia. Moreover, only a few studies have detailed the linguistic impairments of patients by looking at the different phonological or semantic disorders for example. The same observation is made concerning other cognitive abilities.

Furthermore, the size and the localization of the lesion were also often poorly described in the reviewed studies and were rarely taken into account for randomization.

Different studies from same research groups seemed to include same patients. This may artificially increase the number of studies that found positive effects of rTMS (Barwood et al., 2011b, 2011c; Barwood et al., 2012b, 2013; Martin et al., 2014; Naeser et al., 2005), as well as the potential risk of unpublished negative results. Meta-analyses seem to have taken into account this possible bias.

## 4. Discussion

### 4.1. Brain targets, the effects of lesion and/or the pattern of aphasia

Most of the studies described in this review targeted anterior language areas, particularly those in the RH. Indeed, Broca's homolog was inhibited in most of the studies. Interestingly, the studies that used tDCS generally targeted left anterior areas, particularly Broca's area or the motor cortex (for a review, see Biou et al., 2019). Even if these two approaches have the same goal of addressing inter-hemispheric imbalance by decreasing activity in the RH or increasing activity in the LH, the

**Table 3**  
Results of meta-analyses.

Meta-analysis	Number of patients, number of studies	Outcome measures	Standardized mean difference and confidence interval	Conclusions
Yao et al., 2020	536 patients, 18 studies (chronic aphasia in five studies, subacute aphasia in nine studies).	Naming ability	SMD = 0.38, 95 % CI [0.16; 0.60] (13 studies, 339 patients)	LF rTMS improved language ability (repetition, naming, comprehension, and written language). The stimulation was effective at both chronic and subacute stages.
		Repetition ability	SMD = 0.52, 95 % CI [0.15; 0.89] (10 studies, 237 patients)	
		Comprehension	SMD = 0.46, 95 % CI [0.17; 0.75] (10 studies, 237 patients)	
		Written language	SMD = 0.65, 95 % CI [0.23; 1.07] (four studies, 93 patients)	
		Everyday communication	SMD = 0.34, 95 % CI [0.01; 0.68] (four studies, 140 patients)	
Li et al., 2020	384 patients, 11 studies (one study with HF rTMS, one study with high and low rTMS, 10 studies with LF rTMS).	Naming ability	SMD = 0.76, 95 % CI [0.16; 1.36]	Significant effect of rTMS on naming accuracy. LF-rTMS had a significant effect on naming scores only at the subacute stage. No significant effect of rTMS on repetition scores. No effect of rTMS on auditory comprehension scores in studies using LF and/or HF rTMS. However, improvements in auditory comprehension observed in the study using HF stimulation and in the study using combined dual-hemisphere rTMS.
		Repetition ability	SMD 0.55, 95 % CI [-0.37; 1.48]	
		Comprehension	SMD = 0.45, 95 % CI [-0.42; 1.33]	
Bucur and Papagno, 2019 (also investigated effect of tDCS)	439 patients (including 217 who had rTMS), 16 studies (eight TMS and eight tDCS).	Naming accuracy (speech in two studies and WAB scores in one study) at follow-up	SMD = 0.53; 95 % CI [0.30; 0.75]	NIBS had a significant medium- to long-term effect (1–6 months post-stimulation) on patients with post-stroke aphasia. "Treatment effects are maintained in time."
Shah-Bazak et al., 2016 (also investigated effect of tDCS)	143 patients, eight studies (58 chronic patients, 45 subacute, 37 mixed).	Naming accuracy	Chronic patients: SMD = 0.348, 95 % CI [0.14; 0.56] Subacute patients: SMD = 0.667, 95 % CI [-0.24; 1.09] All patients: SMD = 0.448, 95 % CI [0.23; 0.66]	TMS combined with SLT had a significant effect in both chronic and subacute populations. TDCS combined with SLT was effective in chronic but not subacute populations.
Otal et al., 2015 (also investigated effect of tDCS)	183 patients, six studies	Naming accuracy	SMD = 0.53, 95 % CI [0.23; 0.84]	No evidence that cathodal tDCS was effective, but both inhibitory rTMS and tDCS stimulation had a significant effect when combined with SLT (considering all studies that used LF rTMS or cathodal tDCS over the non-lesioned hemisphere). No adverse events.
Li et al., 2015	132 patients, four studies	Naming	SMD = 0.51, 95 % CI [0.16; 0.86]	LF-rTMS improves naming ability but not performance in comprehension subtests or repetition scores in patients with post-stroke aphasia.
		Repetition	SMD = 0.31, 95 % CI [-0.04; 0.65]	
		Comprehension	SMD = 0.31, 95 % CI [-0.14; 0.75]	
		Severity of impairment	SMD = 1.26, 95 % CI [0.80; 1.71]	
		Naming accuracy	SMD = 0.52, 95 % CI [0.18; 0.87]	
Ren et al., 2014	160 patients, seven studies	Repetition	SMD = 0.54, 95 % CI [0.16; 0.92]	LF rTMS targeting the PTR of the rIFG with or without SLT had a clinically positive effect on patients with aphasia following a stroke. Improvements were observed in overall language function including naming, repetition, writing, and comprehension.
		Writing	SMD = 0.70, 95 % CI [0.19; 1.22]	
		Comprehension (TT / BDAE or AAT)	SMD = 0.58, 95 % CI [0.07; 1.09] (TT) SMD = 0.32, 95 % CI [0.08; 0.72] (BDAE/AAT)	

SMD: standardized mean difference; WAB: Western Aphasia Battery.

CI: confidence interval; NIBS: non-invasive brain stimulation.

rIFG: right inferior frontal gyrus; TT: Token Test.

PTr: pars triangularis; BDAE: Boston diagnostic aphasia examination.

SLT: speech language therapy; AAT: Aachen aphasia test.

HF: high frequency.

LF: low frequency.

TMS: transcranial magnetic stimulation.

rTMS: repetitive transcranial magnetic stimulation.  
tDCS: transcranial direct current stimulation.

real effects of these modulations are unknown. Indeed, the effects of facilitation or inhibition are deduced from changes in the amplitude of motor potentials (Di Lazzaro et al., 2004). However, these effects may differ in other cortices and multiple mechanisms may be involved, such as direct activation of pyramidal neurons (i.e., layer V of the cortex) (Di Lazzaro et al., 2004; Di Lazzaro and Rothwell, 2014). However, rTMS also produces neuromodulation via effects on different types of interneurons, particularly GABAergic interneurons (Di Lazzaro et al., 2018). Hence, outside the motor cortex, the effects of rTMS may be different. This could explain the significant effects of antagonistic procedures on a particular target, such as the significant effect on language performance of inhibitory (1 Hz) or excitatory (10 Hz) stimulation of Broca's homolog observed by Hu et al. (2018). These counterintuitive results may also be due to the proximity of contralesional areas that have an effect on language performance. In a recent study, several RH temporal areas had either positive or negative effect on language performance in patients with chronic disease (Hope et al., 2017). Such antagonistic effects of proximal areas in the right frontal cortex may be important at different stages following a stroke. The temporal reorganization of language networks may also be important. Even if right homologous areas are important in early recovery from a stroke (Hartwigsen and Saur, 2017), most studies found that inhibition of these areas was beneficial for both subacute and chronic post-stroke patients. Moreover, Hara et al. found that while inhibitory stimulation over the RH or LH could result in significant language improvement, this correlated with changes in cerebral blood flow in Brodmann area 44 only for RH inhibition (Hara et al., 2015). Such observations provide a better understanding of the dynamic reorganization of language networks following a stroke and, in particular, the precise role of the contralesional hemisphere.

Moreover, although most studies targeted contralesional areas, in those studies that targeted the perilesional cortex, the effect of a lesion may depend on the post-stroke stage. Indeed, altered tissue properties can perturb the stimulating currents during TMS (O'Brien et al., 2016). These properties are modified during post-stroke brain reorganization and histological changes. In addition, although the resting motor threshold can be calculated, anatomical variations may influence the real cortical electric field values delivered (Heikkinen et al., 2019). Interestingly, dynamic interactions between histological changes and neuromodulation should also be taken into account because myelin repair depends on neuronal activity (Jia et al., 2019), which may be increased by rTMS.

Understanding the effect of a lesion on language network reorganization is crucial to understanding the electrophysiological effects of rTMS. However, only a few studies have tried to modulate neural activity using a functional approach, and MRI data have shown that the targeted areas are not necessarily involved in language tasks (for a review, see Hartwigsen and Saur, 2017).

#### 4.2. Stimulation and frequency parameters and the interval between SLT and rTMS

This review helps to identify some of the crucial factors that may influence the effectiveness of rTMS in aphasia rehabilitation, particularly when rTMS is combined with SLT. First, the effects of rTMS depend on the number of pulses given and the durations of the rTMS sessions. For example, the effects of TBS on excitation in the motor cortex depend on the number of pulses given, and the level of excitation decreases over time (Di Lazzaro et al., 2008). Therefore, to obtain maximum benefit from neuromodulation and enhance the effects of rehabilitation and training, SLT should be performed immediately after rTMS. However, the precise interval between rTMS and SLT was not reported in every study.

#### 4.3. Influence of SLT and factors unrelated to rTMS

Several studies found that, unlike treatment using tDCS, rTMS was effective even in the absence of SLT (for a review, see Biou et al., 2019), suggesting that magnetic fields may have a direct effect on language reorganization, whereas electric current does not. Various procedures were used in these studies to combine rTMS with SLT. However, although a dose-dependent effect of SLT on aphasia rehabilitation is well established (Brady et al., 2016), Heikkinen et al. did not find that rTMS had a significant effect on patients with aphasia when rTMS was combined with 3-h sessions of SLT (Heikkinen et al., 2019). Moreover, the benefit of potentialized rTMS effect by adding SLT following the stimulation has not been proven yet because no study explored a design including SLT + rTMS versus rTMS alone. However, such a design would be deleterious for patients because SLT remains the gold standard and is efficient particularly in the subacute phase. However, this design might be used in chronic patients who no longer make progress with SLT.

In most of the studies described in this review, rehabilitation involved naming training or was based on patient's symptoms. However, no particular training method was identified as better than the others. A recent meta-analysis also failed to find significant differences among various rehabilitation methods (Brady et al., 2016). Therefore, future studies should focus on an individualized approach to aphasia rehabilitation and, for neuromodulation, individualized parameters and targets. In our opinion, a crucial challenge is that of determining the best treatment for each patient at each particular time, depending on variation in intrinsic factors (e.g., brain/cognitive reserves, genetic factors, and organization of language networks) and extrinsic factors (e.g., the effects of lesions, environmental factors, and access to care facilities). For instance, patient age may influence the effects of rTMS or TBS on rehabilitation (Di Lazzaro et al., 2008). Indeed, an age-dependent effect on neocortical interneurons has been reported for iTBS (Hoppenrath et al., 2016). Early intervention with rTMS may compensate for low activity in some brain areas. However, sub-analyses of patients grouped according to age were not reported in any of the studies described here, and a recent review found no evidence that patient age had a negative impact on recovery from aphasia (Ellis and Urban, 2016).

rTMS should be included in this individualized approach. Indeed, would a patient with a large lesion in the left hemisphere benefit from inhibition or facilitation in the right one? Chieffo et al. (2014) compared inhibition versus facilitation of the right hemisphere. They found improvement after inhibition as well as facilitation, and the patient with the largest lesion involving cortical frontal regions and severe naming impairment has benefited the most from such facilitation. This underlines the bivalent function of right brain areas (Hope et al., 2017), particularly when language networks in the left hemisphere are quasi totally destroyed.

Another crucial point which could be considered for future studies is the influence of the severity and the pattern of language impairment. Indeed, the severity of aphasia and its impact on rTMS efficacy is poorly described in studies (Chieffo et al., 2014). The pattern of aphasia should be taken into account. Most of patients included in studies of the present review suffered from non-fluent or Broca's aphasia, but positive effects of rTMS were found whatever the aphasia subtype (Thiel et al., 2013), and studies reporting no effect of rTMS included patients with quasi all subtypes. We recommend that the subtype of language impairment should be considered for randomization and treatment. Indeed, a study tried to individualize the neuromodulation choosing the target and parameters of stimulation using fMRI (depending left or right recruitment in language task) (Hara et al., 2015). But it is now known that language features contribute to the prediction of aphasia recovery (Glize et al., 2017). As for fMRI, an individualized approach could be based on linguistic abilities to manage the choice of parameters and to improve

**Table 4**  
Detailed procedures for clinical trials.

Study	Material, diameter, and type of coil	Detailed procedure: total number of pulses, pulses per train, train duration, and interval between train events	Detailed sham procedure, method for checking blinding (where reported)	Details for localization of stimulation
Ren et al., 2019	Device: MagPro®  Coil: 7 cm, 8-shaped, air-cooling	Number of pulses = 1200  Pulses per train =1 Hz over 20 min	Sham procedure: used the same coil but placed vertically over the vertex, with the same stimulation parameters used for real stimulation. Checking for patients' blindness: not reported	F4 and CP6 on a standard EEG 10–20 system.
Heikkinen et al., 2019	Device: Nexstim® stimulator using biphasic pulses  Coil: 7 cm, 8-shaped, cooled	Number of pulses = 1200  Pulses per train =1 Hz continuously over 20 min	Sham procedure: 7.5 cm nonconductive plastic block (Nextim Spacing Part) with similar sound and feel to real stimulation. Checking for patients' blindness: "The subjects had not received rTMS previously, they could not know whether they were receiving real or sham rTMS."	Not reported
Hu et al., 2018	Device: MAGSTIM® rapid stimulator  Coil: 7 cm, 8-shaped, air cooling, magnetic field induction of up to 2 T	For 10 Hz stimulation over Broca's homolog: Train duration = 2 s  Interval = 18 s Number of train events = 30 For 1 Hz over Broca's homolog: 600 pulses in 10 min	Sham procedure: "Coil oriented vertically with respect to the surface of the skull. Patients could hear the sound produced by the stimulator, 1 Hz".  Checking for patients' blindness: not reported.	F4 of the extended international 10–20 system for EEG electrode placement.
Haghighi et al., 2018	Device: MAGSTIM®  Coil: 7 cm, double air film coil	Not reported.  Moreover, contradictory information regarding the duration of stimulation: 1 Hz for 20 min in the intervention section but for 30 min in the abstract and methods section of the manuscript	Sham procedure: stimulation at the vertex with 100 % RMT. The coil was tilted to 90°. Similar sound and feel to real stimulation but with no effect on the underlying cortex.  Checking for patients' blindness: not reported.	Not reported
Devido dos Santos et al., 2017	Not reported	Number of pulses = not reported but calculated as 1200 Pulses per train =1 Hz continuously over 20 min	Sham procedure: sham coil that appears similar to the real coil placed at the same location. Checking for patients' blindness: not reported.	F8 of the standard international 10–20 system.
Rubi-Fessen et al., 2015	Device: MAGSTIM® Rapid 2 Coil: double, 7 cm coil	Number of pulses = not reported but calculated as 1200 Pulses per train =1 Hz continuously over 20 min	Sham procedure: stimulation at the vertex with 90 % RMT Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Yoon et al., 2015	Device: MagPro®  Coil: 8-shaped, cooled with air	Number total of pulses = 1200  Pulses per train =1 Hz continuous over 20min	Sham procedure: no stimulation, SLT only. No blind: patients knew what treatment they were receiving. However, the WAB assessors were blinded.	F8 of the standard international 10–20 system.
Wang et al., 2014	Device: MAGSTIM® rapid  Coil: 7 cm, 8-shaped	Number of pulses = 1200  Pulses per train =1 Hz continuously over 20 min	Sham procedure: placebo coil with an identical paradigm to the TMSsyn stimulation. Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Tsai et al., 2014	Device: MAGSTIM® Rapid  Coil: 7 cm, 8-shaped	Number of pulses = 600  Pulses per train =1 Hz continuously over 10 min	Sham procedure: placebo coil that delivered less than 5% of the magnetic output with an audible 'click' on discharge. Checking for patients' blindness: "Since none of the patients had ever undergone rTMS, they could not identify whether the stimulation was real or sham."	Target identified using neuronavigation based on individual high-resolution MRI.
Khedr et al., 2014	Device: MAGSTIM® Model 200  Coil: 9 cm, 8-shaped	Over the right Broca's homolog: Number of pulses = 1000 (500 over right PTr, 500 over right POp).  Pulses per train =1 Hz continuously (duration not reported). Over Broca's area: Number of pulses = 1000	Sham procedure: same parameters as real stimulation, coil rotated 90° away from the scalp in the sagittal plane with similar sound and feel to real stimulation. Checking for patients' blindness: "Patients had never experienced rTMS previously, they did not know whether they were receiving real or sham."	PTr: "The anterior stimulation site was 2.5 cm posterior to the canthus along the canther-tragus line and 3 cm superior to this line."  POp: "The posterior stimulation site was 4.5 cm posterior and 6 cm superior to the canther-tragus line." Target "was validated in three

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Table 4 (continued)

Study	Material, diameter, and type of coil	Detailed procedure: total number of pulses, pulses per train, train duration, and interval between train events	Detailed sham procedure, method for checking blinding (where reported)	Details for localization of stimulation
Chieffo et al., 2014	Device: MAGSTIM® Rapid 2 Coil: H-coil (no more detail)	Interval = 30 s 5 times over PTr, 5 times over POP Pulse per train = 10 Hz Train duration = 5 s Inhibitory: Number of pulses = 900 Pulses per train = 1 Hz continuously (duration not reported) Excitatory: Number of pulses = 800 Pulses per train = 20 Train duration = not reported Interval = 20 s, 40 times Phase 1: Number of pulses = 600 No more detail Phase 2: Number of pulses = 1200	Sham procedure: sham coil placed on the same Brainsway helmet design. Similar sound and feel to the real H-coil but without an effective field. Checking for patients' blindness: patients did not know which stimulation they received, and different personnel were involved in the stimulation sessions. Sham procedure: the coil was perpendicular to the skull surface (over the PTr). Checking for patients' blindness: "Owing to the difference in sensory experience between real rTMS and sham TMS, it is plausible that some patients receiving sham TMS may be aware of the arm of the study to which they have been randomized," but "no patient in the sham arm of the study receives real rTMS prior to crossing over into the rTMS arm".	patients using a 3-dimensional MRI sequence with vitamin E capsules in place". 1.5 cm lateral and 5 cm anterior to the right motor area.
Garcia et al., 2013	Not reported	No more detail	Sham procedure: stimulation over the midline vertex. "Sham procedure was maximal over the sagittal sinus." Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution fMRI (naming task with oral response).
Thiel et al., 2013	Device: MAGSTIM® Rapid Coil: double, 7 cm	Number of pulses = not reported but calculated as 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: "Sham coil that looks similar to the real coil. Sham coil was placed at the same site that was used during the real rTMS." Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Seniów et al., 2013; Mirowska-Guzel et al., 2013	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped, air-cooled	Number of pulses = 1800 Pulses per train = 1 Hz continuously over 30 min	Sham procedure: "Sham coil that looks similar to the real coil. Sham coil was placed at the same site that was used during the real rTMS." Checking for patients' blindness: "It was assumed that because participants had never experienced rTMS, they would not know whether they were receiving real or sham stimulation."	2.5 cm posterior to the canthus along the canther–tragus line and 3 cm superior to the line.
Heiss et al., 2013	Device: MAGSTIM® Rapid 2 Coil: double, 7 cm	Number of pulses = not reported but calculated as 1200 Pulses per train = 1 Hz continuously over 20 min Phase 1:	Sham procedure: stimulation over the midline at the vertex with identical skin sensation. "This stimulation affects the superior sagittal sinus and does not reach any language related cortex." Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Barwood et al., 2013	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped	Number of pulses = 600 Pulses per train = 1 Hz Phase 2: Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: sham coil, which produced the same noise but not the same sensory sensation as the active coil. Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Medina et al., 2012	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Sham procedure: the coil was perpendicular to the scalp (only the rim of the coil contacted the head), same setup. Checking for patients' blindness: double blind, no more details.	Target identified using neuronavigation based on individual high-resolution MRI.
Waldowski et al., 2012	Device: MAGSTIM® rapid Coil: 7 cm, 8-shaped, air-cooled	Number of pulses = not reported but calculated as 1800 Pulses per train = 1 Hz continuously over 15 min, twice.	Sham procedure: air-cooled sham coil with similar appearance, sound, location, and parameters. Checking for blindness: because the patients had never experienced rTMS, they did not know whether they were receiving real or sham rTMS.	Anterior stimulation: 2.5 cm posterior to the canthus along the canther–tragus line and 3 cm superior to this line. Posterior stimulation: 4.5 cm posterior and 6 cm superior to the canther–tragus line.
Kindler et al., 2012	Device: MagPro® X100 Coil: MC-B70, 8-shaped	Number of pulses = 801 burst = 3 pulses at 30 Hz 267 continuous bursts Train duration = 44 s Interval between bursts = 100 ms	Sham procedure: placebo coil: MC-P-B70 Checking for patients' blindness: not reported	Between C4 and F8 in the 10–20 electroencephalogram system.

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Table 4 (continued)

Study	Material, diameter, and type of coil	Detailed procedure: total number of pulses, pulses per train, train duration, and interval between train events	Detailed sham procedure, method for checking blinding (where reported)	Details for localization of stimulation
Barwood et al., 2012b	Device: MAGSTIM® Rapid 2 Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train =1 Hz continuously over 20 min	Sham procedure: sham coil, identical to the real coil. Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Barwood et al., 2011a	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train =1 Hz continuously over 20 min	Sham procedure: sham coil identical in shape and size to the real stimulation coil but produced no magnetic field. Checking patients' for blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Barwood et al., 2011b	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train =1 Hz continuously over 20 min	Sham procedure: sham coil identical in shape and size to the real stimulation coil but produced no magnetic field. Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Barwood et al., 2011c	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Number total of pulses = 1200 Pulses per train =1 Hz continuously over 20 min	Sham procedure: sham coil identical in shape and size to the real stimulation coil but produced no magnetic field. Checking for patients' blindness: not reported	Target identified using neuronavigation based on individual high-resolution MRI.

MRI: magnetic resonance imaging.

fMRI: functional magnetic resonance imaging.

TMS: transcranial magnetic stimulation.

rTMS: repetitive transcranial magnetic stimulation.

PTt: pars triangularis.

POp: pars opercularis; EEG: electroencephalography.

BA: Brodmann area.

WAB: Western Aphasia Battery.

SLT: speech language therapy.

RMT: resting motor threshold.

rTMS effects. Is it better to target Wernicke's area for patients with Wernicke's aphasia or is it better to facilitate left motor or frontal areas for patients with non-fluent aphasia, etc.? These questions need more investigations, and the best paths to individualize rTMS treatment should also include clinical and linguistic factors in addition to anatomical and functional ones.

Moreover, it has been shown across different post-stroke cognitive consequences that educational levels seem to be associated with less post-stroke cognitive deficits (Nunnari et al., 2014), suggesting that education 'protects' from lesion consequences providing resilience. Other specific cognitive factors have been considered as possibly related to the recovery potential, and for example, new word learning abilities predict the outcome following therapy for anomia in chronic aphasic patients (Dignam et al., 2016). Besides new word learning, attentional capacity is another potential cognitive domain which may be involved in language recovery. The involvement of attentional and executive functions on language performance has been reported on both aphasic and healthy (neurologically unimpaired) speakers. In aphasic speakers, performance declines for instance in several linguistic tasks under shared attention (McNeil et al., 2006; Murray et al., 1997). It has also been suggested that domain-general cognitive control capacity may be related to recovery from aphasia (Brownsett et al., 2014). Such abilities were poorly described in rTMS studies.

#### 4.4. Neural effects of rTMS in aphasia

Several studies used fMRI to investigate changes in brain activity caused by rTMS. Indeed, improvements that result from rTMS stimulating the LH (Dammekens et al., 2012; Griffis et al., 2016; Hara et al., 2017; Szaflarski et al., 2011, 2018; Zhang et al., 2017) or inhibiting the RH (Hara et al., 2017; Harvey et al., 2017; Heiss et al., 2013) are apparently associated with modulation of cerebral activity in perilesional areas (Zhang et al., 2017), LH areas that are crucial for language such as the IIFG (Griffis et al., 2016; Harvey et al., 2017) and left inferior parietal lobe (Szaflarski et al., 2018), or right homologous areas

(Dammekens et al., 2012; Griffis et al., 2016; Harvey et al., 2017; Szaflarski et al., 2018). Therefore, the observed improvements may be associated with changes in the respective roles of these LH or RH areas or with a decrease in the interhemispheric imbalance (Hara et al., 2017; Heiss et al., 2013; Szaflarski et al., 2011).

Little is known about the possible effects of rTMS "in the fourth dimension", which involves investigating the temporal processes that are important for language tasks using magnetoencephalography or electroencephalography (for temporal aspects of neural processes involved in naming and stroke patients, see Laganaro et al., 2013 (Laganaro et al., 2013)). Indeed, rTMS effects may specifically modulate language processes only within particular time windows. For example, changes in the N400 time window for a semantic judgment task were associated with improvements in aphasic symptoms (Barwood et al., 2011c, 2012b). Further studies are needed to understand these relationships.

Interestingly, rTMS interferes with the secretion of brain-derived neurotrophic factor (BDNF) (Luo et al., 2017), known to be involved in better recovery (Schäbitz et al., 2007). The BDNF genotype influences the effects of rTMS on motor recovery (Chang et al., 2016) and possibly aphasia recovery (Mirowska-Guzel et al., 2013), and it also modulates the effects of tDCS (Fridriksson et al., 2018). Another challenge is to identify new molecular pathways that could be targeted to improve aphasia recovery and rTMS efficacy. In addition to genetic factors, epigenetic mechanisms such as post-translational modifications of histone proteins and microRNAs (Kassis et al., 2017), recently known as enhancers of plasticity observed during repair processes after stroke, should be explored and might predict better response to NIBS.

#### 4.5. Value of rTMS for understanding language reorganization and recovery from aphasia

Finally, rTMS is a valuable tool for investigating both language networks in healthy subjects and network reorganization following a stroke in patients with aphasia. Both tDCS and rTMS may be used to

**Table 5**  
Detailed procedure for other studies or case reports.

Study (design)	Material, diameter, and type of coil	Detailed procedure: total number of pulses, pulses per train, train duration, and interval between train events	Location of stimulus
Versace et al., 2020 a	Device: High power Magstim 200  Coil: 9 cm, 8-shaped	Number of pulses = 600  Pulses per train = 10 bursts of three stimuli at 50 Hz Total duration = 200 s Interval = 10 s	CP5 and CP6 on the standard international 10–20 system.
Georgiou et al., 2019 (case report)	Device: Magstim® Rapid 2  Coil: 7 cm 8-shaped, double air film coil	Number of pulses = 600  Pulses per train = 3 Train duration = 40 s Interval = 200 ms	Target identified using neuronavigation based on individual high-resolution MRI.
Harvey et al., 2019 (prospective studies)	Device: Magstim® Super Rapid 2  Coil: 7 cm, 8-shaped	Number of pulses = 600  Pulses per train = 3 Train duration = 40 s Interval = 200 ms	Target identified using neuronavigation based on individual high-resolution MRI.
Szaflarski et al., 2018 (feasibility study)	Device: Magstim® Rapid 2  Coil: 8 shaped	Number of pulses = 600  Pulses per train = 10 bursts of three pulses at 50 Hz Train duration = 2 s Interval = 10 s	Target identified using neuronavigation based on individual fMRI: semantic decision/ tone decision fMRI task.
Rossetti et al., 2019 (case report)	Device: Neuro MS/D therapeutic variant stimulator®  Coil: cooled angular, 8-shaped	Number of pulses = 1200  Pulses per train = 1 Hz continuously (train duration not reported).	Target identified using neuronavigation based on individual high-resolution MRI.
Harvey et al., 2017 (prospective study)	Device: MAGSTIM Rapid®  Coil: 7 cm, 8-shaped	Treatment phase:  Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min Optimal site finding phase: Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min	Target identified using neuronavigation based on individual high-resolution MRI.
Ilkhani et al., 2018 (double-blind study, no control group)	Not reported	Pulses per train = 1 Hz continuously over 10 min  LF-rTMS:	Not reported

**Table 5 (continued)**

Study (design)	Material, diameter, and type of coil	Detailed procedure: total number of pulses, pulses per train, train duration, and interval between train events	Location of stimulus
Hara et al., 2017 (single group intervention study)	Device: MagPro® R30  Coil: 7 cm, 8-shaped	Number of pulses = 2400 Pulses per train = 1 Hz continuously over 40 min HF-rTMS: Number of pulses = 2400 Pulses per train = 10 Hz over 12 min	F8 on the extended international 10–20 System for EEG electrode placement.
Zhang et al., 2017 (case report)	Device: Yiuride CCY-II, Wuhun® Coil: 90-mm round coil stimulator	Not reported	The crossing point between T3-Fz and F7-Cz on the standard international 10–20 system.
Hara et al., 2015 (single group intervention study)	Device: MagPro® R30 stimulator  Coil: 7 cm, 8-shaped	Number of pulses = 2400  Pulses per train = 1 Hz continuously over 40 min	For patients with non-fluent aphasia, F7/8 on the 10–20 electrode system. For patients with fluent aphasia, CP5/6 on the 10–20 electrode system.
Vuksanović et al., 2015 (case report)	Device: MAGSTIM® Rapid  Coil: 7 cm, 8-shaped	cTBS:  Number of pulses = 600 Pulses per train = 50 Hz continuously Train duration = 40 s Interval = uninterrupted iTBS: Number of pulses = 600 Pulses per train = 3 Train duration = 2 s Interval = 8 s Number of pulses = 600 Pulses per train = 3 Train duration = 2 s Interval = 10 s	F7 and F8 on the standard international 10–20 system.
Griffis et al., 2015 (prospective study)	Not reported	Number of pulses = 600 Pulses per train = 3 Train duration = 2 s Interval = 10 s	Target identified using neuronavigation based on individual high-resolution MRI.
Martin et al., 2014 (case report)	Device: MAGSTIM® Super Rapid HF  Coil: 7 cm, 8-shaped, air-cooled	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Target identified using neuronavigation based on structural MRI scan.
Lu et al., 2014 (case report, with a control subject)	Device: MAGSTIM® Rapid 2 Coil: 7 cm, 8-shaped, air-cooled	Number of pulses = 600 Pulses per train = 1 Hz continuously	Broca's area identified as BA 44/45 based on the Juelich Histological Atlas.

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Table 5 (continued)

Study (design)	Material, diameter, and type of coil	Detailed procedure: total number of pulses, pulses per train, train duration, and interval between train events	Location of stimulus
Al-Janabi et al., 2014 (two case reports, with sham treatment)	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped	(train duration not reported). Number of pulses = 600 Pulses per train = 50 Hz Pulse per train = 3 Train duration = 2 s Interval = 10 s	Target identified using neuronavigation based on individual high-resolution fMRI.
Dammekens et al., 2012 (case report)	Device: MAGSTIM® Super Rapid Stimulator Coil: 8-shaped (no more detail)	Number of pulses = 2000 Pulses per train = 200, 10 Hz No more detail	Target identified using neuronavigation based on individual high-resolution MRI.
Barwood et al., 2012a (open protocol case series)	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Target identified using neuronavigation based on individual high-resolution MRI.
Naeser et al., 2012 (case report)	Device: MAGSTIM® Super Rapid HF Magnetic Stimulator Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Target identified using neuronavigation based on individual high-resolution MRI.
Abo et al., 2012 (pilot study)	Device: MagPro® R30 Coil: 7 cm, 8-shaped	Number of pulses = 2400 Pulses per train = 1 Hz continuously over 40 min	F7/8 or CP 5/6 on the standard international 10–20 system.
Naeser et al., 2011	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min 1 train	Target identified using neuronavigation based on individual high-resolution MRI. M1 was identified based on muscle response after stimulation.
Szaflarski et al., 2011 (prospective study)	Device: MAGSTIM® Rapid 2 Coil: 7 cm, 8-shaped	Number of pulses = 600 Pulses per train = 600 Train duration = 2 s Interval = 10 s Total duration = 200 s	Target identified using neuronavigation based on individual high-resolution MRI. fMRI: semantic decision/ tone decision fMRI task.
Weiduschat et al., 2011 (a randomized controlled pilot study)	Device: MAGSTIM® Rapid 2 Coil: double 7 cm	Not reported	Target identified using neuronavigation based on individual high-resolution MRI.
Cotelli et al., 2011 (pilot	Device: MAGSTIM®	Number of pulses = 2000	Target identified using neuronavigation

Table 5 (continued)

Study (design)	Material, diameter, and type of coil	Detailed procedure: total number of pulses, pulses per train, train duration, and interval between train events	Location of stimulus
study, sham condition)		Pulses per train = 40 Train duration = 2 s Interval = 28 s Number of train events = 50	based on MRI template centered on Talairach coordinates X = -35, Y = 24, Z = 48, corresponding to the left dorsolateral prefrontal cortex (BA 8/9).
Jung et al., 2010 (case report)	Coil: double 7 cm air-cooled Device: MAGSTIM® Rapid 2 Coil: 9 cm, round coil	Not reported (protocol: Naeser et al., 2005) Phase 1: Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min Phase 2: Number of pulses = 1200 Pulses per train = 1 Hz continuously (train duration not reported)	P3 on the standard international 10–20 system.
Hamilton et al., 2010 (case report)	Device: 7 cm, 8-shaped	Phase 1: Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min Phase 2: Number of pulses = 1200 Pulses per train = 1 Hz continuously (train duration not reported)	Target identified using neuronavigation based on individual high-resolution MRI.
Kakuda et al., 2010 (case series pilot study)	Device: MAGSTIM® Rapid Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min Phase 1: Number of pulses = 600 Pulses per train = 1 Hz over 20 min Phase 2: Number of pulses = 1200 Pulses per train = 1 Hz over 20 min	Target based on fMRI patient data and identified by an experienced neurosurgeon.
Naeser et al., 2010 (pilot study)	Device: MAGSTIM® Super Rapid HF Coil: 7 cm, 8-shaped	Phase 1: Number of pulses = 600 Pulses per train = 1 Hz over 20 min Phase 2: Number of pulses = 1200 Pulses per train = 1 Hz over 20 min	Target identified using the frameless stereotaxic system based on individual high-resolution MRI.
Naeser et al., 2010 (case report)	Coil: 7 cm, 8-shaped	Phase 1: Number of pulses = 600 Pulses per train = 1 Hz continuously over 10 min Phase 2: Number of pulses = 1200 Pulses per train = 1 Hz continuously over 20 min	Target identified using the frameless stereotaxic system based on individual high-resolution MRI.
Naeser et al., 2010 (case report)	Coil: 7 cm, 8-shaped	Not reported	CP5 on the standard international 10–20 system.

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Table 5 (continued)

Study (design)	Material, diameter, and type of coil	Detailed procedure: total number of pulses, pulses per train, train duration, and interval between train events	Location of stimulus
Martin et al., 2009a,b (pilot study)	Device: MAGSTIM® Super Rapid HF Coil: 7 cm, 8-shaped	Number of pulses = not reported Pulses per train =1 Hz continuously over 20 min	Target identified using a frameless stereotaxic system based on individual high-resolution fMRI.
Martin et al., 2009a,b (case report)	Device: Not reported Coil: 7 cm, 8-shaped	Not reported	Not reported
Heiss et al., 2007	Not reported	Not reported	Not reported
Winhuisen et al., 2005 (prospective study)	Device: MAGSTIM® Coil: 7.6 cm, 8-shaped	Train duration = 10 s (no more detail)	Target identified using neuronavigation based on individual high-resolution MRI.
Naeser et al., 2005 (open protocol study)	Device: MAGSTIM® Super Rapid HF Coil: 7 cm, 8-shaped	Number of pulses = 1200 Pulses per train =1 Hz over 20 min	Target identified using neuronavigation based on individual high-resolution MRI.
Naeser et al., 2005 (case report)	Coil: 7 cm, 8-shaped	Phase 1: Number of pulses = 600 Pulses per train =1 Hz continuously over 10 min Phase 2: Number of pulses = not reported Pulses per train =1 Hz over 20 min	Target identified using a frameless stereotaxic system based on individual high-resolution MRI.
Martin et al., 2004 (crossover, double blind, sham condition)	Device: MAGSTIM® Coil: 7 cm, 8-shaped	Phase 1: Number of pulses = not reported Pulses per train =1 Hz continuously over 10 min Phase 2: Number of pulses = not reported Pulses per train =1 Hz over 20 min	Target identified using neuronavigation based on individual high-resolution MRI.

MRI: magnetic resonance imaging.

fMRI: functional magnetic resonance imaging.

BA: Brodmann area.

TMS: transcranial magnetic stimulation.

rTMS: repetitive transcranial magnetic stimulation.

HF: high frequency.

LF: low frequency.

EEG: electroencephalography.

cTBS: continuous theta burst stimulation.

iTBS: intermittent theta burst stimulation.

clarify the role of the RH in language reorganization. The changes observed in interhemispheric balance due to contralesional homolog activity are not limited to language functions but represent a common phenomenon after a stroke. However, the effects of inhibiting the right homologous language areas, particularly the rIFG, suggest a maladaptive role for the RH in reorganizing the language network. The results of this review suggest that combining rTMS with neuroimaging may

improve our understanding of adaptive processes in the healthy and lesioned language network.

## 5. Conclusion

This systematic review summarizes the results of studies investigating the effects of rTMS on patients with aphasia. Although further studies are needed to understand the neural mechanisms involved more fully, our review shows that rTMS can have beneficial effects in post-stroke patients. Recent studies have shown that rTMS may be safely implemented routinely to enhance the rehabilitation of patients with subacute and chronic aphasia. Research using rTMS may also provide valuable insight into the reorganization of language networks.

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### 3.2. Une approche individualisée de la rTMS

A la lumière de cette revue, nous constatons que l'approche très majoritairement utilisée dans les études incluses, consistait en l'application de rTMS inhibitrice ciblant le gyrus frontal inférieur droit, et ce quel que soit le profil clinique (e.g., type de trouble langagier, sévérité de l'atteinte), le stade de récupération (i.e., subaigu ou chronique), ou la localisation de la lésion (i.e., atteignant des régions corticales ou faisceaux spécifiques, des structures sous-corticales).

Nous nous sommes donc questionnés sur la possibilité et la pertinence de proposer une approche plus individualisée, basée sur les différents facteurs sus-cités. Au-delà de la pertinence d'une telle approche, une étude récente met en lumière le possible effet délétère d'appliquer la même stimulation pour des personnes présentant des profils divers, et dont les mécanismes de récupération pourraient être très différents (Stefaniak et al., 2022).

L'approche en pratique clinique de la rTMS, recommandée par la HAS (HAS, 2022) et questionnée par Liepert (2022), devrait alors prendre en compte ces variabilités inter-individuelles.

Quelles sont les possibilités et la pertinence d' <b>individualiser</b> la rTMS pour les personnes aphasiques post-AVC ?
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## 4. Les techniques de neuroimagerie

La recherche de biomarqueurs de récupération de l'aphasie post-AVC, qu'elle soit spontanée ou induite par des traitements (médicaments, orthophonie, NIBS), peut être réalisée via différentes techniques de neuroimageries telles que l'EEG, la MEG ou l'IRMf. Cependant, il faut en moyenne moins d'une seconde à une personne neurotypique pour dénommer le nom d'un objet à partir d'une image. Ceci explique l'intérêt majeur de la MEG ou de l'EEG, dont la précision temporelle est de l'ordre de la milliseconde, quand la précision temporelle de l'IRMf est de l'ordre de la seconde (Vion-Dury & Blanquet, 2008). Dans cette thèse, nous nous centrerons ainsi uniquement sur les aspects électrophysiologiques pour la récupération du langage post-AVC.

### 4.1. L'EEG et la MEG : généralités

L'EEG permet d'enregistrer l'activité électrique du cerveau. Sa précision spatiale dépendra principalement du nombre d'électrodes. Les bonnets disposant de plus de 64 électrodes permettent de réaliser des analyses de reconstruction de source et de localiser globalement l'origine du signal à l'aide de calculs statistiques (Im, 2018; Vion-Dury & Blanquet, 2008).

La MEG analyse les variations de champs magnétique cérébral et dispose d'une plus grande précision spatiale (2-3mm) (Vrba & Robinson, 2001).

### 4.2. Activité électrophysiologique spontanée

L'analyse en continu pendant des périodes de repos, permet de recueillir différents rythmes d'ondes correspondant à l'activité d'une grande population de neurones et déterminant l'état d'éveil du sujet (Tableau 1) (Vion-Dury & Blanquet, 2008).

*Tableau 1 : Rythmes d'ondes en fonction de l'activité associée (Crespel & Gelisse, 2005; Vieth et al., 1996; Vion-Dury & Blanquet, 2008)*

Rythme d'onde	Bande de fréquences	Activité associée
Delta	1 – 4 Hz	Sommeil à ondes lentes
Thêta	4 – 8 Hz	Sommeil paradoxal
Alpha	8-13 Hz	Repos yeux clos, processus cognitifs de haut niveau
Beta	13-35 Hz	Activité cognitive
Gamma	> 35 Hz	Processus perceptuels

### 4.3. Potentiels évoqués reliés (ERP)

L'analyse de l'activité électrique reliée à une tâche spécifique constitue un potentiel évoqué relié (ERP), et prend en compte une plus petite population de neurones. L'ERP est le résultat de la moyenne de l'ensemble des stimuli répétés (e.g., lors d'une tâche de dénomination d'images), débarrassés de leurs artefacts (e.g., clignements oculaires, mouvements musculaires) (Vion-Dury & Blanquet, 2008).

Les ERPs peuvent ensuite être analysés via :

- Les formes d'ondes (waveform) ou puissance de champ globale (global field power) ;
- Les topographies, qui mettent en évidence des périodes de stabilité du champ électrique/magnétique, durant un temps minimum, localisé dans une zone minimale (i.e., nombres d'électrodes adjacentes), et supposé correspondre à des processus cognitifs spécifiques pouvant être rapprochés de modèles établis (e.g., modèle de dénomination d'images définissant dans le décours temporels des processus visuels, puis lexico-sémantiques, et phonologiques plus tardifs (Indefrey, 2011)) ;
- Le temps-fréquence proposant une décomposition du signal en fonction du temps et de la fréquence, qui permet ainsi une analyse des ondes synchronisées sur un événement spécifique (i.e., apparition d'un stimulus), mais également de celles qui ne le sont pas (Im, 2018).

## 5. Aphasie post-AVC et changements électrophysiologiques

### 5.1. Une revue systématique de littérature

Nous avons rédigé une seconde revue systématique de la littérature incluant l'ensemble des études longitudinales en EEG ou en MEG ayant étudié les changements électrophysiologiques en lien avec la récupération spontanée, ou induite par des traitements (médicaments, orthophonie, NIBS) de l'aphasie post-AVC. Les différents biomarqueurs de réponse aux traitements révélés par certaines études ont été regroupés dans un tableau récapitulatif à la fin de la revue (Tableau 5).

L'article a été publié en 2023 dans la revue « Brain Topography ».

Article n°2 : *Electrophysiological changes in patients with post-stroke aphasia: a systematic review*



# Electrophysiological Changes in Patients with Post-stroke Aphasia: A Systematic Review

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## Abstract

**Background** Magnetoencephalography (MEG) and electroencephalography (EEG) record two main types of data: continuous measurements at rest or during sleep, and event-related potentials/evoked magnetic fields (ERPs/EMFs) that involve specific and repetitive tasks. **In this systematic review**, we summarized longitudinal studies on recovery from post-stroke aphasia that used continuous or event-related temporal imaging (EEG or MEG). **Methods** We searched PubMed and Scopus for English articles published from 1950 to May 31, 2022. **Results** 34 studies were included in this review: 11 were non-interventional studies and 23 were clinical trials that used specific rehabilitation methods, neuromodulation, or drugs. The results of the non-interventional studies suggested that poor language recovery was associated with slow-wave activity persisting over time. The results of some clinical trials indicated that behavioral improvements were correlated with significant modulation of the N400 component. **Discussion** Compared with continuous EEG, ERP/EMF may more reliably identify biomarkers of therapy-induced effects. Electrophysiology should be used more often to explore language processes that are impaired after a stroke, as it may highlight treatment challenges for patients with post-stroke aphasia.

**Keywords** Aphasia · Stroke · Electroencephalography · Magnetoencephalography · Event-related potential · Evoked magnetic field

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## Introduction

Aphasia usually develops after left hemisphere (LH) injury; it affects one-quarter to one-third of stroke patients (Brust et al. 1976; Pedersen et al. 1995) and has a substantial impact on their quality of life (Lam and Wodchis 2010). Spontaneous neuroplasticity is important for the recovery of patients with aphasia, and can be enhanced by speech and language therapy (SLT) (Brady et al. 2016; Stephens 2017), drugs (Berthier 2021; Zhang et al. 2018), or non-invasive brain stimulation (NIBS) (Arheix-Parras et al. 2021; Biou et al. 2019). Neuronal reorganization is based on perilesional and contralesional rearrangement.

To investigate the reorganization of language networks after spontaneous recovery or identify therapy-induced effects, most studies use positron emission tomography or functional magnetic resonance imaging (MRI). Although these methods can accurately examine spatial components, their temporal accuracy is low. In contrast, electroencephalography (EEG) and magnetoencephalography (MEG) accurately record the electrical activity of the brain at the millisecond time scale. This high temporal resolution allows

exploration of other important aspects of brain reorganization during aphasia recovery.

MEG and EEG record two main types of data: continuous and event-related potentials/evoked magnetic fields (ERPs/EMFs). Continuous measurements are mainly recorded at rest or during sleep; they allow observation of spontaneous neural oscillation. Among patients in the subacute stage of recovery from a stroke, abnormal slow-wave activity (SWA) has been detected near brain lesions while at rest (Kamada et al. 1997); reduced interhemispheric synchronization in the alpha frequency band has also been observed (Dubovik et al. 2012). Such changes in neural oscillations merit further exploration in patients with aphasia. Event-related recordings rely on ERPs/EMFs that are associated with specific and repetitive tasks; they can be understood based on waveforms, time-frequency analyses, and topographic analyses (Herrmann et al. 2014; Laganaro 2014). In neurolinguistic studies, evoked potentials are induced by perception/comprehension or production tasks. In perception/comprehension tasks, several ERP components are usually observed in individuals without brain damage; these include Na, Pa, Nb, P300, N1, N200, N400, and mismatch negativity (MMN). In production tasks such as picture naming, alternating positive and negative peaks/ERP components are also typically observed, including P100, N1, P200, N200, and P300 (Laganaro 2017). Moreover, inverse solutions can be used to estimate functional connectivity and identify regions of interest that demonstrate synchronization (in terms of electrical or magnetic activity magnitude). Such ERP components reflect language processes that are impacted by aphasia and may change during post-stroke recovery.

In this review, we decided to focus on longitudinal studies. Even if cross-sectional studies allow to compare electrophysiological data of neurotypical and aphasic individuals, they cannot provide information about changes related to neuroplasticity. The aim of the present review was to highlight how electrophysiological measures could change over time, in order to identify biomarkers for aphasia recovery and rehabilitation. Therefore, we specifically reviewed longitudinal studies that explored recovery from post-stroke aphasia using temporal imaging (EEG or MEG) with continuous or event-related measurements.

## Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al. 2021). We searched PubMed and Scopus for English articles published from 1950 to May 31, 2022, using the following keywords in titles, abstracts, and keywords: “aphasia” AND “EEG” OR “electroencephalography” OR “MEG” OR “magnetoencephalography” OR “ERP” OR “event-related potential.”

Three authors (SAP, BG, and GP) screened the retrieved articles for eligibility. Eligible studies used EEG or MEG to explore post-stroke aphasia while at rest or during various tasks. We excluded articles that focused on primary progressive aphasia, epilepsy, brain tumors, mental disorders, and/or dementia; we also excluded studies that focused on neurotypical individuals, as well as EEG studies that lacked temporal analyses. Because reviewing only randomized clinical trials may not have provided a complete picture of the available literature, we also included case reports and prospective studies.

## Results

On May 31, 2022, after removing duplicates and articles on other topics, the literature search yielded 245 articles. The article selection process was conducted as shown in Fig. 1. Overall, the review included 34 studies on temporal imaging (EEG/MEG) analysis during recovery from post-stroke aphasia. Among these 34 studies, 11 were non-interventional studies after recovery (187 patients), while 23 were clinical trials using specific rehabilitation methods (14 studies, 145 patients), neuromodulation (7 studies, 133 patients), or drugs (2 studies, 48 patients). Tables 1, 2, 3 and 4 summarize the main findings of these articles.

### Non-interventional Studies After Recovery

Table 1 presents the main findings after recovery in 187 patients with post-stroke aphasia reported by 11 non-interventional studies.

### Comparison with Healthy Controls

In all but one non-interventional study (Jabbari et al. 1979), data were also collected from neurotypical individuals for comparison. Two studies (Becker and Reinvang 2007b; Cocquyt et al. 2020) used a control group from a previous study.

### Imaging Modality

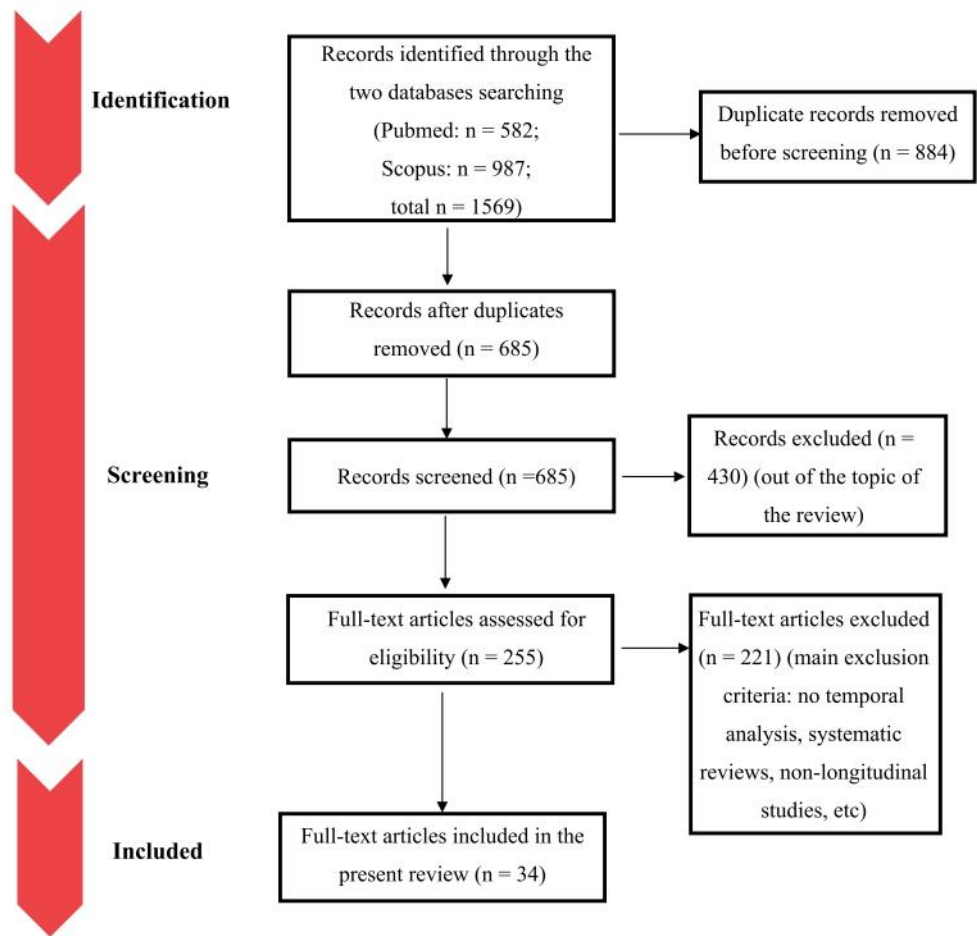
EEG was the imaging modality for all non-interventional studies. High-resolution imaging was used in only two (Dalton et al. 2021; Nicolo et al. 2015) of the 11 studies that involved continuous analyses. All ERP/EMF studies used <64 electrodes for analysis.

### Studies that Used ERPs or EMFs

Seven studies Becker and Reinvang 2007b; Cobiauchi and Giaquinto 2000; Cocquyt et al. 2020; Ilvonen et al., 2003; Nolfé et al. 2006; Praamstra et al. 1993; Rojas Sosa et al.



**Fig. 1** flow diagram adapted from PRISMA 2020



2009) used ERPs (including auditory evoked potentials) or EMFs. All seven studies used repetitive tasks, although two of them (Praamstra et al. 1993; Rojas Sosa et al. 2009) also recorded resting-state data. Moreover, all seven studies focused on speech perception/comprehension; most of the studies conducted waveform analyses of the main ERP components (e.g., N1, N200, N400, P200, P300, and MMN). None of the studies investigated changes in speech production, nor did they report time-frequency or topographic analyses.

Two studies (Praamstra et al. 1993; Rojas Sosa et al. 2009) that recorded auditory evoked potentials focused on middle and late latency responses (i.e., Na, Pa, Nb, N1, and P200 components). Rojas Sosa et al. (2009) found a link between a decrease in middle latencies (Pa and Nb) and increase in language scores: at six months post-stroke, shorter latencies were associated with better aphasia scores. Praamstra et al. (1993) also found a possible link between abnormal auditory evoked potentials and severe auditory comprehension impairments at various stages of recovery, ranging from subacute to chronic. Abnormal auditory evoked potentials were characterized by a reduced response

of the lesioned hemisphere to auditory stimuli, as indicated by dipole source analyses.

In two studies that used MMN (Cocquyt et al. 2020; Ilvonen et al., 2003) during passive listening tasks (e.g., syllable discrimination and watching a silent movie with “improvised sounds”), Ilvonen et al. (2003) found that increased MMN amplitude was correlated with improvements in comprehension test results from 10 days to 3 months post-stroke; Cocquyt et al. (2020) did not find any differences in MMN amplitude or latency at 1 week post-stroke compared with healthy individuals.

In two auditory ERP studies that used tone/syllable discrimination and word/non-word listening tasks (Becker and Reinvang 2007b; Cobiauchi and Giaquinto 2000), increases in P300 amplitude were found during recovery. Another study (Nolfe et al. 2006) showed that the presence of the P300 within the first month after stroke was associated with a better comprehension outcome at six months in patients with global aphasia. The authors also found that if the P300 was present within the first few weeks after stroke, its amplitude in the temporoparietal left electrodes increased during

**Table 1** Design and main results of EEG/MEG non-interventional studies

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Type of temporal imaging, number of channels, and tasks	Outcome measurements (behavioral and neuroimaging)	Longitudinal follow-up (number and interval of EEG/MEG measurements) and speech therapy	Main results
Dalton et al. 2021 Cohort study	19 6 Anomic 3 Conduction 1 Wernicke 1 Transcortical motor 1 Broca 7 above the WAB cut-off for clinical aphasia Chronic (mean 54.2 months post-stroke [range: 15–183 months]) 2 bi/multilingual 15 LH stroke, 4 bilateral stroke 24 healthy controls matched according to age	EEG 64 channels Resting state with eyes open and closed	Sensorimotor function tested with in-house battery that included sensation, proprioception, motricity, and fine motor coordination tasks, RBANS, WAIS-PC, ABA-2, Aprosodia Battery, Discourse Production Test, WAB, BNT, and Discourse Comprehension Test Continuous EEG: delta, theta, alpha, and beta bands	2 measurements separated by 1 month No SLT mentioned	Moderate to good stability in alpha, beta, and theta bands for patients with aphasia in the chronic stage; poor reliability in the delta band for both patients and controls Greater beta power (eyes closed or open) and lower theta power (eyes closed) in patients with aphasia compared with controls Discourse informativeness positively correlated with power in high-frequency bands (alpha and beta) and negatively correlated with power in low-frequency bands (theta)
Cocquyt et al. 2020 Case series	4 T1: 4 Wernicke T2: 3 Amnesic and 1 Unclassified T1 acute (mean 1 week post-stroke [range: 0.7–1.4 weeks]) to T2 chronic (mean 29.8 weeks post-stroke [range: 20.1–48.9 weeks]) 71 healthy controls (normative data from previous study (Aerts et al. 2013))	EEG/ERP 20 channels Auditory phoneme discrimination during one passive condition (MMN) and one attentive condition (P300)	AAT (TT, repetition, naming, written language, and language comprehension), PALPA for 3 patients (phoneme discrimination in words, pseudowords, and auditory lexical decision) ERP: waveform amplitudes (P300 and MMN) and electrode positions	2 measurements separated by 5–12 months ≤ 2 speech therapy sessions of 30 min per week (no details regarding type of therapy)	Behavioral outcome: good recovery in all four patients (best recovery in patients 1 and 3) At T1, similar amplitudes and latencies of phonological MMN for patients and controls Normal P300 (slightly increased latency for patient 3) for patients with better recovery, but P300 with increased latency or decreased amplitude for patients with worse recovery (patients 2 and 4). Early presence of a normal P300 could predict better recovery of language comprehension At T2, MMN and P300 normalized except for patient 1 (P300: reduced amplitude and increased latency) and patient 3 (MMN: increased latency)
Nicolo et al. 2015 Cohort study	24 At least mild motor or language impairment (aphasia type not reported) Subacute (T1: 3 weeks post-stroke; T2: 3 months post-stroke) 15 LH stroke, 9 RH stroke 26 healthy controls matched according to age	EEG 128 channels Task-free state	GeBAS Continuous EEG: coherence of neural oscillations (beta, alpha, and theta), functional connectivity, and weighted node degree	2 measurements separated by 2 months Standard tailored speech therapy sessions (no details regarding frequency or duration)	Better language recovery correlated with T1 measurements: • oscillation coherence between language areas and entire cortex • larger global index of functional connectivity in right Broca homolog Poor clinical improvement correlated with persistent deviation of alpha frequencies toward beta or theta frequencies at T2

Table 1 (continued)

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Type of temporal imaging, number of channels, and tasks	Outcome measurements (behavioral and neuroimaging)	Longitudinal follow-up (number and interval of EEG/MEG measurements) and speech therapy	Main results
Rojas Sosa et al. 2009 Individual cohort study	10 6 Mixed non-fluent 2 Sensory 1 Motor 1 Transcortical sensory Acute (3 days post-stroke) to subacute ( $9.6 \pm 4.2$ days, 2 months, 4 months, 6 months post-stroke) 30 healthy controls matched according to age and sex	EEG/ERP 2 sources (one active at Cz, one reference at the left mastoid) Sleep or quiet rest. (stimuli = condensation pips)	BDAE AEP: waveforms (middle latency auditory responses)	5 measurements: 2 separated by 6 days and 3 separated by 2 months Individual rehabilitation therapy during the first 3 months (no details regarding frequency, duration, or content)	Behavioral outcome: language improvements indexed only by BDAE scale score at baseline (not type of aphasia, age, or sex) Decreased latency of Pa and Nb peaks (toward normalization) for all patients with aphasia during follow-up Increase in BDAE scale score was associated with decreased Nb latency
Becker and Reinvang 2007a Case series	8 3 Global 1 Transcortical sensory 1 Broca 1 Wernicke 1 Mixed transcortical 1 Anomic Subacute (63–130 days post-stroke) to chronic (142–297 days post-stroke) Etiology: 5 LH stroke, 1 traumatic brain injury, 2 RH stroke 2 left-handed 11 healthy controls (normative data from another study (Becker and Reinvang 2007a))	EEG/ERP 17 channels 3 paradigms: - Passive syllable discrimination - Passive tonediscrimination - Active syllable discrimination and identification	Norwegian Basic Aphasia Assessment, TT ERP: waveforms, time from mean latency	2 measurements separated by 4 months Standard rehabilitation (8–12 h per week)	Behavioral outcome: small auditory comprehension improvements P300 and N200: amplitude increase between baseline and 3 months in ipsilesional frontal areas N200: shift (for 5 patients) over time from contralateral to ipsilesional hemisphere (toward normalization). N1: ipsilesional frontal N1 amplitude in subacute stage predicted recovery (smaller amplitude was predictive of greater improvement in auditory comprehension)

Table 1 (continued)

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Type of temporal imaging, number of channels, and tasks	Outcome measurements (behavioral and neuroimaging)	Longitudinal follow-up (number and interval of EEG/MEG measurements) and speech therapy	Main results
Nolfe et al. 2006 Individual cohort study	17 Global aphasia Acute ( $12.9 \pm 5.8$ days post-stroke) to subacute ( $\leq 6$ months post-stroke) 20 healthy controls matched according to age	EEG/ERP 16 channels Auditory stimuli: low pitch (frequent) and high pitch (rare)	AAT (comprehension and TT) ERP: waveforms in the P300 time window	7 measurements separated by 1 month Schuell's aphasia therapy (no details regarding frequency or duration)	Presence of a P300 in the first month after stroke for patients with global aphasia was predictive of good comprehension recovery Compared with controls, mean latency was significantly increased in all channels and amplitude was significantly lower only during P <sub>3</sub> derivation (10–20 system) Fluctuations of P300 presence during follow-up: lost in some patients and regained in others during recovery At baseline: P300 present only in RH derivations for seven patients After 6 months: P300 in 16 of 17 patients Patients with a P300 in LH derivations at baseline showed a higher and well-defined amplitude in temporoparietal left derivation, but negligible amplitude in frontal areas Patients without a P300 in LH derivations at baseline had a P300 in frontal derivations but negligible amplitude in temporoparietal areas

Table 1 (continued)

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Type of temporal imaging, number of channels, and tasks	Outcome measurements (behavioral and neuroimaging)	Longitudinal follow-up (number and interval of EEG/MEG measurements) and speech therapy	Main results
Iivonen et al., 2003 Individual cohort study	8 10 days post-stroke: 3 Global 3 Conduction 2 Wernicke 3 months post-stroke: 2 Global 3 Conduction 1 Wernicke 1 Anomic 6 months post-stroke: 1 Global 2 Transcortical sensory 3 Conduction 1 Wernicke 1 Anomic Acute (4 days post-stroke) to subacute (10 days, 3 months, 6 months post-stroke) 8 healthy controls matched according to age	EEG/ERP 9 channels Watching a silent video and ignoring tones	Subtests from BDAE and TT ERP: waveforms (MMN)	2 measurements separated by 6 days and 2 measurements separated by 3 months No SLT mentioned	Behavioral outcome: improvement in speech comprehension for all patients with aphasia Increased MMN duration correlated with improvements in speech comprehension tests from 10 days to 3 months post-stroke At T1, 4 days post-stroke: significantly attenuated MMN amplitude for right ear stimuli, associated with LH; significantly shorter latency for left ear stimuli, associated with RH At T2, 10 days post-stroke: MMN abnormal for both ears; suspicion of reduced metabolism, blood flow, and diaschisis in RH At T3, 3 months post-stroke: MMN duration greatly increased for right ear stimulation; potential increased metabolism in LH At T4, 6 months post-stroke: MMN amplitude increase for left ear stimuli
Szelies et al., 2002 Individual cohort study	23 5 Wernicke 5 Broca 6 Anomic 2 Transcortical sensory 1 Conduction 4 Residual aphasia (unclassified) Subacute (2 weeks and 8 weeks post-stroke) 43 healthy controls matched according to age	EEG 19 channels Resting state	AAT (including IT) Continuous EEG: quantitative topographic EEG	2 measurements separated by 6 weeks No SLT mentioned	Poor language recovery associated with increases in delta and theta activity in lesioned hemisphere No conclusion possible regarding high-frequency bands (alpha and beta)

Table 1 (continued)

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Type of temporal imaging, number of channels, and tasks	Outcome measurements (behavioral and neuroimaging)	Longitudinal follow-up (number and interval of EEG/MEG measurements) and speech therapy	Main results
Cobianchi and Giaquinto 2000 Case series	2 Expressive aphasia Subacute (patient 1: 47 days post-stroke; patient 2: 73 days post-stroke) to chronic (6 months, 1 year post-stroke) 18 non-matched healthy controls	EEG/ERP 16 channels Passive oddball paradigm (frequent high and infrequent low pitch) (P300) Stimulus: word LEONE (no instruction) (P340) 5 letter words (high frequency, nouns, adjectives, and pseudowords) (N400)	AAT ERP: waveforms (P300, P340, and N400)	3 measurements separated by 4–6 months Aphasia training program (no details regarding frequency or duration)	Behavioral outcome: no improvement Increase (toward normalization) of P300 at 6 months Both patients lacked a defined P340 at baseline but exhibited slow reappearance/increase with recovery toward normalization; however, polarity was frequently inverted N400: almost normal from baseline onward, but longer than in controls
Praamstra et al. 1993 Individual cohort study	20 6 Global 5 Anomic 7 Wernicke 2 Broca 2 groups: 10: moderate/recovered auditory comprehension impairment at T2 10: severe auditory comprehension impairment at T2 2 patients with hemorrhagic stroke Subacute (T1: group one, mean 2.4 [range: 1–8] months post-stroke; group two, mean 5.4 [range: 1–36] months post-stroke) to chronic (T2: group one, mean 51.2 [range: 13–94] months post-stroke; group two, mean 45.5 [range: 12–79] months post-stroke) 2 groups of 15 healthy controls matched according to age	EEG/ERP 14 channels Late AEP Stimuli: 1-Hz tone bursts lasting 50 ms, including rise and fall times of 10 ms Middle AEP Resting to sleep 2–4 series of 1,500 stimuli per ear (10 stimuli per second)	AAT, TT AEP at T2: waveforms (late N1 and P200; middle Na, Pa, and latency auditory responses) and dipole-source analysis	2 measurements: “early” after onset (1–36 months post-stroke) and “later” (12–94 months post-stroke) No SLT mentioned	Behavioral outcome: patients were divided into two groups according to auditory comprehension recovery: moderate impairment/recovered and severe auditory comprehension impairment Between-group differences: severe auditory comprehension impairment was associated with abnormal AEP Most patients in the severe group had a lesion in posterior superior temporal lobe (CT scan finding), but patients in the other group had no lesions No conclusion regarding a relationship between AEP abnormalities and speech perception impairment, because evaluation was based on auditory discrimination performance alone

Table 1 (continued)

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Type of temporal imaging, number of channels, and tasks	Outcome measurements (behavioral and neuroimaging)	Longitudinal follow-up (number and interval of EEG/MEG measurements) and speech therapy	Main results
Jabbari et al. 1979	52 12 Broca 36 Mixed and Global 4 Wernicke Subacute (2–4 weeks post-stroke) to chronic (every 4–6 months for 12–18 months post-stroke) No control group	EEG 16 channels Probably resting state	Clinical assessment based on Benson and Geschwind's approach to aphasia, PICA Continuous EEG: delta, theta, and alpha bands	≥ 2 measurements over 8–24 months 44 of 52 patients received regular speech therapy (no details regarding frequency, duration, or content)	Normal EEG at baseline associated with complete aphasia recovery at discharge Correlation between degree of focal delay in EEG at baseline (slow-waves) and poor language recovery Fast alpha rhythm in contralateral hemisphere correlated with better recovery

*AAT* Aachen Aphasia Test, *ABA* Apraxia Battery for Adults, *AFP* Auditory evoked potentials, *BDAE* Boston Diagnostic Aphasia Examination, *BNT* Boston Naming Test, *CT* Computed tomography, *GeBAS* Geneva Bedside Aphasia Score, *EEG* Electroencephalography, *ERP* event-related potential, *LH* left hemisphere, *MEG* magnetoencephalography, *MMN* mismatch negativity, *PALPA* Psycholinguistic Assessments of Language Processing in Aphasia, *PICA* Porch Index of Communicative Ability, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *RH* right hemisphere, *SLT* speech and language therapy, *SWA* slow-wave activity, *TT*: Token Test, *WAB* Western Aphasia Battery, *WAIS-PC* Wechsler Adult Intelligence Scale–Picture Completion subtest

**Table 2** Design and main results of EEG/MEG drug treatment trials

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Drug tested, dose, frequency, and design	Longitudinal follow-up (number and interval of EEG/MEG measurements), speech therapy content, and frequency	Type of temporal imaging, number of channels, and tasks	Outcome measurements (behavioral and neuroimaging)	Main results
Woodhead et al. 2017	20 9 Global 11 Wernicke Chronic (0.6–8.6 years post-stroke) No healthy controls	Donepezil Placebo then drug or drug then placebo in a cross-over design Weeks 0–5: drug (5 mg) or placebo Weeks 5–10: Earobics associated with drug (10 mg) or placebo Weeks 10–15: wash out Weeks 15–20: placebo or drug (5 mg) Weeks 20–25: Earobics associated with placebo or drug (10 mg)	4 measurements at weeks 5, 10, 20, and 25 Earobics: phonological self-training Two 40-min daily sessions recommended for each 5-week block (total mean duration per block 36 h 38 min [range: 6 h 20 min to 65 h 5 min])	MEG (18 participants) 274 channels EEG (2 participants) 128 channels Spoken syllable discrimination (passive oddball paradigm)	CAT, SART, ASHA FACS ERP/EMF: source localization	Speech comprehension significantly improved after phonological training, but Donepezil alone worsened speech comprehension Behavioral effects stronger in participants with severe aphasia Improved comprehension associated with greater modulation of left STG self-connection and connection from the left HG to STG, as well as STG interhemispheric connections, in patients with severe aphasia
Double-blind placebo-controlled, cross-over randomized clinical trial				Identification of dipole locations underlying MMN response in four spatial models used to estimate effective connectivity/interactions between auditory areas		



Table 2 (continued)

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Drug tested, dose, frequency, and design	Longitudinal follow-up (number and interval of EEG/MEG measurements), speech therapy content, and frequency	Type of temporal imaging, number of channels, and tasks	Outcome measurements (behavioral and neuroimaging)	Main results
Barbancho et al. 2015 Single-center, randomized, placebo-controlled, double-blind, parallel-group randomized clinical trial	27 14 Anomic 8 Broca 3 Conduction 2 Transcortical motor 1 Wernicke Chronic man-tine group (n = 14): 1.8 ± 0.2 years post-stroke Placebo group (n = 13): 6.4 ± 2.1 years post-stroke 15 healthy con-trols	Memantine (10 mg twice daily) Weeks 0–16: memantine or placebo alone Weeks 16–18: memantine (14 patients) or placebo (13 patients) + CIAT Weeks 18–20: memantine or placebo alone	4 measurements: pretreat-ment and weeks 16, 18, and 20 CIAT in groups of 2–3 30 h: 3 h per day for 2 weeks 2 measurements for healthy controls	EEG 21 channels Silent word reading task	WAB-AQ ERP: waveform amplitude (P100 and N400) and RMS	Behavioral outcome: memantine group had better language recovery than placebo group at weeks 16, 18, and 20 Pretreatment: larger amplitudes of P100 and N400 over left temporal and parietal electrodes in ERPs of patients with aphasia compared with controls Week 16 (after memantine/placebo only): increase in WAB-AQ in memantine group only ERP/RMS (N400 and P100) decrease in amplitude for both groups, but greater decrease in memantine group Week 18 (after memantine/pla-cebo+CIAT): increase in WAB-AQ in both groups, but greater increase in memantine group ERP/RMS (N400 and P100) increase in amplitude for both groups Week 20 (after memantine/placebo only): changes persisted

ASHA FACS Social Communication and Daily Planning from the Functional Assessment of Communication Skills for Adults, CIAT constraint-induced aphasia therapy, HG Heschl's gyrus, EEG electroencephalography, EMF evoked magnetic field, ERP event-related potential, MEG magnetoencephalography, RMS root mean square, SART Sustained Attention to Response Test, STG superior temporal gyrus, WAB-AQ Western Aphasia Battery-Aphasia Quotient

**Table 3** Design and main results of speech and language rehabilitation studies including EEG/MEG measurements

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Speech and language treatment (type, frequency, and other relevant variables)	Type of imaging, number of channels, and tasks	Longitudinal follow-up (number and interval of EEG/MEG measurements) Outcome measurements (behavioral and neuroimaging)	Main results
Iyer et al. 2020 Case-control study	8 2 Conduction 6 Anomic Chronic (17–170 months post-stroke) 15 healthy controls matched according to age, sex, and education level	3 naming therapy sessions per week for 4 weeks (12 sessions) 6 sessions with SFA 6 sessions with PCA of different items Type of therapy (SFA/PCA) alternated between sessions; order counterbalanced among participants Individualized treatment items based on pretreatment errors	EEG/ERP 128 channels Picture- auditory word judgment task (ERP aligned to onset of auditory word, presented 1,000 ms after image)	2 measurements separated by 4 weeks (prior to and immediately after therapy) Naming accuracy of treated and untreated items ERP: waveform analysis and source reconstruction with DCM to characterize connectivity (including five ROIs, with two time-windows [150–250 and 300–500 ms post-word onset; N200 and N400])	Improvement in naming for patients who had reduced coupling in contralateral regions post-treatment Increased connection strength between left inferior parietal lobule and left IFG after SFA Pretreatment connection between left inferior parietal lobule and left IFG positively correlated with good SFA outcomes Reduced coupling between contralateral IFG and posterior STG correlated with naming improvements DCM of EEG can identify cortical connections that aid prediction of treatment-induced recovery in picture naming
Lucchese et al. 2017 Case series	10 9 Broca 1 Global Chronic (mean 88.6 months post-stroke [range: 30–245 months]) No healthy controls	3 sessions of 3.5 h per week for 4 weeks (12 sessions) 2 types of therapy focusing on naming or communication requests (based on ILAT/CIAT)	EEG/ERP 128 channels Listen to sentences with nonwords (pseudowords) and syntax	2 measurements separated by 4 weeks (before and after therapy) AAT (TT, comprehension, naming, and repetition) ERP: waveform analysis (MMN)	Significant improvements in language scores (all subtests of AAT) Increase in MMN amplitudes (especially over LH electrodes) in response to all types of stimuli except ungrammatical sentences
Mohr et al. 2016 Case series	12 Broca Chronic (mean 6.13 years post-stroke [range: 1.4–19.5 years]) No healthy controls	5 ILAT sessions of 3–4 h per week for 2 weeks (10 sessions) Group setting with 2 therapists and 3 patients	MEG/EMF 102 channels Listen to words and pseudowords	2 measurements separated by 2 weeks (before and after therapy) BDAE, BNT, TT, and CAL EMF: waveform analysis (magnetic MMN and time window around 200 ms after stimulus)	Behavioral improvements in naming, auditory comprehension, and quality of communication in everyday life Increased magnetic MMN amplitudes in left frontotemporal electrodes only for meaningful words

Table 3 (continued)

Study design	Patients (number, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Speech and language treatment (type, frequency, and other relevant variables)	Type of imaging, number of channels, and tasks	Longitudinal follow-up (number and interval of EEG/MEG measurements) Outcome measurements (behavioral and neuroimaging)	Main results
Radman et al. 2016 Case report	1 Woman, 52 years old, bilingual (L1: Farsi and L2: French) Broca Subacute (16–20 weeks post-stroke) No healthy controls	5 sessions of 1 h for the first week then 5 sessions of 45 min per week for 3 weeks (20 sessions in total) of phonological naming therapy using CAT Therapy only in L2 Therapy based on two parallel lists from EEG tasks (picture-naming and word-picture verification); one for treated items and one for untreated/control items	EEG/ERP 64 channels Picture-naming and word-picture verification tasks	2 measurements separated by 4 weeks (before and after therapy) BAT, picture naming (treated and untreated items in L2 and L1), and word-picture verification (in L1 and L2) ERP: waveform analysis	Improvement in trained L2 items; no generalization to untrained L2 items or L1 items ERP topographic modulations in 500–540 ms time window post-stimulus for L2 trained items Lexical-phonological therapy likely modulated activity in the brain network involved in phonetic encoding (cf. late time window) Modified EEG responses in treated L2 but not untreated L1 (no cross-language generalization in EEG, consistent with behavioral results)
Aerts et al. 2015 Case report	1 Man, 47 years old Non-fluent Subacute to chronic (10–291 days post-stroke) 71 healthy controls (normative data from previous study (Aerts et al. 2013))	5 sessions of 2 h per week for 3 weeks (15 sessions): intensive therapy with lexical-phonological and lexical-semantic content 4 sessions of 1 h per week for 7 weeks (30 sessions): conventional therapy with auditory and visual phonological exercises at word and sentence levels 5 sessions of 2 h per week for 3 weeks (15 sessions): intensive therapy focusing on sublexical processes	EEG/ERP 23 channels Auditory phoneme discrimination (attentive: P300 and pre-attentive: MMN) Auditory word recognition (N400)	5 measurements (before and after every therapy and therapy-free period) AAT and subtests of PALPA ERP: waveform analysis (P300, MMN, and N400)	After completion of therapy: • significant improvements in behavioral measurements • improvements (toward normalization) in neurophysiological measurements (P300, MMN, and N400) Between periods of therapy: enhancement of N400 (for pseudowords) during intensive therapy and reduction of N400 during conventional therapy
Sarasso et al. 2014 Case series	13 5 Broca 1 Wernicke 6 Anomic 1 Conduction Chronic (> 9 months post-stroke) No healthy controls	6 months without therapy 1 session of 3.5 h using imitation-based, computer-assisted rehabilitative protocol (IMITATE) Repetition of words and phrases from video clips	EEG 256 channels Sleep	2 measurements separated by 1 day (before and after single therapy session) Subtest of the WAB, subtests of the Apraxia Battery for Adults, and BNT Continuous EEG: sleep recording focusing on SWA	Behavioral improvements only in WAB Repetition score During REM sleep, increase in EEG SWA and beta EEG activity over bilateral connections between frontoparietal topographies (more consistent changes in RH)

Table 3 (continued)

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Speech and language treatment (type, frequency, and other relevant variables)	Type of imaging, number of channels, and tasks	Longitudinal follow-up (number and interval of EEG/MEG measurements) Outcome measurements (behavioral and neuroimaging)	Main results
Stojanovic et al. 2013 Case series	32 26 Non-fluent 6 Fluent Subacute (1 month post-stroke) 86 healthy controls	2 months of neurorehabilitation including SLT (no further details)	EEG 32 channels Resting state (eyes closed and eyes open)	2 measurements separated by 2 months (before and after therapy) BDAE Continuous EEG: quantitative EEG	Good improvement of post-stroke aphasia in 17 participants and poor improvement in 15 patients At baseline, asymmetry between hemispheres and among main brain regions significantly greater in patients with aphasia than controls Asymmetry smaller in patients with good than poor recovery
Wilson et al. 2012 Case series	9 1 Transcortical motor 1 Conduction 6 Anomic 1 Broca Chronic (0.5–5.5 years post-stroke) Healthy controls (no further details)	5 InteraCT sessions of 5 h per week for 4 weeks (20 sessions) -1 h: language production, comprehension, and motor speech -1 h: reading and writing -1 h: functional communication -1 h: computer skills -1 h: group therapy based on conversation	EEG/ERP 64 channels Picture-name verification task: participant indicates whether picture matches spoken word	2 measurements separated by 4 weeks (before and after therapy) WAB-AQ, Communicative Effectiveness Index, and Communication Activity of Daily Living-2 ERP: waveform analysis	Improvements in language measurements in 6 of 9 patients with aphasia (others had good performance at baseline) and no significant improvement in picture-naming task Normal P100-N1-P200 pattern for both groups, before and after therapy Centroparietal N400: shift from RH to LH after therapy was associated with language improvements (but not normalization); no change in amplitude
Sarasso et al. 2010 Case series	4 Non-fluent Chronic (>9 months post-stroke) No healthy controls	1 3.5-h session using imitation-based, computer-assisted rehabilitative protocol (IMITATE) Repetition of words and phrases from video clips	EEG 256 channels Sleep	2 measurements separated by 1 day (before and after single therapy session) WAB Continuous EEG: sleep recording focusing on SWA	Increased WAB repetition scores after therapy Changes in SWA after intensive session of IMITATE (greater changes in LH than RH) Long-term reorganization of LH and RH language network during functional magnetic resonance imaging after original IMITATE therapy (6 full weeks)

Table 3 (continued)

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and controls (number and matching variables)	Speech and language treatment (type, frequency, and other relevant variables)	Type of imaging, number of channels, and tasks	Longitudinal follow-up (number and interval of EEG/MEG measurements) Outcome measurements (behavioral and neuroimaging)	Main results
Meinzer et al. 2009 Case series	10 1 Wernicke 5 Broca 2 Global 1 Anomic 1 Not classified Chronic (8–64 months post-stroke) 10 healthy controls matched according to age and sex	3 h of therapy per day for 10 consecutive days Group sessions of CIAT	MEG/EMF 148 channels Flash word reading (including pseudoword reading)	2 measurements separated by 2 weeks (before and after therapy) AAT EMF: time-frequency analysis (HFA)	Improvements in AAT scores after therapy Controls: HFA bilaterally distributed, no distinction among word classes (content, function, and pseudowords) Before therapy for patients with aphasia: RH dominance for HFA, no distinction among word classes In high-functioning patients (highest scores in AAT written language), no difference in HFA after therapy = bilateral pattern similar to pattern in controls In low-functioning patients (lowest scores in AAT written language), decreased RH activation and increased bilateral pattern after therapy
Laganaro et al. 2008 Case series	4 3 Phonological impairment after stroke 1 Semantic impairment after herpes encephalitis Subacute (1–4 months post-stroke) 15 healthy controls	3–5 30–60-min sessions per week (no details regarding treatment duration) CIAT for anomia based on written picture naming	EEG/ERP 128 channels Picture naming	2 pretreatment measurements separated by 1 week, 2–3 post-treatment measurements (immediately after intervention, 2–4 weeks after intervention, and [for 2 patients] 6 months after intervention) Picture naming ERP: waveform, topographic analysis, and source reconstruction	Improvements in behavioral results after training For two patients with phonological impairments, normalization of amplitude and topography in first 300 ms, but abnormal amplitude and topographies in later time windows (new or persistent) after therapy At 6 months, normalization of amplitude but not topography In the patient with semantic impairment, increase from baseline to post-treatment of amplitudes diverging from control group (especially during first 300 ms), likely associated with visual and semantic processes In the remaining patient, normalization (from baseline to post-treatment) of amplitudes and topographies in early time windows, but new abnormal topographies after 250 ms Source analysis: RH activation in 3 of 4 patients, but at different stages (baseline, after therapy, or chronic)

Table 3 (continued)

Study design	Patients (number, type of aphasia, stage/time post-stroke, and other relevant variables) and matching variables)	Speech and language treatment (type, frequency, and other relevant variables)	Type of imaging, number of channels, and tasks	Longitudinal follow-up (number and interval of EEG/MEG measurements) Outcome measurements (behavioral and neuroimaging)	Main results
Pulvermüller et al. 2005 Case series	10 2 Wernicke 5 Broca 1 Anomic 1 Transcortical 1 Missing data Chronic (16–233 months post-stroke) No healthy controls	23–33 h of therapy in 10 consecutive workdays Group sessions of CIAT	EEG/ERP 29 channels Lexical decision	2 measurements separated by 2 weeks (before and after therapy) Subtests of AAT ERP: waveform analysis and source localization	After therapy: • improvements in language scores • increased negativity in both hemispheres at around 250–300 ms for words; no change in either hemisphere for pseudowords Negativity around 250–300 ms elicited by words could be an index of recovery
Meinzer et al. 2004 Case series	28 4 Wernicke 13 Broca 2 Anomic 3 Global 6 Not classified Chronic (12–156 months post-stroke) 25 healthy controls (normative data from previous study (Wienbruch et al. 2003))	3 h of therapy per day for 10 consecutive days For 18 patients: CIAT For 10 patients: model-based intervention according to functional impairment	MEG 148 channels Resting period	2 measurements separated by 2 weeks (1 day before and 1 day after end of therapy) AAT Continuous EEG: SWA/ASWAM and delta dipole density	Language improvements in both groups (CIAT or impairment-based intervention) At baseline: abnormal SWA (in almost all patients) only in electrodes surrounding the lesion For some patients (n = 16), language improvements were correlated with a decrease in SWA For other patients (n = 12), language improvements were correlated with an increase in abnormal delta activity around the lesion
Cornelissen et al. 2003 Case series	3 Conduction Broca Residual aphasia Chronic (2–14 years post-stroke) No healthy controls	3 sessions of 1 h per week for 3 weeks (9 sessions) (6 additional sessions for 1 patient) Picture naming with contextual priming technique; 100 treated items and 100 untreated items	MEG/EMF 306 channels Picture naming Resting (eyes open and closed)	4 measurements separated by 2 weeks (2 pretreatment and 2 post-treatment) BDAE, BNT, and other tests that assess semantic and/or phonological/orthographic knowledge of target pictures EMF: waveforms and source of waveforms + spontaneous brain activity (SWA)	Improvement in naming only for treated items SWA surrounding the lesion at baseline Changes in brain activity only in perilesional areas (left inferior parietal lobe) beginning at approximately 300–600 ms after stimulus (and lasting 200–700 ms), likely indicative of therapeutic effects on phonological processing

**Table 3** (continued)

ASWAM abnormal slow-wave activity mapping, AAT Aachen Aphasia Test, BAT Bilingual Aphasia Test, BDAE Boston Diagnostic Aphasia Examination, BNT Boston Naming Test, CAL Communicative Activity Log, CAT computerized aphasia therapy, CIAT constraint-induced aphasia therapy, DCM dynamic causal modelling, EEG electroencephalography, EMF evoked magnetic field, ERP event-related potential, HEA high-frequency activity, IFG inferior frontal gyrus, ILAT intensive language action therapy, IMITATE Intensive Mouth Imitation and Talking for Aphasia Therapeutic Effects, LH left hemisphere, MEG magnetoencephalography, MMN mismatch negativity, PALPA Psycholinguistic Assessment of Language Processing in Aphasia, PCA phonological components analysis, REM rapid eye movement, RH: right hemisphere, ROI: region of interest, SFA: semantic feature analysis, SLT: speech and language therapy, STG: superior temporal gyrus, SWA: slow-wave activity, TT: Token Test, WAB: Western Aphasia Battery

recovery (as determined by monthly follow-up until six months post-stroke); if the P300 was absent in the acute stage of recovery, it appeared later in left frontal electrodes (as determined by computerized maps). In a more recent study (Cocquyt et al. 2020), better clinical recovery was observed in two of four patients who had normal P300 amplitude and latency in the subacute stage. In the chronic stage, a normal P300 was present in all but one patient; that patient exhibited a decreased P300 amplitude and increased P300 latency, although the P300 was normal and the patient demonstrated good recovery at one month post-stroke.

Becker and Reinvang (2007a) found that, in five of eight patients, the N200 shifted between the subacute and chronic stages between electrodes covering the intact hemisphere and electrodes situated on the lesioned hemisphere. They also found that a low-amplitude N1 on the ipsilesional frontal electrodes in the subacute stage was a good predictor of recovery in the chronic stage: a smaller N1 was associated with greater improvement in auditory comprehension.

Cobianchi and Giaquinto (2000) found that the N400 (which appeared to be normal within the first few months after stroke) was unmodulated during auditory tasks that involved passive oddball paradigms or word/non-word listening tasks, in two patients (subacute- and chronic-stage) patients with expressive aphasia.

### Continuous EEG Studies

Four studies (Dalton et al. 2021; Jabbari et al. 1979; Nicolo et al. 2015; Szeliés et al. 2002) recorded continuous EEG; three of the studies used resting-state or task-free conditions. All of these non-interventional studies demonstrated delays in waveform activity (mainly for theta and delta rhythms); abnormally slow rhythms predicted poor recovery. During recovery, rhythms tended to accelerate with progression from the acute to the subacute and chronic stages; rhythm frequency appeared to reach a plateau after six months in one of the studies (Jabbari et al. 1979). In one of the other studies, EEG stability in alpha, beta, and theta bands was observed during the chronic stage of recovery in patients with aphasia, without any intervention; however, unstable activity was seen in the delta band compared with healthy controls (Dalton et al. 2021). Moreover, one study revealed an association between recovery and resting-state alpha rhythm: good recovery was correlated with faster alpha frequency in the contralesional hemisphere in the subacute stage (Jabbari et al. 1979).

### Recovery Stage

Among 11 non-interventional studies, multiple measurements were performed during the acute and subacute stages in five (Ilvonen et al., 2003; Nicolo et al. 2015; Nolfé et al.

**Table 4** Design and main results of non-invasive brain stimulation studies coupled with EEG/MEG

Study design	Patients (number, type of aphasia, and stage/time post-stroke) and controls (number and matching variables)	Stimulation parameters (e.g., neuro-modulation type, frequency, location, and intensity)	Number of sessions, frequency, and language training	Type of imaging, number of channels, and tasks	Longitudinal follow-up (number and interval of EEG/MEG measurements)	Main results
Shah-Basak et al. 2020 Double-blind, randomized controlled trial	11 5 Non-fluent 1 Fluent 3 Anomic 2 Conduction Chronic (mean 8 years post-stroke [range: 4–21 years]) 10 healthy controls matched according to age and sex	tDCS during sentence repetition 2 mA for 20 min 3 pseudorandomized sessions: left perilesional anodal, right contralesional cathodal, and sham Location of center electrode determined individually according to MEG abnormalities	3 training sessions with tDCS and MEG, separated by $\geq 48$ h Cued repetition tasks adapted to aphasia profiles (easy version for non-fluent patients—hard version for the others)	MEG 151 channels Resting-state and delayed word reading task (pre-tDCS and post-tDCS)	2 measurements separated by 20 min (tDCS stimulation/sham), repeated 3 times (6 measurements in total) WAB, BNT, PPVT, and PALPA non-word reading Repetition accuracy Spectral power and multiscale entropy measurements during continuous MEG (10-min recordings) and pre/post-stimulus (during word reading)	After anodal tDCS: improved repetition accuracy correlated with decrease in contralateral theta (4–7 Hz) and coarse-scale multiscale entropy (slow activity), but not in non-fluent patients After cathodal tDCS: MEG modulations not correlated with repetition improvements Resting-state MEG could guide selection of perilesional targets to reduce oscillatory abnormalities Behavioral outcome: improvements in language (PI-WAB) and inhibition (go/no go) Reduction of abnormal neuronal excitability (P200) over temporal electrodes in RH
Chantsoulis et al. 2016 Case report	1 Woman, 72 years old RH stroke Crossed transcortical sensory Chronic (12 months post-stroke) 35 healthy controls matched according to age	rTMS 25 repetitions 1 Hz on LH (no further details) 5 Hz on right temporal area	20 sessions of rTMS and aphasia therapy with a comprehensive rehabilitation model (no further details)	EEG/ERP 19 channels Variant of cued go/no go task	2 measurements separated by 6 months (before and after therapy) PI-WAB ERP: waveform analysis (P200) and quantitative EEG	



Table 4 (continued)

Study design	Patients (number, type of aphasia, and stage/time post-stroke) and controls (number and matching variables)	Stimulation parameters (e.g., neuro-modulation type, frequency, location, and intensity)	Number of sessions, frequency, and language training	Type of imaging, number of channels, and tasks	Longitudinal follow-up (number and interval of EEG/MEG measurements)	Main results
Wu et al. 2015 Blinded, randomized controlled trial	12 8 Broca 2 Mixed 1 Anomic 1 Conduction Post-subacute (3–6 months post-stroke) 12 healthy controls matched according to age, sex, and education level	tDCS during informatized picture-naming treatment Anodal: left posterior perisylvian region 1.2 mA for 20 min 3 successive phases: sham tDCS, real tDCS, and sham tDCS	5 30-min sessions per week for 4 weeks (20 sessions) during each phase (60 sessions in total) Informatized picture-naming treatment with semantic and phonological cues	EEG 16 channels Resting Word repetition	3 measurements separated by 4 weeks (after sham, real, and second sham stimulation) BDAE and PACA Continuous EEG: ApEn	Improvement in picture naming and auditory word-picture identification after real stimulation; no behavioral change after sham stimulation After real stimulation: language improvements correlated with increased LH activation and higher ApEn in left Wernicke and Broca areas, left central/parietal/middle temporal electrodes, and right parietal electrodes/right Wernicke area

Table 4 (continued)

Study design	Patients (number, type of aphasia, and stage/time post-stroke) and controls (number and matching variables)	Stimulation parameters (e.g., neuro-modulation type, frequency, location, and intensity)	Number of sessions, frequency, and language training	Type of imaging, number of channels, and tasks	Longitudinal follow-up (number and interval of EEG/MEG measurements)	Main results
Dammekens et al. 2014 Case report	1 Woman, 55 years old Non-fluent Chronic (39 months post-stroke) Healthy controls matched according to age (no details regarding number of participants)	rTMS Left IFG 80% RMT 10 Hz	5 rTMS sessions per week for 3 consecutive weeks (15 sessions) No SLT	EEG 19 channels Resting	2 measurements separated by 3 weeks (before and after stimulation) and 1 additional measurement after 4 months AAT Continuous EEG: beta and theta bands	After 15 rTMS sessions without SLT: - improvements in repetition, naming, and comprehension (AAT) - decrease in right IFG activity and normalization of left IFG activity for beta3 frequency band; increased activity in right supplementary motor area for beta3 frequency band Increased functional connectivity between left and right IFG for theta and beta frequency bands
Barwood et al. 2012 Single-blind vs. sham, randomized controlled trial	12 Non-fluent Chronic (2–6 years post-stroke) 2 groups: 6 sham and 6 real No healthy controls	rTMS Anterior portion of right PTr (BA 45) 90% RMT 1 Hz for 20 min	5 sessions per week for 2 weeks (10 sessions) No SLT	EEG/ERP 32 channels Written word-picture semantic judgment task	2 measurements separated by 3 weeks (before and 1 week after stimulation) 3 measurements post-stimulation (2, 8, and 12 months) BDAE and BNT ERP: waveform analysis (N400)	Greater improvement in word-picture verification in stimulation than sham group at 2, 8, and 12 months post-stimulation Increased negativity toward normalization of N400 over time ( $\leq 12$ months) in the rTMS but not sham group

Table 4 (continued)

Study design	Patients (number, type of aphasia, and stage/time post-stroke) and controls (number and matching variables)	Stimulation parameters (e.g., neuro-modulation type, frequency, location, and intensity)	Number of sessions, frequency, and language training	Type of imaging, number of channels, and tasks	Longitudinal follow-up (number and interval of EEG/MEG measurements)	Main results
Barwood et al. 2011 Double-blind vs. sham, randomized controlled trial	12 Non-fluent Chronic (2–6 years post-stroke) 2 groups: 6 sham and 6 real No healthy controls	rTMS Anterior portion of right PTr (BA 45) 90% RMT 1 Hz for 20 min	5 sessions per week for 2 weeks (10 sessions) No SLT	EEG/ERP 32 channels Written word-picture semantic judgment task	2 measurements separated by 3 weeks (before and 1 week after stimulation), and 1 measurement 2 months after stimulation BDAE, BNT ERP: waveform analysis (N400)	Greater improvement in word-picture verification in stimulation than sham group between baseline and 2 months post-stimulation At 1 week post-stimulation, no EEG difference between groups At 2 months post-stimulation, significant ERP differences between sham and stimulation groups in mean amplitude, area under the curve, and peak amplitude of N400

Table 4 (continued)

Study design	Patients (number, type of aphasia, and stage/time post-stroke) and controls (number and matching variables)	Stimulation parameters (e.g., neuro-modulation type, frequency, location, and intensity)	Number of sessions, frequency, and language training	Type of imaging, number of channels, and tasks	Longitudinal follow-up (number and interval of EEG/MEG measurements)	Main results
Fedorov et al. 2010 Double-blind, randomized controlled trial	23 of 98 participants with aphasia Motor Sensory Mixed Chronic 3 groups: - Drugs (n = 30; 22.7 ± 1.8 months post-stroke) - rtACS (n = 32; 21.4 ± 4 months post-stroke) - Drugs + rtACS (n = 36; 20 ± 2.9 months post-stroke) No healthy controls	rtACS 0.2–0.4 mA inter-pulse intervals: 23–190 ms (both eyes separately) 30–40 min Drug: depending on each patient's needs (e.g., fluoxetine, baclofen, and vinpocetine)	Daily during 12 consecutive days No SLT	EEG 19 channels Resting	2 measurements separated by 12 days (before and after stimulation) 1 measure after 1 month without stimulation National Institutes of Health Stroke Scale Continuous EEG: alpha, beta, and theta bands	Improvements in aphasia scores for both rtACS and Drugs + rtACS groups after stimulation and at 1 month follow-up. no reduction of speech impairment in Drug group Follow-up at 1 month: stable impairment in rtACS group but further improvements in Drugs + rtACS group Improvement of EEG synchronization between temporal RH and temporal LH, specifically in theta range (absent from injured hemisphere at baseline), immediately after stimulation and persisting for 1 month post-stimulation

*ApEn* approximate entropy, *BA* Brodmann area, *BDAE* Boston Diagnostic Aphasia Examination, *BNT* Boston Naming Test, *EEG* electroencephalography, *ERP* event-related potential, *IFG* inferior frontal gyrus, *LH* left hemisphere, *MEG* magnetoencephalography, *PACA* Psycholinguistic Assessment in Chinese Aphasia, *PALPA* Psycholinguistic Assessment of Language Processing in Aphasia, *PI-WAB* Polish version of the Western Aphasia Battery, *PPVT* Peabody Picture Vocabulary Test, *PTr* pars triangularis, *RH* right hemisphere, *RMT* resting motor threshold, *rtACS* repetitive transorbital alternating current stimulation, *rTMS* repetitive transcranial magnetic stimulation, *SLT* speech and language therapy, *tDCS* transcranial direct current stimulation

2006; Rojas Sosa et al. 2009; Szeliés et al. 2002). In five other studies (Becker and Reinvang 2007b; Cobiañchi and Giaquinto 2000; Cocquyt et al. 2020; Jabbari et al. 1979; Praamstra et al. 1993), electrophysiological information was recorded during the subacute and chronic stages of recovery in patients with post-stroke aphasia. The remaining study (Dalton et al. 2021) focused only on the chronic stage.

Among the studies that analyzed chronic-stage patients, only two (Dalton et al. 2021; Jabbari et al. 1979) involved several continuous EEG measurements during the chronic stage; one of those studies reported spontaneous electrophysiological changes in the delta band; however, the changes were present in both patients with post-stroke aphasia and healthy controls (Dalton et al. 2021), suggesting that they were not associated with aphasia.

### Concomitant SLT

Among the 11 non-interventional studies, seven (Becker and Reinvang 2007b; Cobiañchi and Giaquinto 2000; Cocquyt et al. 2020; Jabbari et al. 1979; Nicolo et al. 2015; Nolfé et al. 2006; Rojas Sosa et al. 2009) included standard rehabilitation such as SLT. The type of therapy was not specified, except by Nolfé et al. (2006), who described an intensive program based on auditory stimulation. The amount of therapy was also unspecified, except by Cocquyt et al. (2020), i.e.,  $\leq$  two sessions of 30 min per week.

### Clinical Trials

Tables 2, 3 and 4 summarize 23 clinical trials in which patients with aphasia were treated with drugs, rehabilitation techniques, or NIBS; EEG/MEG recordings were performed before and after the intervention in each study. In total, 398 patients with aphasia were included. The cross-sectional characteristics of these 23 clinical trials are described below.

### Drugs Associated with Specific Rehabilitation Methods

Table 2 summarizes two double-blind placebo-controlled studies (Barbancho et al. 2015; Woodhead et al. 2017) that tested two different drugs in patients with chronic aphasia during speech and language rehabilitation. Both studies used ERP/EMF to investigate the relationships of behavioral outcomes with electrophysiological changes. In the first study (Woodhead et al. 2017), a phonological therapy (Earobics) increased speech comprehension skills, while donepezil decreased comprehension accuracy, particularly in patients with severe aphasia. Furthermore, comprehension improvements in patients with severe aphasia were associated with greater connectivity involving the left superior temporal gyrus (self-connectivity toward the left Heschl's gyrus and right hemisphere [RH]) (Woodhead et al. 2017). The second

study (Barbancho et al. 2015) showed that, regardless of whether patients received constraint-induced aphasia therapy (CIAT), memantine had a positive impact on chronic aphasia. These improvements were systematically associated with changes in N400 and P100 amplitudes recorded during a silent reading task.

### Specific Language Rehabilitation Methods

Table 3 summarizes 14 studies that investigated behavioral and electrophysiological changes induced by language rehabilitation programs for aphasia. Various therapies were provided to participants. Five studies (Lucchese et al. 2017; Meinzer et al. 2004, 2009; Mohr et al. 2016; Pulvermüller et al. 2005) used intensive constraint-induced language therapy: ILAT (Intensive Language Action Therapy), CIAT (Constraint-Induced Aphasia Therapy) or CILT (Constraint Induced Language Therapy), where participants were required to communicate using structured language. Wilson et al. (2012) provided intensive therapy, called InteRACT, which targeted language production, comprehension and motor speech, reading and writing, functional communication, and computer skills through group therapy focusing on conversation. Four studies provided computer-assisted rehabilitation that targeted either lexical-phonological processes (Laganaro et al. 2008; Radman et al. 2016) or word and sentence repetition (Sarasso et al. 2010, 2014; Iyer et al. 2020) studied the impact of semantic feature analysis and phonological components analysis protocols that consisted of picture-naming tasks with semantic and phonological cues, respectively. Cornelissen et al. (2003) used a contextual priming technique that involved picture naming with visual semantic primes to enhance semantic network representation. Aerts et al. (2015) compared the effects of intensive and conventional therapies (according to the Belgium National Institute for Health and Disability Insurance) on a single patient with subacute aphasia. Stojanovic et al. (2013) did not include a description of the language rehabilitation provided.

All 14 studies showed positive behavioral impacts related to their rehabilitation protocols; most of the studies also showed changes in electrophysiological measurements. 10 of the 14 studies used ERP/EMF (Aerts et al. 2015; Cornelissen et al. 2003; Iyer et al. 2020; Laganaro et al. 2008; Lucchese et al. 2017; Meinzer et al. 2009; Mohr et al. 2016; Pulvermüller et al. 2005; Radman et al. 2016; Wilson et al. 2012); most of these 10 studies focused on the major ERP/EMF components such as MMN, P300, or N400. Four studies used continuous EEG that focused on SWA during sleep (Sarasso et al. 2010, 2014) or while at rest (Meinzer et al. 2004; Stojanovic et al. 2013).

## Neuromodulation

Table 4 summarizes seven EEG/MEG studies that used NIBS for patients with aphasia. Two studies of the same patients (Barwood et al. 2011, 2012) applied “low” repetitive transcranial magnetic stimulation (rTMS) to the contralesional hemisphere, while another study (Dammekens et al. 2014) used “high” rTMS on the lesioned hemisphere; Chantsoulis et al. (2016) compared these two stimulation techniques. Two studies (Shah-Basak et al. 2020; Wu et al. 2015) used transcranial direct current stimulation (tDCS): Wu et al. (2015) targeted left posterior perisylvian areas using anodal tDCS, while Shah-Basak et al. (2020) targeted both hemispheres using perilesional cathodal tDCS and contralesional anodal tDCS. An earlier study (Fedorov et al. 2010) used repetitive transorbital alternating current stimulation (rtACS). In all studies, language improvements were associated with electrophysiological changes. Four studies recorded continuous EEG (Dammekens et al. 2014; Fedorov et al. 2010; Shah-Basak et al. 2020; Wu et al. 2015); the most recent of these (Shah-Basak et al. 2020) also included source imaging. Finally, three ERP/EMF studies focused on the N400 (Barwood et al. 2011, 2012) or P200 (Chantsoulis et al. 2016) component.

## Control, Sham, and Placebo Groups

Patient data were compared with findings from healthy controls in one of two clinical drug trials (Barbancho et al. 2015), seven of 14 clinical trials of rehabilitation techniques (Aerts et al. 2015; Iyer et al. 2020; Laganaro et al. 2008; Meinzer et al. 2004, 2009; Stojanovic et al. 2013; Wilson et al. 2012), and four of seven clinical trials of NIBS (Chantsoulis et al. 2016; Dammekens et al. 2014; Shah-Basak et al. 2020; Wu et al. 2015). Placebo/sham stimulation was used for between-participant comparisons in three of 23 clinical trials (Barbancho et al. 2015; Barwood et al. 2011, 2012); it was used for within-participant comparisons in three other studies (Shah-Basak et al. 2020; Woodhead et al. 2017; Wu et al. 2015). Only one study included both a healthy control group and a group of patients receiving placebo treatment (Barbancho et al. 2015).

## Recovery Stage

With the exception of four studies (Aerts et al. 2015; Radman et al. 2016; Stojanovic et al. 2013; Wu et al. 2015), all clinical trials involved patients with aphasia in the chronic stage of recovery, to minimize the influence of spontaneous recovery. Three studies (Aerts et al. 2015; Stojanovic et al. 2013; Wu et al. 2015) of patients with subacute

aphasia included a control group of neurotypical individuals, whereas one study (Radman et al. 2016) did not include a control group of healthy individuals or a group of patients receiving placebo treatment.

## Imaging Techniques

In terms of imaging techniques, 17 studies used EEG, five used MEG, and one (Woodhead et al. 2017) used both. In terms of electrode number, high-resolution imaging with  $\geq 64$  electrodes was used in 14 of 23 studies. Among the 16 ERP/EMF studies, 10 used high-resolution imaging. Among the eight studies with continuous EEG/MEG recording, five used high-resolution imaging.

## Studies Using ERPs or EMFs

Fifteen clinical trials used ERPs/EMFs with various tasks: go/no go (Chantsoulis et al. 2016), picture naming (Cornelissen et al. 2003; Laganaro et al. 2008; Radman et al. 2016), picture-word verification (Barwood et al. 2011, 2012; Iyer et al. 2020; Radman et al. 2016; Wilson et al. 2012), distinguishing words/pseudowords or identifying sentences with correct/deviant syntax (Lucchese et al. 2017; Mohr et al. 2016; Pulvermüller et al. 2005), auditory phoneme or syllable discrimination (Aerts et al. 2015; Woodhead et al. 2017), silent reading with flash presentation (Meinzer et al. 2009), and silent reading without flash presentation (Barbancho et al. 2015). Two studies (Chantsoulis et al. 2016; Cornelissen et al. 2003) recorded both continuous and ERP/EMF measurements; however, they recorded spontaneous EEG only to remove SWA from ERP/EMF measurements when necessary.

**Waveform Analyses** Waveform analyses were performed in 13 studies (Aerts et al. 2015; Barbancho et al. 2015; Barwood et al. 2011, 2012; Chantsoulis et al. 2016; Cornelissen et al. 2003; Iyer et al. 2020; Laganaro et al. 2008; Lucchese et al. 2017; Mohr et al. 2016; Pulvermüller et al. 2005; Radman et al. 2016; Wilson et al. 2012); in five of these studies (Barbancho et al. 2015; Chantsoulis et al. 2016; Cornelissen et al. 2003; Iyer et al. 2020; Pulvermüller et al. 2005), source localization was conducted using inverse solutions.

Six studies (Aerts et al. 2015; Barbancho et al. 2015; Barwood et al. 2011, 2012; Iyer et al. 2020; Wilson et al. 2012) demonstrated changes in the N400 during picture-word verification (Barwood et al. 2011, 2012; Iyer et al. 2020; Wilson et al. 2012), auditory word recognition (Aerts et al. 2015), and silent reading (Barbancho et al. 2015; Aerts et al. 2015) reported reductions of the N400 component when speech-training intensity was decreased (Aerts et al. 2015) or memantine was administered (Barbancho et al.

2015). Reduction of the N400 was associated with language improvement in the work by Barbancho et al. (2015), while it was associated with declining or static language scores in the case report of Aerts et al. (2015). After the addition of SLT to their drug treatment regimen, Barbancho et al. (2015) observed enhancement of the N400, as did Barwood et al., in two low-rTMS studies; this was also reported by Aerts et al. in the context of enhanced training intensity (Aerts et al. 2015; Barwood et al. 2011, 2012). In a picture-word verification task, Wilson et al. (2012) reported an abnormal shift of the centroparietal N400 waveform from the RH to the more lateralized LH after therapy; however, they found no change in amplitude associated with language improvement.

The P100 ERP component was also modulated by Barbancho et al. (2015); amplitudes decreased upon the introduction of memantine, but later increased upon the addition of SLT, similar to the findings for the N400. All of those modulations were associated with language improvements. The reduction of an abnormal P200 in a go/no go task after rTMS followed by SLT was associated with improvements in language and cognitive control in a single patient with crossed aphasia (Chantsoulis et al. 2016). In a study by Wilson et al. (2012) that involved participants with chronic aphasia and (predominantly) expressive impairments, the P200 amplitude was normal and no changes in picture naming were observed after therapy.

Three studies (Aerts et al. 2015; Lucchese et al. 2017; Mohr et al. 2016) used the MMN as a neurophysiological biomarker of therapeutic effects. To elicit MMN, the authors included unexpected/deviant items (e.g., pseudowords and ungrammatical sentences) in their ERP task (phoneme, syllable or word discrimination, and listening to words or sentences). These studies demonstrated improved MMN responses toward normalization, particularly for left electrodes, while listening to words and pseudowords (Lucchese et al. 2017; Mohr et al. 2016), and for right frontotemporal electrodes while listening to impromptu auditory stimuli listening (Aerts et al. 2015). The MMN amplitude improvement reported by Mohr et al. (2016) was only associated with meaningful words, and was seen only for left frontotemporal electrodes. Aerts et al. (2015) studied the P300 and MMN, and reported increases in P300 amplitude during two periods of rehabilitation, along with differences between intensive and conventional therapy.

Cornelissen et al. (2003) showed that EMF changes could be induced by picture-naming therapy involving both lexical-semantic and phonologic representations, beginning 300–600 ms after picture presentation in regions surrounding the LH lesion; the RH was not involved after therapy. Notably, the three patients in that study had greater phonological than semantic impairment. Radman et al. (2016) reported topographic changes in late time windows (540–600 ms) during a picture-naming task after phonological therapy.

After CIAT, one study (Pulvermüller et al. 2005) reported increased negativity bilaterally around 250–300 ms during a lexical decision task, for words but not pseudowords. Iyer et al. (2020) found that significant naming improvement after therapy was associated with low intrahemispheric coupling in the RH, particularly in the inferior frontal gyrus and posterior superior temporal gyrus, in two time windows that included N200 and N400.

**Topographic Analysis** Only one of the clinical trials used ERP/EMF topographic analyses. Those analyses segments ERP/EMFs focused on periods of quasi-stable magnetic or electrophysiological patterns at scalp (covering a cluster of adjacent electrodes) that lasted from 10 to several hundred milliseconds. The variability of ERPs is thus compressed in a series of topographic maps that can be compared across experimental conditions (Laganaro 2014; Murray et al. 2008).

Laganaro et al. (2008) reported the activation of electrodes situated above the RH during a picture-naming task at different stages of recovery, from 2 weeks to 6 months post-stroke, as well as before and after therapy. Increases in amplitude and changes in topography after therapy were visible in different time windows according to the underlying impairment: in the first 300 ms in a patient with semantic impairments and after 250 ms in patients with phonological impairments.

**Time-frequency Analysis** Time-frequency analysis was conducted in only one study (Meinzer et al. 2009). The authors analyzed variations in frequency over time during a flash reading task; they mainly focused on high-frequency activity (HFA) in the gamma band. They concluded that language improvement after therapy was associated with reduced HFA in the RH; this pattern suggested normalization, in contrast to the initial bilateral activation pattern.

### Continuous EEG and MEG Studies

Among the eight continuous EEG and MEG studies (Dammeke et al. 2014; Fedorov et al. 2010; Meinzer et al. 2004; Sarasso et al. 2010, 2014; Shah-Basak et al. 2020; Stojanovic et al. 2013; Wu et al. 2015), two were sleep studies by Sarasso et al. (2014, 2010) that investigated the impact of an intensive single session of IMITATE therapy on patients with chronic aphasia. The authors found improvements in behavioral measurements (repetition accuracy) associated with increased SWA during rapid eye movement sleep. Although the changes were bilateral in both studies, they were more consistent in the ipsilesional hemisphere in the first study (Sarasso et al. 2010) and in the contralesional hemisphere in the second study (Sarasso et al. 2014).

Another study (Meinzer et al. 2004) focused on SWA while at rest, rather than during sleep. Abnormal SWA was observed in the vicinity of the lesion; in 16 of 28 patients with aphasia, improvements after speech therapy led to a decrease in SWA.

Two studies (Dammekens et al. 2014; Fedorov et al. 2010) demonstrated improvements in interhemispheric connectivity after therapy (along with language improvement), in beta and theta ranges (Dammekens et al. 2014) or only in the theta range (Fedorov et al. 2010; Dammekens et al. 2014) observed beta band normalization in the LH and decreased beta band activity in the RH after rTMS. Shah-Basak et al. (2020) reported a decrease in theta band activity in contralesional areas after anodal tDCS targeting perilesional areas; these results were associated with improved repetition accuracy in patients with chronic aphasia. The authors also found an increase in fast-wave activity (gamma band) after perilesional anodal stimulation or contralesional cathodal stimulation.

Wu et al. (2015) used EEG nonlinear analysis with approximate entropy, which is a statistical method that quantifies the extent of serial interrelationships (0 indicates perfectly ordered measurements, while infinity indicates random measurements). As approximate entropy increased, irregularity increased; this change in irregularity was associated with increased nonlinear cell-dynamics or interactions among cortical networks. In their study, Wu and collaborators compared a patient with aphasia and a healthy control on two conditions (resting and repetition). They found correlations between improved behavioral measurements and increased EEG approximate entropy indices in the LH and some isolated RH areas.

## Summary

In order to illustrate the convergence/divergence of the literature, main findings are summarized in Table 5 per type of data, type of analysis and type of biomarker.

## Discussion

Non-interventional studies focused strictly on speech perception/comprehension and amplitude analyses; they did not consider the potential effect of neurorehabilitation on electrophysiological changes. Among clinical trials, drug studies were rare and showed that drugs might have a detrimental effect on behavior. SLT studies often used EEG/MEG tasks that were not relevant to the training used (e.g., listening or reading words during EEG/MEG under treatment targeting the oral production of sentences), and NIBS studies did not provide sufficient details regarding the SLT for replication.

In the following sections, we discuss potential electrophysiological biomarkers for language impairments or recovery. We also suggest electrophysiological modulations that could be used as biomarkers of therapeutic efficacy. In addition, we discuss how the reviewed studies contributed to theoretical models of language. Finally, we identify methodological issues and future research questions.

## Electrophysiological Biomarkers of Language Recovery or Impairment

Several studies using continuous EEG or ERP/EMF showed electrophysiological changes associated with language recovery. In a study by Jabbari et al. (1979), five of 52 patients exhibited mild non-fluent Broca aphasia and had normal EEG rhythms in the subacute stage. Those patients completely recovered in the chronic stage, suggesting that EEG rhythms should be regarded as predictors of aphasia recovery. This assumption is supported by the results of a more recent study, which demonstrated a positive correlation between the informativeness of the patient's discourse and presence of alpha and beta bands in EEG, along with a negative correlation between the informativeness of the patient's discourse and presence of SWA (theta band) in the chronic stage (Dalton et al. 2021). In this review, we observed that fast rhythms (e.g., alpha rhythms) were correlated with marked improvements in several studies (Dalton et al. 2021; Jabbari et al. 1979; Nicolo et al. 2015). Furthermore, Nicolo et al. (2015) reported that beta oscillations were associated with the establishment of new synaptic connections and thus—in patients with brain lesions—neural reorganization and recovery. In contrast, abnormal SWA (theta band) was associated with poor recovery and persisted for long periods of time (Dalton et al. 2021; Hensel et al. 2004; Jabbari et al. 1979; Nicolo et al. 2015; Szeliés et al. 2002).

Concerning specific ERP components, the presence of the P300 (and/or enhancement of the P300 amplitude) from the subacute stage to the chronic stage was considered a good sign of recovery in several studies (Becker and Reinvang 2007b; Cobiañchi and Giaquinto 2000; Cocquyt et al. 2020; Nolfé et al. 2006). Changes in MMN were also associated with comprehension improvements in a non-interventional study by Ilvonen et al. (2003). Electrophysiological patterns tend to normalize during language recovery. However, despite improvements in language, ERP abnormalities can appear or increase. Indeed, in the case report by Aerts et al. (2015) and the study by Becker and Reinvang (2007a), improvements in language performance were not associated with a tendency for ERP components to return to normal. Aerts et al. reported changes in electrophysiological measurements (P300, MMN, and N400), which became increasingly unusual after a therapy-free period. Similarly, Cocquyt et al. (2020) found that MMN and P300 normalized during



the chronic stage in all of their participants, except two who showed gradual changes in latency and amplitude despite normal findings in the subacute stage. Notably, in the studies by Aerts et al. (2015) and Cocquyt et al. (2020), improvements in language scores continued despite deviations from normal findings. Thus, changes in electrophysiological measurements can also be interpreted as a sign of recovery, even if they do not involve normalization. Indeed, after a stroke, some networks in the RH and networks responsible for other cognitive functions could be involved in language tasks (for a review, see Stefaniak et al. 2020).

The results of some studies suggest that specific electrophysiological patterns reflect specific language impairments. For instance, after a stroke, abnormal rhythms (e.g., SWA while awake) were found in the vicinity of the lesion (Hensel et al. 2004; Kamada et al. 1997). The studies included in this review showed relationships between spontaneous resting-state rhythms and aphasia severity. In addition to rhythms, some ERP components may be useful biomarkers of specific language impairments. For instance, in studies that used semantic judgment tasks (Barwood et al. 2011, 2012; Iyer et al. 2020), the N400 was normal in patients without comprehension impairment but was abnormal in patients with such impairment, suggesting that the N400 can serve as a biomarker of spared or impaired comprehension (Aerts et al. 2015; Cobianchi and Giaquinto 2000). This potential role for the N400 was discussed in the review by Meechan et al. (2021), who suggested its use as a biomarker of aphasia; they also concluded that further studies were needed regarding this issue.

The current findings underscore the relevance of electrophysiology for the diagnosis of aphasia and/or specific language impairments. Even if a diagnosis of aphasia cannot be achieved through combined use of electrophysiological and clinical findings, EEG or MEG data might improve knowledge regarding the pathophysiology of aphasia.

### Electrophysiological Biomarkers of Therapeutic Efficiency

Electrophysiological changes can reflect the neural effects of aphasia treatment (Pulvermüller et al. 2005) and indicate the induction of neuroplasticity. For instance, changes in spontaneous EEG have been interpreted as an electrophysiological biomarker of SLT or NIBS outcomes. Indeed, Meinzer et al. (2004) observed a reduction of abnormal resting-state SWA in the vicinity of the lesion among approximately 60% of patients who exhibited language task improvement after CIAT. In a randomized clinical trial (Shah-Basak et al. 2020), the improvements in sentence repetition accuracy after anodal tDCS targeting left perilesional areas were correlated with decreases in SWA and theta bands, but only in a subgroup of patients who did not exhibit non-fluent aphasia.

In addition, in the two sleep studies included in this review (Sarasso et al. 2010, 2014), an increase in normal SWA during sleep after one day of therapy was a good predictor of language improvement. The training approach used in these two studies (IMITATE®) was based on imitation after repeatedly watching video clips of various people uttering words or sentences. The results suggested that this training could induce the formation of new cerebral connections similar to those that form during memory/learning tasks; these connections were sustained by changes occurring during non-rapid eye movement sleep (corresponding to the period of SWA) that have been associated with declarative learning (Maquet 2001).

ERP components may also serve as relevant biomarkers of therapy-induced effects and highlight the benefits of SLT, as well as its impacts on specific language processes. Indeed, the N400 may be a good measure of therapeutic effects (Aerts et al. 2015; Barwood et al. 2011, 2012); during recovery, its amplitude increased in lexical-semantic processing and semantic integration tasks (Barwood et al. 2011, 2012). The MMN changes were also associated with improvements in all behavioral measurements (in both expressive and receptive tasks) in three studies (Aerts et al. 2015; Lucchese et al. 2017; Mohr et al. 2016). Finally, one clinical trial (Aerts et al. 2015) showed that the amplitude of the P300 increased and decreased with SLT intensity (i.e., higher amplitude with more intensive therapy and lower amplitude with less intensive therapy).

The use of electrophysiological changes as biomarkers of therapeutic efficiency might improve our understanding of language processes, as well as aid identification of processes that are impacted by specific therapies. Such information could help speech therapists and researchers identify the most beneficial approach according to clinical and electrophysiological findings.

### Contribution of Language Models to the Understanding of Temporal Processes

ERPs/EMFs also improve understanding of the temporal aspects of language processes. Picture naming was the most frequently used task among the studies included in this review. However, the processes that underlie picture-naming task results in healthy individuals are well-characterized (Laganaro 2017). For instance, in the model described by Indefrey (2011), semantic and lexical processes onset approximately 175–200 ms after picture presentation, while phonological code retrieval occurs after approximately 275 ms; after 400 ms, phonological-phonetic encoding occurs (Indefrey 2011; Laganaro 2017). ERP changes associated with impairments were identified in two studies by Laganaro et al. (2013, 2009). Topographic and waveform differences were present in early time windows (< 300 ms post-picture

onset) in patients with semantic impairments, in the time window of 30–400 ms in patients with lexical-phonological impairments, and after 400 ms in patients with phonological-phonetic impairments; the ERP patterns were otherwise similar to those of healthy control participants. The same group of researchers (Laganaro et al. 2008) described increases in amplitude and topographic changes after therapy in distinct time windows after treatment for anomia: during the first 300 ms in a patient with semantic impairment and after 250 ms in patients with phonological impairments. Radman et al. (2016) studied a clinical case of bilingualism and reported topographic changes in a late time window (540–600 ms after picture onset) after lexical-phonological therapy. Among patients with (predominantly) phonological impairments, Cornelissen et al. (2003) found changes in EMF patterns in perilesional regions, which were induced by contextual priming technique-based therapy at 300–600 ms after stimulus onset. All of these studies described various patterns of language impairment and compared patients with control participants. The changes observed in patients were either normalization (i.e., changes towards the neurotypical pattern) or the appearance/persistence of divergent electrophysiological patterns compared with the ERPs of healthy control participants. Moreover, the changes observed in topographic and waveform analyses of ERP/EMF appeared in time windows specifically associated with language impairments (e.g., semantic or phonological) or trainings.

### Methodological Issues and Future Research Questions

Regarding the electrophysiological changes caused by different interventions during longitudinal follow-up in patients with post-stroke aphasia, several studies have suggested that the electrophysiological patterns underlying language processes were stable in the chronic or subacute stages. However, this assumption must be validated, particularly at the individual level. Among 23 clinical trials, only four included a placebo/sham group of patients with aphasia (Barbancho et al. 2015; Barwood et al. 2011, 2012; Meinzer et al. 2004), while four used a cross-over design (Aerts et al. 2015; Shah-Basak et al. 2020; Woodhead et al. 2017; Wu et al. 2015) in which each patient initially received either placebo or actual stimulation, followed by the other condition. Seven other studies included at least one group of healthy controls (Chantsoulis et al. 2016; Dammekens et al. 2014; Iyer et al. 2020; Laganaro et al. 2008; Meinzer et al. 2009; Stojanovic et al. 2013; Wilson et al. 2012). All other studies, with the exception of Radman et al. (2016), examined patients with aphasia in the chronic stage; they characterized stability at this stage as described above. This assumption of stability has been supported by interventional studies conducted

outside of the treatment period, which showed behavioral and electrophysiological, or MRI-based stability at this stage. For example, Lucchese et al. (2017) proposed such an assumption of stability based on the results of three studies: one demonstrated behavioral stability over 6 months in the chronic stage after therapy (Meinzer et al. 2005); one used functional MRI (Fridriksson et al. 2006) to explore changes in three patients and reported stability at baseline or during the post-rehabilitation period based on three functional MRI scans performed at intervals of 2 to 3 days; and one used MEG post CIAT (Breier et al. 2009). This assumption of stability is controversial. Indeed, long-term recovery (including behavioral changes) after a stroke has been observed in many patients still years after stroke (Smania et al. 2010; Stark 2010). Moreover, other MRI-based studies of anatomical changes revealed that cortical thickness in the RH was altered in association with behavioral improvement in patients with chronic aphasia who did not complete a specific rehabilitation program (Hope et al. 2017). Electrophysiological changes were also reported, particularly in the delta band, in patients with post-stroke aphasia during the chronic stage of recovery, as well as in healthy controls (Dalton et al. 2021); changes in ERP waveform analysis were observed in a placebo group composed of patients in the chronic stage of recovery (Barbancho et al. 2015). Thus, the consensus view of behavioral stability (without rehabilitation) during the chronic stage (Pedersen et al. 1995) requires further scrutiny. Thus, there is a need to include control groups, perform repeated baseline assessments, or modify the research design to ensure behavioral, functional, or electrophysiological stability. This critically important temporal variation is particularly complex in the subacute stage. For instance, one case report (Radman et al. 2016) focused on a patient in the subacute stage; the findings were compared with a placebo control group. In addition to behavioral changes, substantial interpatient variability in electrophysiological pattern alterations are seen during this stage, as demonstrated in several non-interventional studies included in this review (Ilvonen et al., 2003; Nolve et al. 2006; Rojas Sosa et al. 2009). The inclusion of patients in the subacute stage is important but requires a more rigorous experimental design, such as the Single-Case Experimental Design (SCED), for tighter control of within-participant comparisons (Krasny-Pacini and Evans 2018).

Finally, various approaches can be used for ERP analysis. However, among the 22 ERP/EMF studies included in the present review, only one used time-frequency analysis (Meinzer et al. 2009), while another used topographic analysis (Laganaro et al. 2008). Most of the ERP/EMF studies focused on waveform analyses. Moreover, only nine of 22 studies used high-density EEG (i.e.,  $\geq 64$  electrodes). However, using  $< 64$  electrodes does not permit several analyses (e.g., source localization, topographic analysis,

**Table 5** Summary of main findings per type of data, type of analysis and type of biomarker

Type of data	Type of analysis	Number of studies	Biomarker of interest	Main correlations or associations with aphasia recovery
Continuous (resting state/sleeping)	Rhythm analysis	11	Low frequency rhythms (e.g., decrease in the brain rhythm, power in low-frequency band, decrease of SWA)	<p>Theta power (spectral analysis) negatively correlated with discourse informativeness scores (Dalton et al. 2021)</p> <p>Decreased theta band in the contralateral hemisphere (multitaper spectral analysis in MEG) correlated with repetition improvement after tDCS (Shah-Basak et al. 2020)</p> <p>Theta oscillation (index of functional connectivity reflected by synchronization between critical brain areas and the rest of the brain) in the contralesional hemisphere associated with a good recovery according to the Geneva Bedside Aphasia Scale (Nicolo et al. 2015)</p> <p>Out of 28 patients, decrease in perilesional SWA in 16 cases (delta dipole density in MEG) after therapy and increase in 12 cases both associated with improvements in Token test and AAT scores (Meinzer et al. 2004)</p> <p>Delta and theta activity (<b>spectral analysis</b>) in the ipsilesional hemisphere associated with poor language recovery measured by the Token Test (Szeliets et al. 2002)</p> <p>Focal slowing activity (visual analysis of specific bands and rhythms) correlated with poor language recovery (Jabbari et al. 1979)</p> <p>Alpha and beta bands (spectral analysis) correlated with better discourse informativeness (Dalton et al. 2021)</p> <p>Beta oscillation in the ipsilesional hemisphere (index of functional connectivity reflected by synchronization between critical brain areas and the rest of the brain) correlated with improvement measured by the Geneva Bedside Aphasia Scale (Nicolo et al. 2015)</p> <p>Increased in beta band (spectral analysis) associated with better scores in naming, repetition and comprehension after rTMS (Dammekens et al. 2014)</p> <p>Higher alpha band in contralateral hemisphere (visual analysis of specific bands and rhythms) correlated with better recovery (Jabbari et al. 1979)</p>
			High frequency rhythms (e.g., increase in the brain rhythm, power in high-frequency band)	

Table 5 (continued)

Type of data	Type of analysis	Number of studies	Biomarker of interest	Main correlations or associations with aphasia recovery
			Area or hemisphere synchronization	Coherence between left IFG and other healthy brain areas (index of functional connectivity reflected by synchronization between critical brain areas and the rest of the brain) associated with improvement measured by the Geneva Bedside Aphasia Scale (Nicolò et al. 2015)
				Increased EEG ApEn indices in the LH and some isolated RH areas (approximate entropy analysis reflecting interaction of cortical networks) correlated with picture naming improvements after tDCS (Wu et al. 2015)
				Increased synchronization between right and left IFG in theta and beta bands (spectral analysis) associated with improvements in naming, repetition and comprehension after rTMS (Dammekens et al. 2014)
				Differences in the index of asymmetry and limits of variability significantly decreased (spectral analysis) after SLT for patients with good improvement compared to patients with poor improvement (Stojanovic et al. 2013)
				Increased synchronization between temporal right and temporal left areas in theta range (spectral analysis) correlated with improvements in stroke severity level including aphasia severity after repetitive transorbital alternating current stimulation (Fedorov et al. 2010)
			SWA during sleep	Increased SWA during rapid eye movement sleep (spectral density analysis) associated with improvements in WAB repetition scores after imitation-based SLT (Sarasso et al. 2010, 2014)
Event-related (AEP/ERP/EMF)	Waveform analysis	17	Nb	Latency of the Nb peak at hospital discharge correlated with score increase of the BDAE at 6 months post-stroke (Rojas Sosa et al. 2009)

Table 5 (continued)

Type of data	Type of analysis	Number of studies	Biomarker of interest	Main correlations or associations with aphasia recovery
			MMN	<p>Increased MMN amplitude for grammatically correct sentences after SLT (Lucchese et al. 2017)</p> <p>Increased MMN amplitude on left frontotemporal electrodes for meaningful words related to improvements in Token Test scores after SLT (Mohr et al. 2016)</p> <p>Variation in MMN amplitude associated with SLT intensity. Increased MMN amplitude toward normalization associated with improvement in AAT scores, mainly after intensive SLT (Aerts et al. 2015)</p> <p>Increased MMN duration correlated with language comprehension improvements (Ilvonen et al., 2003)</p>
			P100	<p>Decreased P100 amplitude in patients with chronic aphasia after drug administration, and smaller decrease also observed in the placebo group, correlated with improvements in aphasia severity score in both groups ; increased P100 amplitude after SLT associated with improvements in aphasia severity score ; stability of P100 amplitude after a period without SLT associated with stability in aphasia severity score (Barbancho et al. 2015)</p>
			P200	<p>Reduction of P200 abnormal excitability over temporal electrodes of the contralateral hemisphere associated with normalization of WAB scores (Chantsoulis et al. 2016)</p>
			P300	<p>Early presence of a normal P300 associated with better recovery of language comprehension after 6 months of rehabilitation (Cocquyt et al. 2020)</p> <p>Modulation of P300 amplitude associated with SLT intensity ; changes in P300 toward normalization associated with improvement in AAT scores, mainly after intensive SLT (Aerts et al. 2015)</p> <p>Increased P300 amplitude in ipsilesional frontal areas associated with mild comprehension improvements (Becker and Reinvang 2007a)</p> <p>Presence of a P300 early post-stroke (&lt; 1 month) in patients with global aphasia associated with better comprehension recovery (Nolfe et al. 2006)</p>
			N100	<p>Smaller N100 amplitude at subacute stage associated with better improvement in auditory comprehension (Becker and Reinvang 2007a)</p>

Table 5 (continued)

Type of data	Type of analysis	Number of studies	Biomarker of interest	Main correlations or associations with aphasia recovery
			N200	Increased N200 amplitude in ipsilesional frontal electrodes associated with mild comprehension improvement (Becker and Reinvang 2007a)
			N400	Increased N400 amplitude after a period of intensive SLT associated with improvements in AAT scores, lexical decision and repetition ; decreased N400 amplitude after less intensive SLT conventional therapy associated with decrease in auditory pseudoword discrimination scores ; increased N400 amplitude after intensive SLT associated with improvements in auditory pseudoword discrimination scores (Aerts et al. 2015) Decreased N400 amplitude in patients with chronic aphasia after drug administration, and smaller decrease observed in the placebo group, correlated with improvements in aphasia severity score in both groups ; increased N400 amplitude after SLT associated with improvements in aphasia severity score ; stability of the N400 amplitude after a period without SLT associated with stability in aphasia severity score (Barbancho et al. 2015) N400 shift from RH to LH after SLT associated with increase in WAB scores and/or communication scores for 6 out of 9 patients, without change in the N400 amplitude (Wilson et al. 2012) Increased N400 negativity after rTMS associated with improvement in written word-picture semantic judgement (Barwood et al. 2011, 2012)

Table 5 (continued)

Type of data	Type of analysis	Number of studies	Biomarker of interest	Main correlations or associations with aphasia recovery
			Changes toward normalization or appearance of new abnormalities in specific time-windows	<p><b>In picture naming tasks:</b>            Changes in late time-windows post picture onset (500-540ms) after lexical-phonological SLT for a bilingual patient, associated with naming improvement in the trained language (Radman et al. 2016)            Increased in amplitude after naming therapy in different time-windows according to the underlying impairments and associated with improvements in picture naming: first 300ms for semantic impairments and after 250ms post picture onset for phonological impairments (Laganaro et al. 2008)            Changes in brain activity between 300-600ms post picture onset associated with improved phonological processing after SLT (Cornelissen et al. 2003)  <b>In lexical decision tasks:</b>            Increased negativity around 250-300ms post stimulus onset associated with improvement in Token Test scores (Pulvermüller et al. 2005)            Decreased RH activation and increased bilateral pattern after SLT associated with better scores in written language, except for high-functioning patients (best scores at baseline) (Meinzer et al. 2009)            Changes in topography after therapy in different time-windows according to the underlying impairment, and associated with improvements in picture naming: first 300ms for semantic impairments and after 250ms post picture onset for phonological impairments (Laganaro et al. 2008)            Better modulation of left STG self-connection, and connection from the left Heschl's gyrus to STG, as well as STG interhemispheric connections, associated with improvements in comprehension tasks after phonological training (Woodhead et al. 2017)            Significant asymmetries of auditory evoked dipole source potentials more frequent in the severely impaired group compared with the moderate/recovered auditory comprehension group at follow-up (Praamstra et al. 1993)</p>
	EMF time-frequency analysis	1	HFA	
	ERP topography analysis	1	Different time-windows during a picture naming task	
	ERP source localization	5	Identification of dipole locations underlying MMN response in four spatial models  Dipole source analysis for AEP	

Table 5 (continued)

Type of data	Type of analysis	Number of studies	Biomarker of interest	Main correlations or associations with aphasia recovery
			Connectivity in time-windows including N200 and N400	Reduced coupling in contralateral regions (contralateral IFG and posterior STG) and good pretreatment connectivity between left inferior parietal lobule and left IFG correlated with improvement in picture naming after SLT (Iyer et al. 2020)
			Hemispheric activation	RH activation at different stages of recovery, before or after SLT, associated with improvement in picture naming (Laganaro et al. 2008) Increased negativity in both hemispheres associated with improvement in Token Test scores (Pulvermüller et al. 2005)

*AAT* Aachen Aphasia Test, *ApEn* approximate entropy, *BDAE* Boston Diagnostic Aphasia Examination, *HFA* high-frequency activity, *IFG* inferior frontal gyrus, *LH/RH* left/right hemisphere, *rTMS*: repetitive transcranial magnetic stimulation, *STG* superior temporal gyrus, *tDCS* transcranial direct current stimulation, *WAB* Western Aphasia Battery

and spatiotemporal analysis) (Im 2018), although methods for better channel selection are being explored to reduce the electrode number (Montoya-Martínez et al. 2021; Pal et al. 2019). This limitation could partly explain the small numbers of studies that use topographic, source localization, or time-frequency analyses. Therefore, future electrophysiological studies should use high-density EEG to better decipher the spatiotemporal dynamics of post-stroke aphasia recovery.

Finally, network-based analyses could be of great interest to estimate the association's strength between connected areas based on the value of temporal correlations (Zalesky et al. 2010). Such functional measures seem to be largely unexploited in the field, but connectivity differences between individuals with and without aphasia could be interpreted as network disconnections and further linked with aphasia recovery.

## Conclusion

Longitudinal EEG and MEG measurements may be appropriate for the exploration of neural processes associated with spontaneous or therapy-induced recovery in patients with post-stroke aphasia; however, such measurements are currently poorly applied. Indeed, there have been few high-density EEG studies and few reports of source localization, topographic analysis, and spatiotemporal analysis. Continuous brain activity recordings are useful for predicting language recovery or monitoring interhemispheric connectivity; however, such recordings are insufficient for demonstrating specific therapeutic effects or distinguishing responders and non-responders to therapy. ERP/EMF may be more useful than continuous EEG for identifying biomarkers of therapy-induced effects. Electrophysiological biomarkers could also be used to identify and improve impaired neural processes. Indeed, Fellinger et al. (2012) identified travelling waves—corresponding to the propagation of electrical activity during cognitive tasks—associated with language activities in healthy individuals. Beuter et al. (2020) suggested that EEG could be used to identify impaired processes; the courses of disturbed waves could then be “repaired” via brain stimulation. More frequent use of electrophysiology to explore language impairments after a stroke could help identify treatment challenges for patients with post-stroke aphasia.

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## Declarations

**Competing Interests** The authors declare no competing interests.

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## 5.2. Changements électrophysiologiques induits par la rTMS

Comme l'indique cette revue systématique, les deux études de Barwood et al. (2011; 2012), constituent à notre connaissance, les seules études ayant étudié l'impact de la rTMS sur les tracés ERPs dans une tâche linguistique. Ces chercheurs révèlent notamment une augmentation de l'amplitude de la N400 lors d'une tâche de jugement sémantique de mots écrits/images post-rTMS, liée à des améliorations cliniques. Ces changements avaient même tendance à augmenter jusqu'à un an post-stimulation.

Aucune étude à notre connaissance n'a ainsi investigué les changements ERP induits par la rTMS dans des tâches de production du langage, comme de la dénomination d'images, qui est pourtant la tâche majoritairement utilisée pour juger de l'efficacité de la rTMS dans les études recensées, et qui permet de mettre en évidence une anomie, présente dans tous les types d'aphasies (Arheix-Parras et al., 2021).

Quelles sont les modifications électrophysiologiques induites par la rTMS chez les personnes aphasiques post-AVC en dénomination orale d'images ?

## **Partie 2. Individualisation de la rTMS pour le traitement de l'aphasie post-AVC**

### **1. Méthodologie des études SCED**

Développés dès les fondements de la recherche en psychologie, les SCED (en anglais, Single Case Experimental Design), constituent la méthodologie la mieux adaptée lors de l'exploration d'une nouvelle méthode de traitement, ou pour des participants présentant des profils atypiques (Robert, 2019). Elle apparaît comme une méthodologie de recherche appropriée pour le questionnement à propos de l'individualisation du traitement.

Le SCED inclut une seule personne ou un groupe de participants étudiés de manière individuelle. Cette méthodologie est considérée comme présentant un haut niveau de preuve (« Levels of Evidence 2, Oxford Center for Evidence-Based Medicine », Howick et al., 2011), et nécessite le respect de contraintes méthodologiques (échelle d'évaluation RoBiNT, Tate et al., 2014). Ainsi, les études de cas au format SCED présentent une rigueur suffisante pour participer à l'évaluation des pratiques fondées sur les preuves (en anglais Evidence-Based Practice, EBP) (Tate et al., 2014). Cependant, afin d'être généralisables, les résultats issus d'un SCED doivent être répliqués, incluant au total 5 études issues de 3 laboratoires différents, si possible sans recouvrement entre les chercheurs impliqués (Kratochwill et al., 2013).

Nous décrivons dans les prochaines sections les caractéristiques générales du SCED et justifieront les choix méthodologiques réalisés.

#### **1.1. Principales caractéristiques**

##### *1.1.1. Les mesures répétées*

La caractéristique fondamentale du SCED est le fait que la variable dépendante est évaluée de manière fréquente et répétée, avec un minimum de 5 points par phase (Kratochwill et al., 2013; Tate et al., 2013). Ceci permet d'établir la stabilité de la ligne de base, ou de prendre en compte sa tendance, c'est-à-dire une éventuelle évolution pré-intervention (e.g., effet d'apprentissage, récupération spontanée en phase subaiguë post-AVC). Cette répétition permet également de mettre en évidence une variabilité dans les performances, qui peut être importante dans certains types de cas, et dépendre de facteurs externes. De plus, toutes les sessions doivent être réalisées de manière régulière, si possible dans les mêmes conditions

(e.g., lieu de passation), et à heures fixes, permettant de diminuer les risques de biais dus à ces facteurs extérieurs (Robert, 2019).

### 1.1.2. SCED en lignes de bases multiples

Il existe plusieurs types de plans expérimentaux en modèle SCED (voir Krasny-Pacini & Evans, 2018). Les études en lignes de bases multiples constituent les plans expérimentaux les plus adaptés compte tenu du maintien dans le temps des effets cliniques induits par la rTMS (i.e., pas de retour à la ligne de base lors de l'arrêt de l'intervention) (Arheix-Parras et al., 2021; Krasny-Pacini & Evans, 2018; Robert, 2019).

Dans ce type de modèle, les effets retrouvés chez un participant doivent être répliqués pour être validés, en proposant la même intervention auprès de plusieurs participants, ou bien différentes interventions auprès de la même personne (Robert, 2019). Ce design propose une randomisation de la durée de la ligne de base (i.e., le nombre de points de ligne de base est tiré au sort), pouvant décaler le début de l'intervention. Cette randomisation assure que les effets observés sont liés à l'intervention, et non à l'évolution normale après un même délai de présentation de la mesure répétée (Robert, 2019).

Nous avons utilisé des SCED en lignes de bases multiples au travers des participants pour les articles 3 et 4, avec la même intervention pour tous les participants de l'étude. Pour l'article 5, nous avons utilisé un plan expérimental en lignes de bases multiples à travers les interventions, indiquant que différentes interventions, à différents points, ont été appliquées chez une même personne.

## 1.2. Evaluation des effets induits

### 1.2.1. L'analyse visuelle

L'analyse visuelle du SCED constitue la méthode originalement utilisée afin de déterminer l'efficacité de l'intervention. Les critères spécifiques et principaux à prendre en compte sont les suivants (Kratochwill et al., 2013; Robert, 2019) (Figure 2) :

- **Les différences de niveau et de tendance**, entre la phase d'intervention et la ligne de base ;
- **La variabilité**, c'est-à-dire les points s'éloignant de la ligne de régression ;
- **L'immédiateté de l'effet**, difficilement applicable dans le champ des NIBS, où les effets cliniques peuvent apparaître à distance ;
- **Le non-chevauchement**, c'est-à-dire les points ne se recouvrent pas entre la ligne de base et l'intervention ;

- **La similarité**, consistant à comparer les données entre les participants ou entre les conditions.

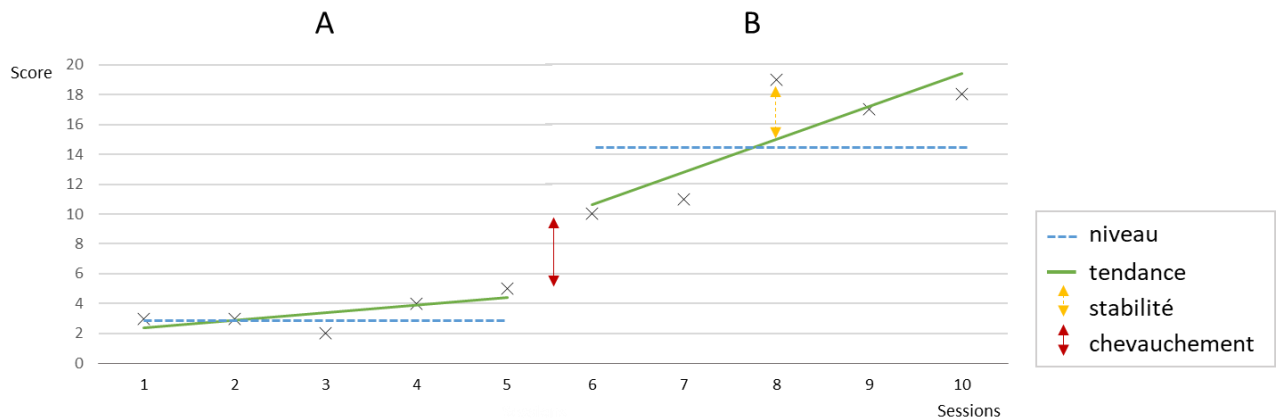


Figure 2 : Critères de l'analyse visuelle du SCED

Ainsi, lorsque la ligne de base ne présente pas de tendance spécifique (i.e., pas d'augmentation ou de diminution des scores), les résultats peuvent être présentés avec la moyenne de la ligne de base et une enveloppe de 2 écart-types. Par ailleurs, si la ligne de base présente une tendance (e.g., amélioration des scores), il est possible de représenter la ligne de tendance et un intervalle interquartile, ou bien une enveloppe représentant les 20% de la médiane (suivant la règle des 80%-20%, voir Manolov et al., 2016) qui suit cette même ligne de tendance durant l'intervention. Plus les points se situent hors de l'enveloppe ( $\geq 3$  points), plus on pourra évoquer un effet de l'intervention (Kratochwill et al., 2013). La prise en compte de la ligne de tendance pour l'analyse visuelle permet de diminuer les risques de conclure à un effet de l'intervention, alors qu'il ne s'agissait que de l'évolution naturelle des scores (e.g., effet d'apprentissage, récupération spontanée).

### 1.2.2. L'analyse statistique

Plus récemment, des calculs statistiques ont été proposés pour permettre de compléter ces analyses visuelles. Différentes analyses sont possibles mais celles recommandées, car en accord avec les analyses visuelles, sont le calcul du Tau-U (Robert, 2019). Celui-ci consiste en un calcul de non-chevauchement des points grâce au calcul d'un Tau. Si une tendance significative se dégage lors de la ligne de base, il est possible de calculer un Tau corrigé à partir de cette ligne de base (Parker et al., 2011). Le score obtenu est compris entre -1 et 1 (un Tau positif indiquant une augmentation et négatif une régression des scores). La valeur absolue de la taille d'effet obtenue, peut être interprétée par un changement léger en dessous de 0.2, un changement modéré entre 0.2 et 0.6, un changement large entre 0.6 et 0.8, et un changement large à très large au-delà de 0.8 (Tate & Perdices, 2018; Vannest & Ninci, 2015).

## 2. Stimulations magnétiques transcrâniennes auprès des personnes présentant une aphasie sévère

Nous avons réalisé une première étude SCED qui s'est centrée sur des personnes présentant une aphasie sévère chronique post-AVC. En effet, la revue de littérature en rTMS (article n°1) a mis en évidence que ce type de profil est souvent mis à l'écart des études en stimulations cérébrales non invasives. Nous supposons que ceci est dû à la complexité de ces troubles, pouvant entraîner des difficultés pour que les participants comprennent les principes des études proposées, mais également du fait de moins bonnes perspectives de récupération.

L'hypothèse de ce travail est que les participants présentant une aphasie sévère post-AVC présenteront des progrès langagiers supérieurs via l'utilisation de la rTMS facilitatrice plutôt qu'inhibitrice du gyrus frontal inférieur (en anglais, Inferior frontal Gyrus : IFG) droit. En effet, nous remettons ainsi en question dans cet article le principe de balance interhémisphérique (voir partie 1, section 1.2.3), largement utilisé dans les études à propos des NIBS dans le cadre de lésions cérébrales. En effet, cette théorie pourrait ne pas être applicable dans le cadre de troubles langagiers sévères, induits par des lésions larges ou impactant des zones cruciales aux processus langagiers (Watila & Balarabe, 2015). Ainsi, les processus de récupération par rétablissement ou par compensation périlésionnelle seraient insuffisants, entraînant des séquelles langagières encore majeures à la phase chronique. Nous proposons ainsi de favoriser une récupération par réorganisation des réseaux langagiers, en facilitant les zones homologues contralésionnelles de l'hémisphère droit. Ceci soutient l'importance de l'hémisphère droit dans la récupération de l'aphasie post-AVC, même à la phase chronique (Varkanitsa et al., 2020). En effet, l'implication de l'hémisphère droit dans la récupération reste encore mal déterminée. Selon les études, son rôle n'est pas nécessairement négatif (Hartwigsen et al., 2020; Schneider et al., 2022; Stefaniak et al., 2021; Stockert et al., 2020), et ceci amène à repenser les principes d'inhibition des zones contralésionnelles.

L'article sera envoyé en publication au cours du mois de juillet au journal « Annals of Physical and Rehabilitation Medicine ».

*Article n°3: Transcranial Magnetic Stimulation for people with severe post-stroke aphasia*



## **Transcranial Magnetic Stimulation for people with severe post-stroke aphasia**

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## **Abstract**

**Introduction.** Studies highlighted that repetitive Transcranial Magnetic Stimulation (rTMS) using inhibitory parameters and targeting the right Inferior Frontal Gyrus (rIFG) can enhance post-stroke aphasia recovery. Such inhibitory stimulations aim to reduce the maladaptive effect of the right hemisphere (RH). However, the complex role of the RH in language processes, particularly in participants with severe post-stroke aphasia, is poorly understood. Indeed, severe chronic aphasia is associated with large brain lesions or lesions localized in crucial areas for language processes. As language recovery may be led by compensatory mechanisms rather than a return to premorbid patterns, facilitatory parameters targeting the left hemisphere might be an alternative to consider in severe aphasia. We aimed to compare language improvements induced by facilitatory versus inhibitory rTMS targeting the rIFG in people with severe post-stroke aphasia.

**Method.** Using a Single Case Experimental Design in a cross-over design, we included six patients suffering from severe chronic post-stroke aphasia. During two periods of six weeks, participants received inhibitory and facilitatory rTMS targeting the rIFG (facilitatory then inhibitory, or the reverse order). Participants performed picture naming and lexical decision tasks three times a week during the two periods of six weeks. They received rTMS three times a week for two weeks, without additional speech therapy.

**Result.** We found heterogeneous clinical results across participants. Only two out of six participants experienced clinical changes in picture naming accuracy: P6 improved in the inhibitory period, and P3 showed improvements after both types of stimulation. Regarding lexical decision accuracy, P6 showed an improvement induced by facilitatory rTMS, whereas P1 experienced a decrease after inhibitory rTMS and P5 showed a decrease after both types of stimulation.

**Discussion.** The present study puts into question the interhemispheric competition model, in specific cases such as severe aphasia. It highlighted the importance of individualizing rTMS, as using the same parameters and the same anatomical target might induce heterogeneous clinical changes. As severe aphasias englobe a variety of underlying impairments, cognitive-linguistic profiles of the patients could serve as a future basis for individualization.

**Key-words:** aphasia, stroke, rehabilitation, repetitive transcranial magnetic stimulation, individualization

## 1. Introduction

Non-invasive brain stimulations (NIBS) such as repetitive Transcranial Magnetic Stimulation (rTMS) are promising techniques to improve the recovery of post-stroke aphasia (Arheix-Parras et al., 2021). The main theory for its use is the interhemispheric competition model (Carson, 2020; Stefaniak et al., 2020). As aphasia often follows a left hemispheric (LH) lesion, many rTMS studies used facilitatory stimulation targeting the left inferior frontal gyrus, i.e., Broca's area, or inhibitory stimulation targeting its right homolog (Arheix-Parras et al., 2021).

Indeed, it has been shown that the undamaged right hemisphere (RH) could play a maladaptive role in post-stroke aphasia recovery (Sihvonen et al., 2023) and that a return to perilesional LH language activation at a chronic stage was associated with better language recovery (Saur et al., 2006). However, the longitudinal study of Saur et al. (2006) included only people with mild to moderate post-stroke aphasia. Hence, some factors such as the size or the site of the lesion, or aphasia severity could question the supposed maladaptive effect of the RH (Price et al., 2010; Watila & Balarabe, 2015). Indeed, if the lesion includes white matter fasciculi such as the corpus callosum, it might mitigate the expected benefits of RH inhibition on the LH networks (Anglade et al., 2014; Carson, 2020). Moreover, people with post-stroke aphasia could be more likely to recruit homolog regions depending on the lesion site (i.e., left extreme capsule, frontal lobe) (Schneider et al., 2022; Stockert et al., 2020). Additionally, some studies also suggested the beneficial role of the RH in aphasia recovery (Heath et al., 2022; Hope et al., 2017; Varkanitsa et al., 2020). Finally, in specific cases, rTMS could be used to potentialize the compensatory role of the RH using facilitatory stimulation (Mylius et al., 2012).

Hence, two NIBS studies in post-stroke aphasia used facilitatory stimulation targeting the right Inferior Frontal Gyrus (rIFG) both associated with Melodic Intonation Therapy (MIT) (Al-Janabi et al., 2014; Vines et al., 2011). On the one hand, Vines et al. (2011) found language improvements in people with moderate to severe non-fluent aphasia, using facilitatory tDCS targeting the rIFG versus sham stimulation. On the other hand, Al-Jabani et al. (2014) found mixed results using facilitatory rTMS targeting the rIFG; one participant suffering from moderate aphasia experienced language improvements, while the other participant with moderate-to-severe aphasia did not show any behavioral improvement associated with the stimulation. Another study concluded that both inhibition (low-frequency rTMS) and facilitation (high-frequency rTMS) over the rIFG were efficient to improve language performance in people with left post-stroke aphasia, compared to sham stimulation (Hu et al.,

2018). More precisely, the authors reported that the effect size was larger for inhibitory versus facilitatory stimulation. However, Hu et al., (2018) did not report lesion data or aphasia severity, and people suffering from severe aphasia might have better improvement using facilitatory stimulation through the undamaged hemisphere.

Single-case Experimental Design (SCED) helps to individualize treatment for a very specific population (Kratochwill et al., 2013). This design is based on a few numbers of participants, repeated measures, the randomized beginning of the intervention, and intrasubject analysis (see guidelines in Krasny-Pacini & Evans, 2018). Hence, we developed a study using a cross-over, multiple baseline design, across participants. We hypothesize that people with severe chronic aphasia following a LH stroke will benefit more from facilitatory rather than inhibitory rTMS targeting the rIFG, and we will analyze language changes in both production and comprehension tasks.

## **2. Materials and methods**

### **2.1. Participants**

Six participants suffering from severe aphasia following a LH stroke (Figure 1, see Supplementary Tables 1 to 6 for more details about lesion localization) were recruited at Bordeaux University hospital from January 2021 to September 2022.

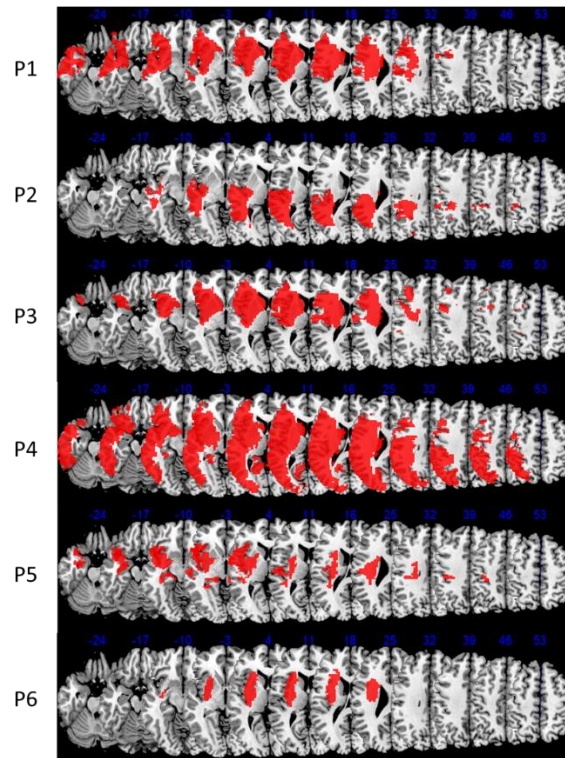


Figure 1: left hemisphere lesions of the participants in red

The study was approved by French Ethics Committee and all participants gave written informed consent, according to the Declaration of Helsinki. All participants were right-handed according to the Edinburgh questionnaire (Oldfield, 1971) and native French speakers. They all presented a single event of stroke. Table 1 regroups participants' main demographic characteristics.

Table 1: demographic and stroke data of the participants

	Gender	Age	Time post-stroke (months)	Type of stroke
P1	M	65	114	Ischemic
P2	M	76	41	Ischemic
P3	M	61	10	Ischemic
P4	M	44	16	Ischemic
P5	F	67	11	Ischemic
P6	M	74	10	Hemorrhagic

All participants suffered from severe aphasia according to the Aphasia Severity Rating Scale (Boston Diagnostic Aphasia Examination, Kaplan & Goodglass, 1981) (see Table 2), but presented sufficient comprehension to understand the main goal of the study and the linguistic tasks.

Non-inclusion criteria were non-stabilized epilepsy, severe depression, psychiatric antecedent, illiteracy, known neurodegenerative disorder, and severe uncorrected visual or hearing impairment.

The participants performed a cognitive and language assessment with a speech-language pathologist that combined different tests: e-Gebas (electronic Geneva Bedside Aphasia Scale) (Chicherio et al., 2020), subtests from the BECLA (Batterie d'Évaluation Cognitive du Langage) (Macoir et al., 2016), go/no go task from the TEA (Tests d'Évaluation de l'Attention) (Zimmermann & Fimm, 2002), TMT (Trail Making Test) (Bowie & Harvey, 2006), SPART 10/36 Test (Rao, 1990), and visuospatial working memory subtest from the MEM-IV (Daniel, 2013). We also investigated depression and quality of life using tools adapted for people with post-stroke aphasia: the Aphasic Depression Rating Scale (ADRS) (Benaim et al., 2004) and the Sickness Impact Profile (SIP-65) (Bénaïm et al., 2003). All scores are summarized in Table 2.

P1 suffered from severe non-fluent aphasia characterized by extreme difficulty to produce informative oral language. He could not produce any sentences but may produce words occasionally. However, he could use nonverbal communication such as gestures and mimics to communicate. He also had difficulties in word and sentence repetition. Auditory comprehension was preserved for words but impaired for long sentences. Mental flexibility was hard to assess because of language difficulties (errors in alphabetical order in the TMT). Other cognitive skills assessed (i.e., non-verbal inhibition and non-verbal memory) were preserved.

P2 suffered from severe fluent aphasia characterized by jargon, with many neologisms, perseverations, phonological, and semantic errors. Only some automatic sentences could be produced correctly. Auditory comprehension was preserved for words but impaired for long sentences. Other cognitive skills (i.e., non-verbal inhibition, mental flexibility, and visuospatial memory) were difficult to assess because of additional visuospatial and attentional impairments.

P3 suffered from severe non-fluent aphasia characterized by difficulty to produce oral language, anomia, and latencies. He could not produce any complete sentences, but informativeness was relatively preserved thanks to isolated words and few automatic sentences. Auditory comprehension was preserved for words, but mildly impaired for sentences likely due to attentional deficits. Mental flexibility was impaired, but other cognitive skills assessed (i.e., non-verbal inhibition and non-verbal memory) were preserved.

P4 suffered from severe non-fluent aphasia characterized by a stereotypy inducing impaired informativeness. However, he could use a communication binder with pictograms to improve communication possibilities. Auditory comprehension was preserved for words and sentences. Processing speed and mental flexibility were impaired. Other cognitive skills assessed (i.e., non-verbal inhibition and non-verbal memory) were preserved.

P5 suffered from severe non-fluent aphasia characterized by stereotypy inducing impaired informativeness. She could use gestures, mimics, and prosody to communicate in basic conversations. She presented a semantic deficit, inducing auditory comprehension impairments. However, the context (i.e., gestures, written language) permitted sufficient mutual understanding. Executive functions assessed (i.e., mental flexibility and non-verbal inhibition) were impaired, but non-verbal memory skills were preserved.

P6 suffered from severe non-fluent aphasia characterized by a reduction of speech inducing impaired informativeness. In spontaneous speech, he produced perseverations, neologisms, phonological, and semantic errors. He presented a semantic deficit. Hence, auditory comprehension was impaired, but the context (i.e., gestures, written language) permitted sufficient mutual understanding. We could not assess mental flexibility due to severe apraxia. Other cognitive skills assessed (i.e., non-verbal inhibition and non-verbal memory) were impaired.

Table 2: cognitive and language baseline pre-stimulation

	P1	P2	P3	P4	P5	P6
<b>Language</b>						
<u>ASRS</u>						
	1	1	1	0	0	1
<u>e-Gebas score</u>						
Spontaneous oral expression (cut-off=10)	1/10	0/10	4/10	0/10	0/10	4/10
Automated sequences (cut-off=5)	3/5	2.5/5	5/5	2/5	1/5	1.5/5
Picture naming	1/10 z-score <-3.0	0/10 z-score <-3.0	6.5/10 z-score <-3.0	1/10 z-score <-3.0	0/10 z-score <-3.0	5/10 z-score <-3.0
Repetition (phonemes, words, sentences)	5/10; z-score <-3.0	2/10; z-score <-3.0	6/10; z-score <-3.0	3/10; z-score <-3.0	2/10; z-score <-3.0	6/10; z-score <-3.0
Auditory comprehension: close-ended questions	9/10; z-score <-3.0	9/10; z-score <-3.0	9/10; z-score <-3.0	10/10	7/10; z-score <-3.0	6/10; z-score <-3.0
Auditory comprehension: spoken word picture matching and commands	5/10; z-score <-3.0	5.5/10; z-score <-3.0	9/10; z-score <-3.0	7.5/10; z-score <-3.0	9/10; z-score <-3.0	4.5/10; z-score <-3.0
Written production (word and sentence dictation, word spelling, copy, first name and family name)	1/10; z-score <-3.0	AB	5/10; z-score <-3.0	4/10; z-score <-3.0	2/10; z-score <-3.0	4/10; z-score <-3.0
Reading (words, sentences, and spoken word-written word matching) (cut-off=10)	2/10	0/10	8/10	0/10	1/10	8/10
Temporal and spatial orientation	4/5; z-score <-3.0	NP	4.5/5; z-score <-3.0	4/5; z-score <-3.0	4.5/5; z-score <-3.0	3/5; z-score <-3.0
Calculation	4/10; z-score <-3.0	4/10; z-score <-3.0	7/10; z-score =-2.13	4/10; z-score <-3.0	3/10; z-score <-3.0	6/10; z-score <-3.0
<u>BECLA subtests</u>						
Auditory discrimination	29/36 pc5-10	34/36; pc25-50	31/36; pc10	30/36; pc5-15	25/36; <pc1	22/36; <pc 1
Semantic association of pictures	15/20; <pc1	16/20; <pc1	NP	19/20; pc25	16/20; <pc1	7/20; <pc 1
Spoken word-picture matching	19/20; pc2	19/20; pc2	NP	20/20; pc>10	12/20; <pc1	15/20; <pc 1
Word repetition	1/15; <pc1	3/15; <pc1	11/15; pc<1	2/15; <pc1	1/15; <pc1	10/15; <pc1
Non-word repetition	1/10; <pc1	0/10; <pc1	4/10; pc<1	0/10; <pc1	0/10; <pc1	8/10; pc10-15



Executive functions						
Go/no go (TEA)						
<i>Omissions</i>	0; >pc14	AB	0; >pc14	0; >pc14	6; pc0	1; pc4
<i>Errors</i>	1; pc58		1; pc58	0; >pc62	12; pc0	8; pc12
Trail Making Test						
<i>Part A</i>	122s; -1.05SD	>3min	73s; -1.33SD	76s; -2.42SD	120s; -1.01SD	>3min
<i>Part B</i>	>3min	AB	>3min	>4min	AB	AB
Memory						
SPART 10/36 Test						
<i>Immediate recalls</i>	11/30; -0.87SD	6/30 ; -1.86SD	15/30; -0.08SD	15/30; -0.67SD	12/30; -0.68SD	5/30; -2.06SD
<i>Delayed Recall</i>	5/10; 0SD	2/10 ; -1.85SD	7/10; 0.74SD	6/10; -0.25SD	5/10; -0.3SD	4/10; -0.81SD
Visuo spatial working memory (MEM-IV)						
<i>Raw score</i>	4	AB	10	7	7	5
<i>Standard score</i>	5	AB	9	5	7	2
Psychological aspects						
Aphasic Depression Rating Scale (ADRS) (cut-off=9)	7/32	4/32	4/32	10/32	7/32	0/32
Sickness Impact Profile (SIP-65)	33/61; 54%	31/60; 52%	29/61; 48%	32/60; 53%	24/51; 47%	30/56; 54%

AB: abandoned; NP: not performed; SD: standard deviation.

Scores are considered pathological under pc5 or -2.0 for the z-score

## 2.2. Experimental design

This study was a cross-over randomized multiple baselines design across participants that followed SCED protocols and was based on Krasny-Pacini et al. guidelines (2018) (Figure 2). The protocol consisted of two periods of six weeks, where participants received facilitatory rTMS or inhibitory rTMS targeting the rIFG. They were pseudo-randomly assigned to one of two cross-over groups (facilitatory then inhibitory, or inhibitory then facilitatory). P1, P2, and P3 were in the group with facilitation then inhibition. P4, P5, and P6 were in the group with inhibition then facilitation. We added a wash-out period of four weeks minimum between the two periods.

During each period (facilitatory or inhibitory), participants performed a picture naming task and a lexical decision task three times a week for six weeks (18 measures for each period, 36 measures in total). These linguistic tasks were considered as the repeated measures.

They received rTMS facilitating or inhibiting the rIFG three times a week for two weeks (six rTMS sessions in each period). The stimulation was off-line and no rehabilitation was

performed after the stimulation. All participants followed their usual SLT (speech-language therapy) in ambulatory care in a clinical routine. The duration of the baseline pre-rTMS varied across participants (six, nine, or 12 time-points chosen at random). Thus, intervention started at different time points for every participant.

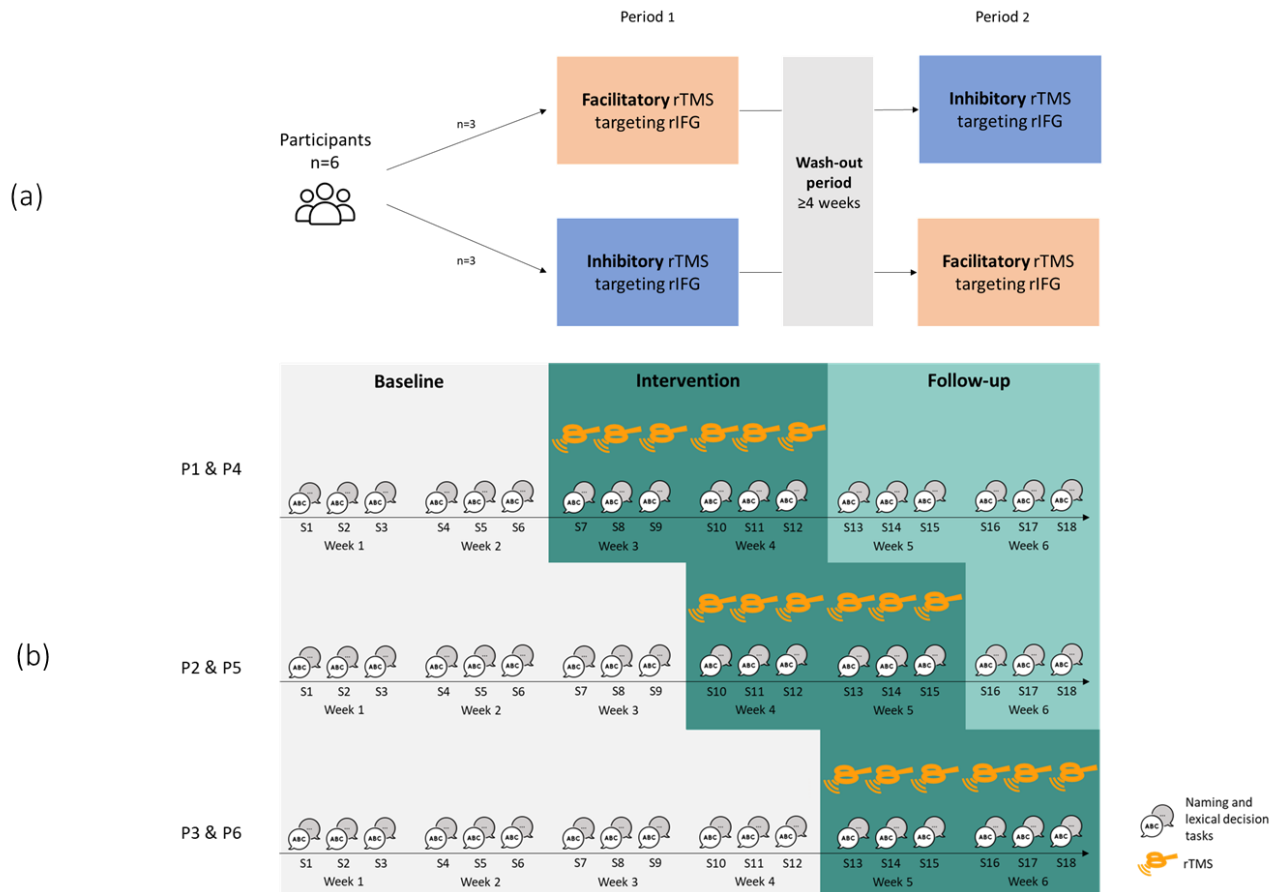


Figure 2: (a) cross-over design (b) multiple baselines design across participants with rTMS intervention

## 2.3. Material and procedure

### 2.3.1. Repeated measure

#### *Picture naming task*

Participants performed a picture naming task (D120) containing 120 pictures (black line drawings on white squares) of monosyllabic (N=40), bisyllabic (N=60) and trisyllabic (N=20) words of various lexical frequencies according to a French lexical database (New et al., 2004). For more detail about the stimuli, see Laganaro et al., 2013.

Participants were tested individually and sat approximately 60cm in front of a PC screen. Trials' presentation was controlled by E-Prime 2.0 software (E-Studio). Before the experiment, all participants underwent a familiarization with all pictures and their corresponding written names. At this time of the experiment only, if the participant produced an error, a feed-back was provided and the expected target was given orally. The experimental trial had the following structure: first, a "+" sign was presented for 500ms on screen. Then, the picture appeared for 3000ms. Participants had to produce the word corresponding to the picture and the production was recorded with a Jabra® Speakerphone 510. Each stimulus was launched manually by the experimenter. The 120 pictures were presented in two different orders alternatively.

Response accuracy was analyzed with the speech analysis software CheckVocal (Protopapas, 2007). Errors were classified in five different categories: semantic (e.g., the picture of a "cube" named "square"), phonological (e.g., "broom" named "proom"), perseveration (i.e., repetition of a previous response in the absence of the corresponding stimulus), omission (i.e., no response given within three seconds), and other.

#### *Lexical decision task*

Participants performed a lexical decision task (Majerus et al., 2005; Van der Kaa & Majerus, 2007) containing 100 audio recordings with frequent (n=25), uncommon words (n=25), and non-words (n=50). Participants were tested individually and sat approximately 60cm in front of a PC screen. Trials' presentation was controlled by E-Prime 2.0 software (E-Studio).

Participants had to determine if the word heard through a Jabra® Speakerphone 510 belonged to the French lexicon or if it was a non-word. They answered manually by pressing a keyboard key. The experimental trial had the following structure: first, a "+" sign was presented for 500ms on screen. Then, the participant could hear the recording. Each stimulus was launched manually by the experimenter. We analyzed the percentage of response accuracy for both words and non-words answers, and reaction time in ms, i.e., the time separating the audio onset and the manual response onset.

#### **2.3.2. rTMS**

We applied transcranial magnetic stimulation using a 75mm 8-shaped coil (Cool-B65 Butterfly Coil, MagVenture ®) connected to MagPro X100unit. The intervention consisted in three stimulations a week during two weeks targeting the rIFG, at each period: (1) using continuous

theta burst stimulation (continuous TBS: 600 pulses, burst frequency at 5 Hz, burst of three pulses at 50Hz) or (2) using high frequency stimulation (HF: 10 Hz, 50 pulses per train, 20 trains, at least five seconds interval inter-train). The coil was oriented to induce posterior-to-anterior current flow in M1. The stimulation intensity corresponded to 90% of the Resting Motor Threshold (RMT). RMT was recorded from the abductor pollicis brevis muscle of the left upper limb, using surface electrodes (Neuroline, Ambu®). Signals were sampled at 10kHz, amplified (1000gain), filtered (20–1000Hz) using LabChart7.3.7 software (ADInstrument). RMT evaluation were assessed by using standard protocols (Rossini et al., 1994). RTMS target, i.e., rIFG, was memorized using Neuronavigation with TMS Navigator Software (Localite®) based on the anatomical MRI (Magnetic Resonance Imaging) of each participant.

### **2.3.3. Statistical analysis**

Statistical tests were chosen according to the SCED guidelines (Krasny-Pacini & Evans, 2018). Graphs and statistical analyses were performed using two websites specialized for analyses of SCED (Manolov & Solanas, 2018; Tarlow, 2016). For all behavioral results (i.e., picture naming accuracy, number of errors per error type, lexical decision accuracy, and latencies), we estimated the monotonic trend of the baseline, then we could correct the result if necessary, using Kendall's Tau rank correlation coefficient using the website from Tarlow (2016). Hence, a baseline-corrected Tau-U was calculated when the baseline showed a significant positive or negative trend. The baseline-corrected or -uncorrected Tau-U calculation (Parker et al., 2011) generated effect sizes interpreted as a small change below 0.2, a moderate change between 0.2 and 0.6, a large change between 0.6 and 0.8, and a large to very large change above 0.8 (Tate & Perdices, 2018; Vannest & Ninci, 2015). For visual analysis, when the baseline did not show any trend, we represented the mean during the baseline and the 2-SD (Standard deviations) envelope after the beginning of the intervention. When the baseline showed a significant trend, we illustrated the trend during the baseline and a median-based envelope after the start of the intervention (Manolov et al., 2016). We also checked the baseline stability of the points during each period (i.e., baseline and intervention) using the 80%-20% formula (based on Manolov et al., 2016).

## **3. Results**

Half of the participants did not complete the entire protocol or missed several sessions during the two periods of 18 sessions each. We also encountered some technical issues with the

behavioral data collection in several sessions (for more detail, see Table 2). However, all participants performed at least five measures per phase (i.e., baseline and intervention) and received every rTMS planned. No adverse effects occurred throughout the protocol. However, P4 suffered from a seizure three days after the last rTMS session (facilitatory protocol targeting the rIFG), just before week 5. This seizure is not considered an explicit adverse effect for several reasons: 1) the time gap between the stimulation and the seizure is not in line with previously reported adverse effects (Rossi et al., 2021), 2) the medical history reported high-risk factors of seizure the day of this issue (severe lack of sleep and alcohol consumption) that were considered as the cause of his seizure by the emergency unit.

Table 2: additional explanation for missing data

Participant	Technical issues	Missed or uncompleted sessions
P1	<u>Period 1:</u> LDT session 1 (baseline, week 1). <u>Period 2:</u> none.	<u>Period 1:</u> none. <u>Period 2:</u> missed session 1 (baseline, week 1) because he was unwell, and 18 (follow-up, week 6) because of transportation issues.
P2	<u>Period 1:</u> LDT session 9 (baseline, week 3). <u>Period 2:</u> none.	<u>Period 1:</u> none. <u>Period 2:</u> none.
P3	<u>Period 1:</u> LDT sessions 6 (baseline, week 1) and 13 (intervention, week 5). PNT session 11 (baseline, week 4). <u>Period 2:</u> LDT sessions 1, 2 (baseline, week 1) and 18 (intervention, week 6).	<u>Period 1:</u> missed session 1 (baseline, week 1) because he was unwell, did not complete session 13 (i.e., received rTMS, but did not perform any language tasks) due to transportation issues (week 5, intervention). <u>Period 2:</u> missed session 6 (baseline, week 2) because of transportation issues.
P4	<u>Period 1:</u> none. <u>Period 2:</u> none.	<u>Period 1:</u> did not complete session 9 (intervention, week 3) because he was unwell. <u>Period 2:</u> missed from session 13 (follow-up, week 5) to session 17 (follow-up, week 6) because of the seizure.
P5	<u>Period 1:</u> none. <u>Period 2:</u> LDT session 2 (baseline, week 1).	<u>Period 1:</u> none. <u>Period 2:</u> none.

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	<u>Period 1:</u> LDT sessions 7	<u>Period 1:</u> none.
P6	and 9 (baseline, week 3).	<u>Period 2:</u> none.
	<u>Period 2:</u> none.	

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LDT: Lexical Decision Task; PNT: Picture Naming Task

### 3.1. Picture naming D120

For the picture naming accuracy (D120), results were heterogeneous across participants, and according to the type of stimulation (Figure 3).

For P1, visual analyses did not show a baseline trend during the two inhibitory and facilitatory periods in picture naming accuracy (Figure 3). During the facilitatory stimulation, P1 experienced a trend toward improvement, with one point above the two standard deviations (2SD) band (Figure 3). He showed a trend towards a decrease in accuracy during the inhibitory stimulation with two points under the 2SD band (Figure 3). However, the percentage of accuracy was very low ( $\leq 4$  items named out of 120), and statistical analyses did not find any significant change during any stimulation periods (Tables 3 and 4).

For P3, the four-week baseline was statistically stable ( $p > 0.05$ ) during the two periods (Figure 3). Visual analyses showed a trend toward improvement during the facilitatory intervention, with one point above the 2SD band (Figure 3). During the inhibitory intervention, P3 experienced a clearer improvement with three points above the 2SD band (Figure 3). Statistical analysis confirmed these significant improvements in naming accuracy for both stimulations ( $p < 0.05$ ), with a greater effect size for inhibitory compared to facilitatory rTMS (Tables 3 and 4).

For P6, the four-week baseline did not show any statistically significant trend in the two periods ( $p > 0.05$ ). However, naming accuracy scores were quite variable, mostly due to the presence of perseverations (i.e., trend stability during the facilitatory period: 66.7%, during the inhibitory period: 41.7%). He did not show any change in naming accuracy in the facilitation period, but a trend towards improvement in the inhibition period, with two points above the 2SD band. Those results were confirmed by statistical analyses with non-significant results in the facilitation period ( $p > 0.05$ ) (Table 3), but significant improvement in the inhibition period ( $p < 0.05$ ) (Table 4).

P2, P4, and P5 did not experience any change in picture naming accuracy during the two periods of stimulation in visual analyses (Figure 3). As they produced hardly any words

throughout the picture naming task, statistical analyses were not performed for them. Moreover, P2 produced mostly neologisms, and few perseverations on unrelated errors. P4 and P5 did not produce any word at any session, but almost always had the same stereotypy regardless of the stimuli. Hence, we did not analyze the type of errors for these participants.

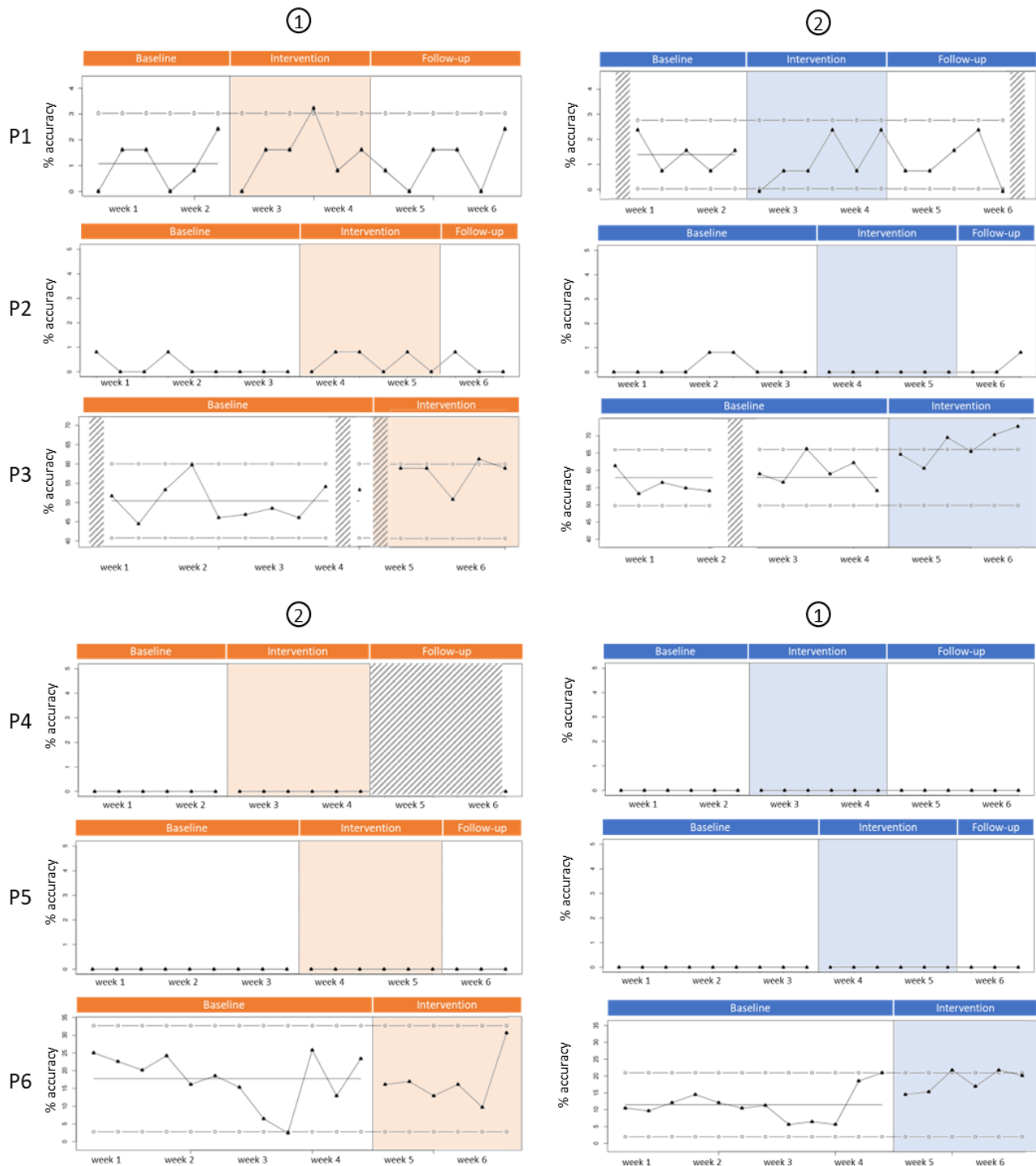


Figure 3: percentage of accuracy during the naming task with mean solid line during the baseline and two-standard deviation dashed lines. Inhibitory period is represented in blue and facilitatory period in orange. Incomplete data are represented in grey. ① and ② correspond to the order of the stimulation.

Regarding omissions, P1 showed no significant trend during the baseline in both periods and no effect of both interventions. P3 did not show a baseline trend during both periods of stimulation. He presented no effect of the intervention in the facilitatory period, while he experienced a decrease in the number of omissions in the inhibitory period. During the facilitatory period, P6 did not show a significant trend during the baseline and no effect of the intervention. However, he experienced a decrease during the baseline of the inhibitory period, and no effect of the intervention. This baseline decrease could be linked with a learning effect, as inhibitory period was the first period of inclusion for P6 (Tables 3 and 4, Figure 4).

More precisely, the number of phonological errors did not change for P1 and P6 in the two periods. However, P3 experienced a decrease in phonological errors in both periods ( $p < 0.05$ ), but the decrease was greater for the facilitation period according to statistical analysis.

We did not analyze semantic errors for P1 because he produced very few of that type of errors. For P3, the number of semantic errors did not change in both periods. For P6, the number of semantic errors was stable during the inhibition period. However, we observed a significant decrease in semantic errors during the four-week baseline ( $p < 0.05$ ) that was temporary, as the number of semantic errors significantly increased after the beginning of the facilitatory stimulation ( $p < 0.05$ ).

Only P6 produced enough perseveration to analyze. During the first inhibitory period, we found an increase in the number of perseverations during the baseline ( $p < 0.05$ ). After the beginning of the intervention, the number of perseverations statistically decreased ( $p < 0.05$ ). During the facilitatory period, the baseline showed no significant trend and we found no change induced by the intervention. However, in both periods, the number of perseverations was unstable during the baseline (trend stability during the inhibitory period: 50%, during the facilitatory period: 58%), indicating that exterior factors could induce change in the number of perseverations.





Figure 4: number of errors per category during the picture naming task D120 for P1, P3 and P6. Inhibitory period is represented in blue and facilitatory period in orange. Incomplete data are represented in grey. ① and ② correspond to the order of the stimulation.

Table 3: statistical analyses for the percentage of overall accuracy and the number of errors per type in the facilitatory period during the picture naming task

		P1	P3	P6
Naming accuracy	BL trend	No trend	No trend	No trend
	Size-effect	Tau=0.000 p=1.040, SE <sub>Tau</sub> =0.333	<b>Tau=0.481</b> <b>p=0.042, SE<sub>Tau</sub>=0.320</b>	Tau=-0.106 p=0.639, SE <sub>Tau</sub> =0.331
Omissions	BL trend	No trend	No trend	No trend
	Size-effect	Tau=-0.328 p=0.130, SE <sub>Tau</sub> =0.315	Tau=-0.279 p=0.244, SE <sub>Tau</sub> =0.351	Tau=-0.048 p=0.851, SE <sub>Tau</sub> =0.333
Phonological errors	BL trend	No trend	No trend	No trend
	Size-effect	Tau=0.201 p=0.367, SE <sub>Tau</sub> =0.327	<b>Tau=-0.516</b> <b>p=0.034, SE<sub>Tau</sub>=0.313</b>	Tau=-0.070 p=0.777, SE <sub>Tau</sub> =0.333
Semantic errors	BL trend	NC	No trend	<b>Negative trend</b>
	Size-effect	NC	Tau=0.075 p=0.801 SE <sub>Tau</sub> =0.364	<b>BC Tau=0.550</b> <b>p=0.009,</b> <b>SE<sub>Tau</sub>=0.278</b>
Perseverations	BL trend	NC	NC	No trend
	Size-effect	NC	NC	Tau=0.183 p=0.399, SE <sub>Tau</sub> =0.328

BL: baseline / NC: Non-Calculated / SE: standard error / Score in bold are statistically significant

Table 4: statistical analysis for the percentage of accuracy and the number of errors per type in the inhibitory period during the picture naming task

		P1	P3	P6
Naming accuracy	BL trend	No trend	No trend	No trend
	Size-effect	Tau=-0.172 p=0.510, SE <sub>Tau</sub> =0.348	<b>Tau=0.598</b> <b>p=0.006, SE<sub>Tau</sub>=0.275</b>	<b>Tau=0.552</b> <b>p=0.009, SE<sub>Tau</sub>=0.278</b>
Omissions	BL trend	No trend	No trend	Negative trend
	Size-effect	Tau=0.039 p=0.908, SE <sub>Tau</sub> =0.353	<b>Tau=-0.536</b> <b>p=0.014, SE<sub>Tau</sub>=0.290</b>	BC Tau=-0.392 p=0.142, SE <sub>Tau</sub> =0.361
Phonological errors	BL trend	No trend	No trend	No trend
	Size-effect	Tau=-0.200, p=0.421 SE <sub>Tau</sub> =0.346	<b>Tau=-0.463</b> <b>p=0.041, SE<sub>Tau</sub>=0.304</b>	Tau=-0.080 p=0.741 SE <sub>Tau</sub> =0.332
Semantic errors	BL trend	NC	No trend	No trend
	Size-effect	NC	Tau=-0.369, p=0.103 SE <sub>Tau</sub> =0.319	Tau=0.413, p=0.058 SE <sub>Tau</sub> =0.304
Perseverations	BL trend	NC	NC	Positive trend
	Size-effect	NC	NC	<b>BC</b> <b>Tau=-0.618</b> <b>p=0.003, SE<sub>Tau</sub>=0.262</b>

BL: baseline / NC: Non-Calculated / SE: standard error / Score in bold are statistically significant

### 3.2. Lexical decision

For the lexical decision task in terms of accuracy and latencies, clinical results were also very heterogeneous across participants and types of stimulation (Tables 5 and 6, Figure 5).

Regarding accuracy, P1 did not show a trend during the two-week baseline in both stimulation periods. For the facilitatory period, we observed a trend toward improvement at the beginning of the follow-up, but the improvement did not sustain. For the inhibitory period, we observed a decrease in the scores with four points under the 2SD band. Statistical analyses confirmed these visual analyses with no significant change for the facilitation period and a significant decrease in accuracy during the inhibition period ( $p < 0.05$ ). P1 did not experiment with any changes in latencies during the lexical decision task (Table 5 and Table 6).

P2 did not experiment with any changes in accuracy and latencies during the lexical decision task.

For P3, visual and statistical analyses did not show any change in accuracy induced by inhibitory or facilitatory stimulations. Regarding latencies during the lexical decision task, P3 was quicker after facilitatory rTMS according to statistical analyses on median reaction time ( $p < 0.05$ ) but showed no change after inhibitory rTMS (Tables 5 and 6).

Regarding accuracy, P4 showed no change in visual and statistical analyses induced by inhibitory or facilitatory stimulations. He presented no change in latencies during the facilitatory period. However, he experienced a significant decrease in latencies during the two-week baseline ( $p < 0.05$ ), but this improvement was transient, as reaction time scores increased after the beginning of inhibitory rTMS ( $p < 0.05$ ).

P5 showed a statistically significant improvement during the three-week baseline in both facilitatory and inhibitory periods for the accuracy scores ( $p < 0.05$ ). Taking into account this baseline trend, all nine points were under the median-based envelope for the inhibition period and six points were below it in the facilitatory period. These visual analysis highlighted a possible decrease in the lexical decision accuracy scores in both stimulations. Statistical analysis confirmed those results, with a significant decrease in accuracy taking into account the baseline trend, after both stimulations ( $p < 0.05$ ), with equivalent size effects. P5 did not experiment with any changes in latencies during the lexical decision task.

Regarding accuracy, P6 showed stability of the four-week baseline during the facilitation period and a trend towards improvement with one point above the 2SD after the beginning of the

intervention. During the inhibition period, P6 experienced a slight but significant decrease in accuracy during the four-week baseline ( $p < 0.05$ ), and no effect of the intervention. The scores of P6 might have reached the ceiling with the median-base envelope including points above 100%. Statistical analyses confirmed a moderate size effect of the facilitatory stimulation ( $p < 0.05$ ) and a non-significant effect of the inhibition. P6 showed no change in latencies during the facilitatory period but a decrease in reaction time in the inhibitory period according to statistical analyses ( $p < 0.05$ ).

Table 5: statistical analyses for the percentage of accuracy and the latencies in the facilitatory period during the lexical decision task

		P1	P2	P3	P4	P5	P6
Accuracy	BL trend	No trend	No trend	No trend	No trend	Positive trend	No trend
	Size-effect	Tau=-0.234 p=0.280 SE <sub>Tau</sub> =0.344	Tau=0.193 p=0.386 SE <sub>Tau</sub> =0.337	Tau=0.098 p=0.713 SE <sub>Tau</sub> =0.363	Tau=-0.475 p=0.063 SE <sub>Tau</sub> =0.345	<b>BC</b> <b>Tau=-0.728</b> <b>p=0.001</b> <b>SE<sub>Tau</sub>=0.235</b>	<b>Tau=0.443</b> <b>p=0.035</b> <b>SE<sub>Tau</sub>=0.299</b>
Reaction time: median	BL trend	No trend	No trend	No trend	No trend	No trend	No trend
	Size-effect	Tau=-0.411 p=0.058 SE <sub>Tau</sub> =0.313	Tau=-0.141 p=0.532 SE <sub>Tau</sub> =0.340	<b>Tau=-0.607</b> <b>p=0.008</b> <b>SE<sub>Tau</sub>=0.290</b>	Tau=-0.158 p=0.567 SE <sub>Tau</sub> =0.387	Tau=-0.243 p=0.268 SE <sub>Tau</sub> =0.333	Tau=-0.345 p=0.141 SE <sub>Tau</sub> =0.343

BC: baseline corrected / SE: standard error / Score in bold are statistically significant

Table 6: statistical analysis for the percentage of accuracy and the latencies in the inhibitory period during the lexical decision task

		P1	P2	P3	P4	P5	P6
Lexical decision Accuracy	BL trend	No trend	No trend	No trend	No trend	Positive trend	Negative trend
	Size-effect	<b>Tau=-0.573</b> <b>p=0.012</b> <b>SE<sub>Tau</sub>=0.290</b>	Tau=-0.009 p=1.000 SE <sub>Tau</sub> =0.333	Tau=0.460 p=0.086 SE <sub>Tau</sub> =0.348	Tau=-0.268 p=0.227 SE <sub>Tau</sub> =0.330	<b>BC</b> <b>Tau=-0.728</b> <b>p=0.000</b> <b>SE<sub>Tau</sub>=0.229</b>	<b>BC</b> Tau=0.166 p=0.480 SE <sub>Tau</sub> =0.349
Reaction time: median	BL trend	No trend	No trend	No trend	Negative trend	No trend	No trend
	Size-effect	Tau=-0.357 p=0.113 SE <sub>Tau</sub> =0.330	Tau=-0.404 p=0.052 SE <sub>Tau</sub> =0.305	Tau=0.000 p=1.058 SE <sub>Tau</sub> =0.392	<b>BC</b> <b>Tau=0.699</b> <b>p=0.001</b> <b>SE<sub>Tau</sub>=0.245</b>	Tau=0.117 p=0.596 SE <sub>Tau</sub> =0.331	<b>Tau=-0.516</b> <b>p=0.013</b> <b>SE<sub>Tau</sub>=0.285</b>

BC: baseline corrected / SE: standard error / Score in bold are statistically significant

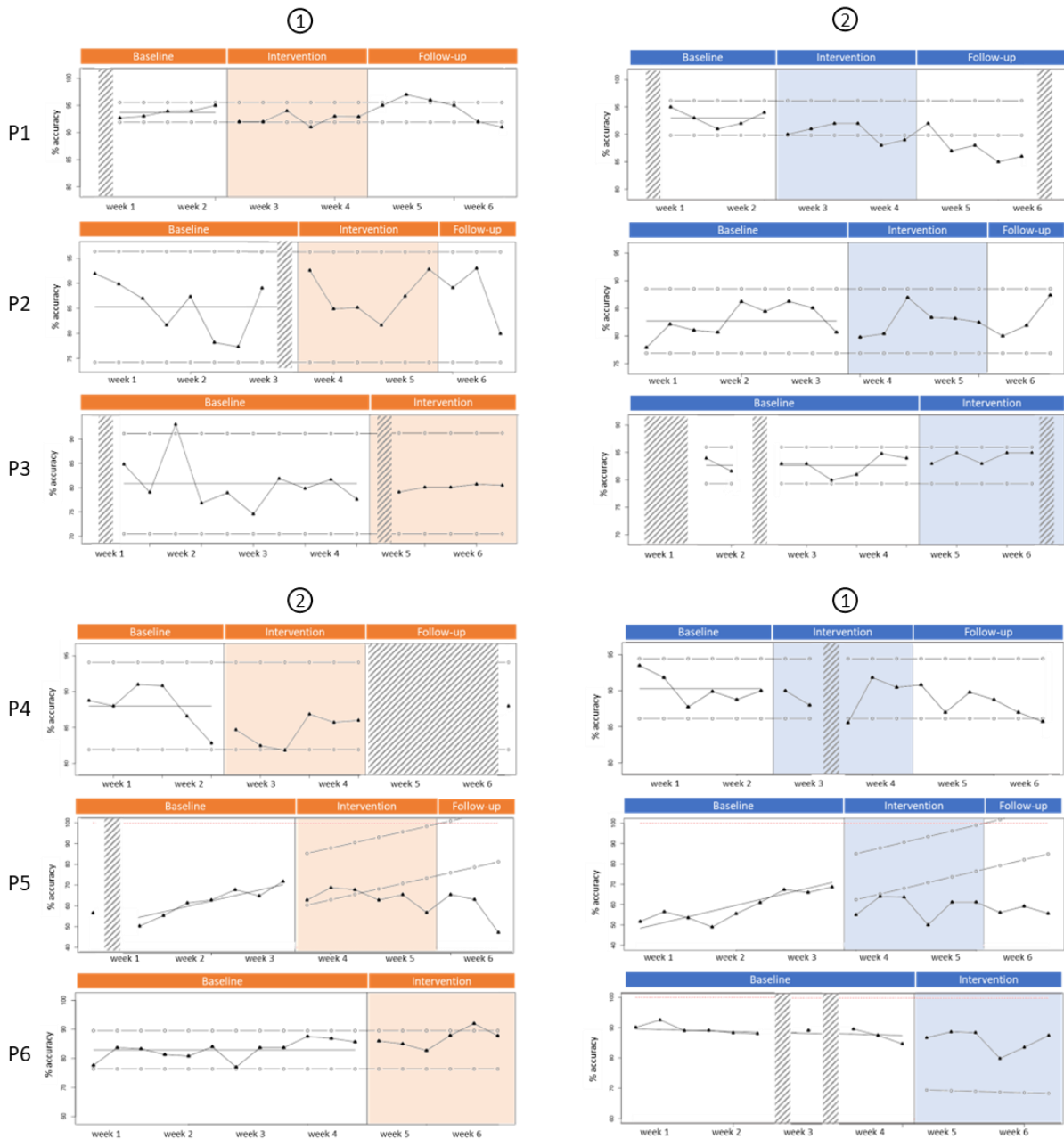


Figure 5: percentage of accuracy during the lexical decision task with mean solid line during the baseline and two-standard deviation dashed line, or trend solid line (for P5 and P6) during the baseline and median based envelop. In blue, inhibitory rTMS, in orange, facilitatory rTMS. Incomplete data are represented in grey. ① and ② correspond to the order of the stimulation.

#### **4. Discussion**

The present study aimed to compare the efficacy of inhibitory versus facilitatory rTMS targeting the rIFG on expressive and receptive language performance in people with severe chronic post-stroke aphasia. Behavioral results were heterogeneous across participants (for a visual summary, see Figure 6). In picture naming, there was:

- no change in accuracy or number of errors during both facilitation and inhibition periods for four participants (P1, P2, P4, and P5)
- an improvement for one participant (P3) during both inhibitory and facilitatory stimulation, with greater effect size during the inhibitory period, a decrease in the number of phonological errors during both stimulations and a decrease in the omissions in the inhibitory period.
- an improvement in the accuracy for one participant (P6) during the inhibitory period, while he experienced an increase in the number of semantic errors using facilitatory rTMS

In the lexical decision task, results revealed:

- no effect of the stimulation on accuracy for three participants (P2, P3, and P4)
- a decrease in the accuracy for one participant (P1) in the inhibitory period and for another participant (P5) in both facilitatory and inhibitory periods.
- an improvement in accuracy for one participant (P6) during the facilitatory period, and a decrease in latency during the inhibitory period
- a decrease in latency during the facilitatory period for one participant (P3), while another participant (P4) experienced an increase in latency during the inhibitory period.

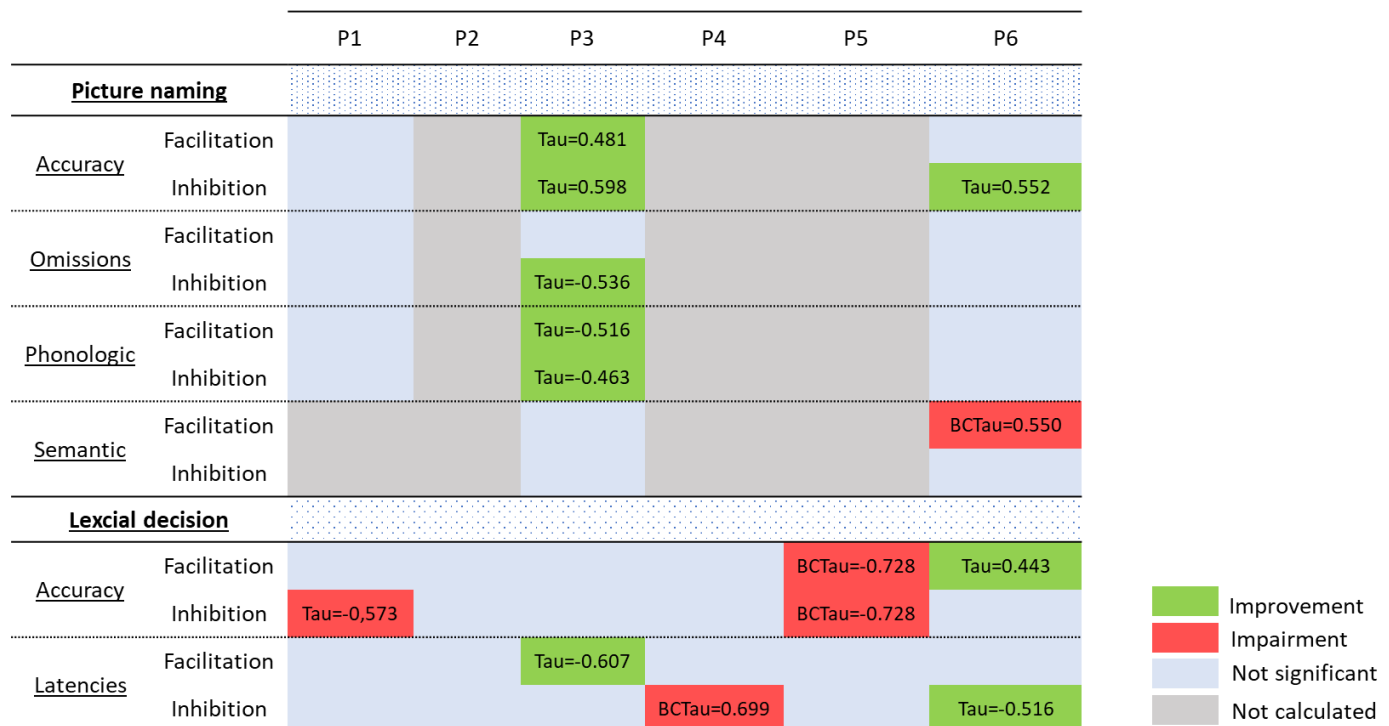


Figure 6: summary of the statistical analysis for the picture naming and the lexical decision tasks per participant and type of stimulation

#### 4.1. Individual variability

We hypothesized that people suffering from severe chronic aphasia would experience a greater language improvement using facilitatory versus inhibitory rTMS targeting the rIFG, by enhancing compensatory networks in the contralesional hemisphere. This postulate was based on the impact of large brain lesions or lesions localized in crucial nodes for language networks (Hope et al., 2017; Price et al., 2010; Watila & Balarabe, 2015). Across the six participants included in the present study, we did not observe opposite effects after inhibition versus facilitation of the rIFG. Whereas opposite results could have been expected based on the theory of interhemispheric imbalance, only P1 exhibited a slightly negative effect of inhibitory rTMS targeting the undamaged RH, showing a decrease in lexical decision accuracy. Focusing on this patient, facilitatory rTMS did not induce improvement. This first result suggests that the concept of interhemispheric imbalance might be too simplistic taking into account the organization of language networks in the brain, particularly for people with severe aphasia (Carson, 2020).

As noted in a previous study with a larger sample (though not reporting the effects at the individual level) (Hu et al., 2018), we observed significant improvements in picture naming accuracy for P3 using both inhibitory and facilitatory stimulations, suggesting the involvement

of RH in language processes for this particular participant. However, the effect size was greater using inhibitory stimulation. This underlines that the role of the RH remains poorly understood, either allowing a positive or negative contribution (Hope et al., 2017). Inhibition of the rIFG also allowed improvements in picture naming accuracy for P6, confirming that the rationale of interhemispheric competition seems adapted in some cases (Stefaniak et al., 2020). Interestingly, P3 and P6 had the less severe profiles and were the only ones to experience significant improvements in picture naming during the inhibitory period. When word production was severely disturbed but still possible to some extent, decreasing the activity of the contralesional hemisphere had a positive impact on both production and comprehension processing (Harvey et al., 2017; Lin et al., 2022). However, when naming was almost impossible due to severe word production impairments (e.g., jargon, stereotypy, mutism), we found no effect of rTMS on picture naming accuracy. Even if brain processes might have been impacted by rTMS, positively or negatively, we may be unable to observe the impact extended to behavioral changes in picture naming, because of the severity of the impairments (i.e., slight change that cannot be observed in a linguistic task). On the one hand, an easier production task, such as a word repetition task, may have been a better marker of improvement. On the other hand, imaging data, such as electroencephalography (EEG), may help to highlight such an impact, putting forward biomarkers of therapy-induced effects (Arheix-Parras et al., 2023). As for the lexical decision task, accuracy or latency was impacted in three out of these four patients who could not produce, either negatively (P1 and P4 in the inhibition period, P5 in both periods), or positively after facilitation (non-significant trend non-maintained over the time for P1, decrease in latencies for P3). This suggests that rTMS had an impact on language comprehension, that was mainly negative for participants that could not produce.

#### **4.2. Inhibition vs facilitation**

Both inhibitory and facilitatory rTMS induced similar changes in language performance for two participants: while P3 benefited from both techniques on picture naming accuracy, P5 experienced a decrease in lexical decision accuracy during both inhibitory and facilitatory periods. These results are counterintuitive: if stimulations were antagonists, they would have induced opposite or at least dissimilar behavioral effects. As mentioned above, another study reported the positive effect of rTMS using inhibition or facilitation targeting the rIFG on language performance (Hu et al., 2018). Interestingly, rTMS parameters supposed to induce



inhibition versus facilitation of targeted areas, are deduced from studies about the motor cortex (Berardelli et al., 1998; Chen et al., 1997; Huang et al., 2005; Quartarone et al., 2006). However, Siebner et al. (2022) warned about the validity of this transposition outside the motor cortex of the hand; indeed, the histology of the motor cortex is unique and based on connections through pyramidal neurons. Moreover, using inhibitory TBS targeting the rIFG in neurotypical individuals, Nicolo et al., (2016) showed that high alpha-band coherence, between the rIFG and the other areas before the stimulation, induced expected inhibition, contrary to low alpha-band coherence that induced an increase in coherence post-rTMS. Hence, rTMS inhibitory or facilitatory effects might also depend on the state of functional connectivity of the targeted area, before the stimulation (Nicolo et al., 2016). Furthermore, even the validity of the RMT, used to calibrate the intensity of the stimulation, could be questioned, as it only reflects the structural organization of motor areas (Siebner et al., 2022). The present study questions the validity of transposing the inhibitory versus facilitatory rationale widely used in the motor domain to language and cognitive domains (Arheix-Parras et al., 2021). This question is particularly relevant considering the entire language network, as inhibitory rTMS targeting a specific area might induce both facilitatory and inhibitory effects on interconnected networks (Duffau et al., 2014; Quartarone et al., 2006). Indeed, in a randomized double-blinded controlled study, Lee et al., (2022) showed that inhibitory rTMS targeting the rIFG induced both higher RH connectivity (i.e., caudate nucleus, insular cortex, dorsolateral prefrontal gyrus) and lower connectivity in the right thalamus and left superior parietal cortex.

### **4.3. The dark side of rTMS**

Unfortunately, rTMS reinforced pathological behaviors for some participants, as semantic errors in picture naming increased for P6 in the facilitatory period, and lexical decision accuracy decreased during the inhibitory period for P1 and in both periods for P5. Indeed, an fMRI (functional MRI) study warned about the possibility to induce negative effects using the same target in NIBS in people with post-stroke aphasia presenting different clinical profiles (Stefaniak et al., 2022). Particularly focusing on the RH, a previous longitudinal study using structural brain imaging data found that the hypertrophy in the precentral gyrus was associated with language decrease, contrary to hypertrophy in the anterior temporal region that was associated with language improvement, suggesting that some RH areas could be beneficial for language recovery (Hope et al., 2017). Our findings suggest that in some patients, modulating

the rIFG could disturb language processing. Precise effects induced by the modulation of specific areas on the entire network remain poorly understood, but the present findings underline the complex role of the RH in language recovery, particularly when patients suffer from severe aphasia. Interestingly, to our knowledge, only one study reported negative effects of inhibitory rTMS targeting the rIFG in a woman suffering from severe post-stroke aphasia at a chronic stage (Georgiou et al., 2019). In the present study, half of the participants (3 out of 6) had negative results for at least one of the stimulations. This high proportion of negative effects contrasting with the rest of the rTMS literature could be due to several reasons. Besides a possible publication bias, other studies did not 1) use the SCED methodology with numerous repeated measures, 2) use the same tasks (picture naming in production and lexical decision in reception), and 3) include patients with minimal speech output (i.e., scoring 0/120 in picture naming as in here).

#### **4.4. Combining factors to individualize rTMS**

The individualization of NIBS is needed to improve the effect size on language performance, and also to include people with aphasia presenting unusual profiles (e.g., crossed aphasia) (Arheix-Parras et al., 2021). Indeed, our team recently highlighted the possibility to use inhibitory rTMS targeting the right motor cortex of the lips to induce clinical improvement in people with post-stroke aphasia suffering from phonological impairments (Arheix-Parras et al., in prep). However, the present study highlighted some limits of the individualization of the stimulation, when strictly based on aphasia severity.

On the one hand, the individualization of the stimulation in people with severe chronic aphasia should take into account more precise clinical parameters, such as language fluency, the level of breakdown (semantic, phonological, syntactic, etc.), the impairment in production as well as in comprehension, executive functioning and the residual abilities in specific tasks related to aphasia recovery, such as word repetition (Glize et al., 2017; Tábuas-Pereira et al., 2020). On the other hand, further rTMS studies focusing on the individualization of rTMS for severe aphasia could use data from electrophysiology such as motor evoked potentials (Glize et al., 2018), data from EEG or more fine-grained data about the size and site of the lesion to guide the stimulation rationale. Indeed, the “disconnectome” profile induced by the stroke could help to decide the best area to target for the stimulation, highlighting the integrity or impairment of possible compensatory network for recovery (Talozzi et al., 2023). Moreover, investigating the

“disconnectome” could also help to understand why rTMS is ineffective for some people with severe post-stroke aphasia. Indeed, one participant of the present report did not experience any change during both inhibition and facilitation periods, in both picture naming and lexical decision tasks (P2).

#### **4.5. Limitations**

Our study has several limitations. First, we included participants presenting heterogeneous clinical profiles and stroke characteristics, although they all suffered from “severe aphasia”. Second, we did not add speech and language therapy, such as MIT, after rTMS. Combining rTMS with SLT might have increased effect size. Third, the picture naming task was too difficult for several participants, as they produced zero to four words out of 120 at every session. Hence, such a task may not be a good marker of improvement, and we could have used other measures such as word repetition.

#### **5. Conclusion**

The present study highlighted that using the same parameters and target with rTMS in people with severe chronic post-stroke aphasia can induce various behavioral changes. For some patients rTMS may be ineffective or even counterproductive. Our results put forward the need to individualize rTMS, and showed that the aphasia severity criterion might not have been precise enough to allow such individualization. Further studies could therefore propose more precise language criteria (e.g., fluent versus non-fluent, comprehension impairments, type of processes impaired, type of errors in production). Finally, the use of a combination of different factors could improve the benefit of rTMS using other parameters such as disconnectome data to understand the possible trajectories for recovery (Talozzi et al., 2023), or biomarkers of impairments in EEG to reveal the type of processes impaired (Arheix-Parras et al., 2023).

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### Supplementary material

Supplementary Table 1: (a) lesioned cortical areas and (b) lesioned white matter tracts for P1 respectively based on standard anatomy in the AAL template (Tzourio-Mazoyer et al., 2002) and the Natbrainlab template (Catani et al., 2012)

<b>(a) Area</b>	<b>Damaged volume per area in cc</b>	<b>Percentage of damage per area</b>
Precentral_L	3.321	11.8
Frontal_Sup_Orb_L	0.115	1.5
Frontal_Mid_L	3.522	9.1
Frontal_Mid_Orb_L	0.934	13.1
Frontal_Inf_Oper_L	6.361	76.9
Frontal_Inf_Tri_L	15.286	76
Frontal_Inf_Orb_L	9.403	69.2
Rolandic_Oper_L	6.963	87.7
Olfactory_L	0.234	10.3
Insula_L	14.43	96
Hippocampus_L	1.51	20.2
ParaHippocampal_L	0.741	9.4
Amygdala_L	1.249	72.1
Fusiform_L	0.942	5.1
Postcentral_L	5.486	17.7
Parietal_Inf_L	0.07	0.4
SupraMarginal_L	1.183	11.9
Caudate_L	4.786	62.3
Putamen_L	7.195	90.6
Pallidum_L	0.635	27.8
Thalamus_L	0.002	0
Heschl_L	1.448	80.3
Temporal_Sup_L	5.316	29
Temporal_Pole_Sup_L	5.364	52.4
Temporal_Mid_L	10.044	25.5
Temporal_Pole_Mid_L	3.368	56.3
Temporal_Inf_L	7.299	28.5
<b>(b) White matter networks</b>	<b>Damage volume in cc</b>	<b>Percentage of damage per network</b>
Anterior_Commissure_Left	1.521	31.2
Arcuate_Anterior_Segment_Left	3.196	78
Long_Segment_Left	2.146	71.9
Arcuate_Posterior_Segment_Left	0.024	0.4
Cingulum_Left	0.071	0.2
Corpus_Callosum_Left	2.96	6.4
Cortico_Ponto_Cerebellum_Left	0.227	3.4
Cortico_Spinal_Left	6.462	23.2
Fornix_Left	0.733	7.2
Inferior_Longitudinal_Fasciculus_Left	4.336	31.3
Inferior_Occipito_Frontal_Fasciculus_Left	5.167	46.8
Internal_Capsule_Left	1.736	17.2

Optic_Radiations_Left	0.462	10.5
Uncinate_Left	4.853	66.4
<b>Total</b>	<b>151.3</b>	<b>/</b>

Supplementary Table 2: (a) lesioned cortical areas and (b) lesioned white matter tracts for P2 respectively based on standard anatomy in the AAL template (Tzourio-Mazoyer et al., 2002) and the Natbrainlab template (Catani et al., 2012)

<b>(a) Area</b>	<b>Damaged volume per area in cc</b>	<b>Percentage of damage per area</b>
Precentral_L	0.3	0.074
Rolandic_Oper_L	29.4	2.331
Insula_L	22.9	3.434
Hippocampus_L	0.1	0.004
Calcarine_L	0.1	0.018
Occipital_Sup_L	0.4	0.038
Occipital_Mid_L	5.7	1.493
Postcentral_L	3.9	1.201
Parietal_Sup_L	0.1	0.009
Parietal_Inf_L	10.6	2.054
SupraMarginal_L	42.5	4.214
Angular_L	27.7	2.581
Caudate_L	0.8	0.06
Putamen_L	12.3	0.973
Pallidum_L	0.9	0.02
Heschl_L	88.3	1.593
Temporal_Sup_L	74.8	13.691
Temporal_Pole_Sup_L	0.7	0.074
Temporal_Mid_L	43.1	16.975
Temporal_Inf_L	0.4	0.094
<b>(b) White matter networks</b>	<b>Damage volume in cc</b>	<b>Percentage of damage per network</b>
Anterior_Commissure_Left	0.003	0.1
Arcuate_Anterior_Segment_Left	2.009	49.1
Long_Segment_Left	1.379	46.2
Arcuate_Posterior_Segment_Left	5.872	96.7
Cingulum_Left	0.014	0
Corpus_Callosum_Left	0.446	1
Cortico_Ponto_Cerebellum_Left	0.397	5.9
Cortico_Spinal_Left	2.681	9.6
Fornix_Left	0.038	0.4
Inferior_Longitudinal_Fasciculus_Left	3.561	25.7
Inferior_Occipito_Frontal_Fasciculus_Left	0.696	6.3
Internal_Capsule_Left	0.663	6.6
Optic_Radiations_Left	2.593	58.7
Uncinate_Left	0.046	0.6
<b>Total</b>	<b>75.1</b>	<b>/</b>

Supplementary Table 3: (a) lesioned cortical areas and (b) lesioned white matter tracts for P3 respectively based on standard anatomy in the AAL template (Tzourio-Mazoyer et al., 2002) and the Natbrainlab template (Catani et al., 2012)

<b>(a) Area</b>	<b>Damaged volume per area in cc</b>	<b>Percentage of damage per area</b>
Precentral_L	2.788	9.9
Frontal_Sup_L	0.035	0.1
Frontal_Sup_Orb_L	0.141	1.8
Frontal_Mid_L	4.17	10.8
Frontal_Mid_Orb_L	0.329	4.6
Frontal_Inf_Oper_L	6.47	78.2
Frontal_Inf_Tri_L	13.09	65.1
Frontal_Inf_Orb_L	5.755	42.3
Rolandic_Oper_L	4.781	60.2
Olfactory_L	0.353	15.6
Rectus_L	0.098	1.4
Insula_L	14.376	95.7
Hippocampus_L	0.233	3.1
ParaHippocampal_L	0.052	0.7
Amygdala_L	0.717	41.4
Occipital_Sup_L	0.01	0.1
Postcentral_L	2.658	8.6
Parietal_Sup_L	0.219	1.3
Parietal_Inf_L	0.031	0.2
SupraMarginal_L	0.289	2.9
Caudate_L	5.847	76.1
Putamen_L	7.927	99.8
Pallidum_L	2.229	97.5
Thalamus_L	0.279	3.2
Heschl_L	1.126	62.4
Temporal_Sup_L	1.439	7.9
Temporal_Pole_Sup_L	1.232	12
Temporal_Mid_L	0.002	0
<b>(b) White matter networks</b>	<b>Damage volume in cc</b>	<b>Percentage of damage per network</b>
Anterior_Commissure_Left	2.839	58.2
Arcuate_Anterior_Segment_Left	1.489	36.4
Long_Segment_Left	1.116	37.4
Cingulum_Left	0.004	0
Corpus_Callosum_Left	3.402	7.3
Cortico_Ponto_Cerebellum_Left	0.378	5.7
Cortico_Spinal_Left	7.938	28.5
Fornix_Left	0.72	7.1
Inferior_Longitudinal_Fasciculus_Left	0.203	1.5
Inferior_Occipito_Frontal_Fasciculus_Left	5.051	45.8
Internal_Capsule_Left	2.048	20.3
Optic_Radiations_Left	0.591	13.4
Uncinate_Left	3.058	41.8
<b>Total</b>	<b>105.13</b>	<b>/</b>

Supplementary Table 4: (a) lesioned cortical areas and (b) lesioned white matter tracts for P4 respectively based on standard anatomy in the AAL template (Tzourio-Mazoyer et al., 2002) and the Natbrainlab template (Catani et al., 2012)

(a) Area	Damaged volume per area in cc	Percentage of damage per area
Precentral_L	9.125	32.4
Frontal_Sup_L	0.172	0.6
Frontal_Sup_Orb_L	1.05	13.7
Frontal_Mid_L	5.337	13.8
Frontal_Mid_Orb_L	2.338	32.9
Frontal_Inf_Oper_L	6.949	84
Frontal_Inf_Tri_L	13.826	68.8
Frontal_Inf_Orb_L	10.966	80.7
Rolandic_Oper_L	7.471	94.1
Olfactory_L	0.699	30.9
Rectus_L	0.169	2.5
Insula_L	15	99.8
Cingulum_Post_L	0.011	0.3
Hippocampus_L	0.769	10.3
ParaHippocampal_L	0.632	8
Amygdala_L	0.273	15.8
Calcarine_L	3.166	17.4
Cuneus_L	3.129	25.8
Lingual_L	1.279	7.6
Occipital_Sup_L	6.286	58.3
Occipital_Mid_L	19.58	75.3
Occipital_Inf_L	3.76	49.9
Fusiform_L	1.842	10
Postcentral_L	12.767	41.1
Parietal_Sup_L	4.833	29.3
Parietal_Inf_L	17.414	89.5
SupraMarginal_L	9.346	94.3
Angular_L	8.58	92.1
Precuneus_L	1.388	4.9
Caudate_L	4.638	60.4
Putamen_L	7.621	96
Pallidum_L	2.005	87.7
Thalamus_L	1.839	21.1
Heschl_L	1.792	99.3
Temporal_Sup_L	17.472	95.4
Temporal_Pole_Sup_L	5.076	49.6
Temporal_Mid_L	35.889	91.2
Temporal_Pole_Mid_L	3.147	52.6
Temporal_Inf_L	19.283	75.2
Cerebellum_Crus1_L	0.51	2.5
Cerebellum_4_5_L	0.008	0.1
Cerebellum_6_L	0.19	1.4
Vermis_4_5	0.016	0.3

<b>(b) White matter networks</b>	<b>Damage volume in cc</b>	<b>Percentage of damage per network</b>
Anterior_Commissure_Left	2.19	44.9
Arcuate_Anterior_Segment_Left	4.094	100
Long_Segment_Left	2.924	98
Arcuate_Posterior_Segment_Left	5.931	97.7
Cingulum_Left	3.209	8.2
Corpus_Callosum_Left	6.114	13.2
Cortico_Ponto_Cerebellum_Left	0.862	12.9
Cortico_Spinal_Left	11.619	41.7
Fornix_Left	1.379	13.6
Inferior_Longitudinal_Fasciculus_Left	7.061	50.9
Inferior_Occipito_Frontal_Fasciculus_Left	4.725	42.8
Internal_Capsule_Left	3.157	31.3
Optic_Radiations_Left	2.315	52.4
Uncinate_Left	4.736	64.8
<b>Total</b>	<b>332.25</b>	<b>/</b>

Supplementary Table 5: (a) lesioned cortical areas and (b) lesioned white matter tracts for P5 respectively based on standard anatomy in the AAL template (Tzourio-Mazoyer et al., 2002) and the Natbrainlab template (Catani et al., 2012)

(a) Area	Damaged volume per area in cc	Percentage of damage per area
Precentral_L	0.026	0.1
Frontal_Inf_Oper_L	0.706	8.5
Frontal_Inf_Tri_L	1.233	6.1
Frontal_Inf_Orb_L	1.759	12.9
Rolandic_Oper_L	2.391	30.1
Olfactory_L	0.05	2.2
Insula_L	7.495	49.9
Hippocampus_L	3.388	45.4
ParaHippocampal_L	0.924	11.7
Amygdala_L	1.181	68.1
Lingual_L	0.188	1.1
Fusiform_L	0.229	1.2
Postcentral_L	1.108	3.6
Parietal_Inf_L	0.295	1.5
SupraMarginal_L	0.126	1.3
Caudate_L	0.124	1.6
Putamen_L	4.282	53.9
Pallidum_L	0.867	37.9
Thalamus_L	0.041	0.5
Heschl_L	0.974	54
Temporal_Sup_L	4.51	24.6
Temporal_Pole_Sup_L	5.012	49
Temporal_Mid_L	1.354	3.4
Temporal_Pole_Mid_L	0.146	2.4
Temporal_Inf_L	0.09	0.4
Cerebelum_4_5_L	0.004	0
(b) White matter networks	Damage volume in cc	Percentage of damage per network
Anterior_Commissure_Left	1.385	28.4
Arcuate_Anterior_Segment_Left	1.694	41.4
Long_Segment_Left	1.812	60.7
Arcuate_Posterior_Segment_Left	0.521	8.6
Cingulum_Left	0.614	1.6
Corpus_Callosum_Left	0.398	0.9
Cortico_Ponto_Cerebellum_Left	0.352	5.3
Cortico_Spinal_Left	5.737	20.6
Fornix_Left	0.729	7.2
Inferior_Longitudinal_Fasciculus_Left	1.304	9.4
Inferior_Occipito_Frontal_Fasciculus_Left	2.29	20.8
Internal_Capsule_Left	1.238	12.3
Optic_Radiations_Left	0.64	14.5
Uncinate_Left	3.022	41.3
<b>Total</b>	<b>58.24</b>	<b>/</b>

Supplementary Table 6: (a) lesioned cortical areas and (b) lesioned white matter tracts for P6 respectively based on standard anatomy in the AAL template (Tzourio-Mazoyer et al., 2002) and the Natbrainlab template (Catani et al., 2012)

<b>(a) Area</b>	<b>Damaged volume per area in cc</b>	<b>Percentage of damage per area</b>
Precentral_L	0.033	0.1
Frontal_Inf_Oper_L	0.377	4.6
Frontal_Inf_Tri_L	0.048	0.2
Rolandic_Oper_L	0.218	2.7
Insula_L	5.149	34.3
Hippocampus_L	0.002	0
Amygdala_L	0.002	0.1
Caudate_L	0.389	5.1
Putamen_L	5.979	75.3
Pallidum_L	0.678	29.7
Thalamus_L	0.047	0.5
Heschl_L	0.1	5.5
Temporal_Sup_L	0.005	0
<b>(b) White matter networks</b>	<b>Damage volume in cc</b>	<b>Percentage of damage per network</b>
Anterior_Commissure_Left	0.075	1.5
Arcuate_Anterior_Segment_Left	0.181	4.4
Long_Segment_Left	0.504	16.9
Cingulum_Left	0.001	0
Corpus_Callosum_Left	0.593	1.3
Cortico_Ponto_Cerebellum_Left	0.17	2.5
Cortico_Spinal_Left	3.906	14
Fornix_Left	0.006	0.1
Inferior_Longitudinal_Fasciculus_Left	0.02	0.1
Inferior_Occipito_Frontal_Fasciculus_Left	2.983	27
Internal_Capsule_Left	1.177	11.7
Optic_Radiations_Left	0.482	10.9
Uncinate_Left	0.777	10.6
<b>Total</b>	<b>25.65</b>	<b>/</b>

*Fin de l'article n°3:  
"Transcranial Magnetic Stimulation for people with severe post-stroke aphasia"*



### 3. Stimulations magnétiques transcrâniennes auprès des personnes présentant une aphasie caractérisée par des troubles phonologiques

Dans la continuité de la revue systématique de rTMS réalisée (Arheix-Parras et al., 2021), nous nous sommes également questionnés sur la possibilité d'augmenter la taille d'effet de la rTMS en proposant une individualisation de la cible corticale, en fonction de la spécificité des troubles langagiers.

Notre hypothèse était que les participants présentant une aphasie légère à modérée et caractérisée par des troubles phonologiques (i.e., paraphasies phonologiques, difficultés de répétition de mots) obtiendraient une amélioration langagière à la suite d'une stimulation inhibitrice du cortex moteur des lèvres à droite.

En effet, le cortex moteur des lèvres est impliqué dans la production de mots par la voie dorsale (Duffau et al., 2014; Hesling et al., 2019; Schwartz et al., 2012), cette dernière étant en charge des aspects phonologiques du langage (Duffau et al., 2014; Hickok & Poeppel, 2007). De plus, l'excitabilité du cortex moteur est prédicteur de la récupération de l'aphasie, au même titre que les scores de répétition de mots (Glize et al., 2017, 2018; Tábuas-Pereira et al., 2020).

Compte tenu de ces points, nous pensons que le cortex moteur des lèvres pourrait constituer une cible corticale pertinente en rTMS pour des personnes présentant des troubles phonologiques.

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*Article n°4 : Neuromodulation of the motor cortex of the lips using rTMS to improve post-stroke aphasia symptoms: a Single Case Experimental Design*

## **Neuromodulation of the motor cortex of the lips using rTMS to improve post-stroke aphasia symptoms: a Single Case Experimental Design**

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## **Abstract**

**Purpose.** Repetitive Transcranial Magnetic Stimulation (rTMS) can enhance aphasia recovery. Most studies have used inhibitory stimulation targeting the right inferior frontal gyrus. However, the motor cortex, known to contribute to the prediction of aphasia recovery, is involved in word production and could be an interesting target for rTMS. We aimed to observe behavioral changes in a picture naming task induced by inhibitory rTMS targeting the right motor cortex of the lips in people with post-stroke aphasia.

**Methods.** We included three patients with chronic post-stroke aphasia and a phonological deficit. Using a Single Case Experimental Design, participants performed a picture naming task three times a week for six weeks. They received inhibitory continuous Theta Burst Stimulation targeting the right motor cortex of the lips, three times a week for two weeks, without additional speech therapy.

**Results.** Visual analysis showed a positive effect of rTMS for P2 and P3 on picture naming accuracy, and a tendency towards improvement for P1. Statistical analysis showed an improvement after rTMS for P1 (Tau=0.544,  $p=0.013$ ,  $SE_{\text{Tau}}=0.288$ ) and P2 (Tau=0.708,  $p=0.001$ ,  $SE_{\text{Tau}}=0.235$ ). For P3, even if the intervention allowed some improvement, this was statistically non-significant due to a learning effect during the baseline. Regarding specific language features, phonological errors significantly decreased in all patients.

**Conclusions.** The motor cortex of the lips can be an interesting target for rTMS to improve naming in people with post-stroke aphasia suffering from a phonological deficit. This suggests the possibility to individualize the target for rTMS, according to the patient's linguistic impairment.

## Introduction

Non-invasive brain stimulations (NIBS) such as repetitive Transcranial Magnetic Stimulation (rTMS) might enhance post-stroke aphasia recovery (Arheix-Parras et al., 2021; Biou et al., 2019). The main theory for the use of NIBS on people post-stroke is based on transcallosal imbalance (Carson, 2020; Stefaniak et al., 2020). According to this theory, most rTMS studies used inhibitory stimulation targeting the right inferior frontal gyrus (rIFG), i.e., Broca's homolog (Arheix-Parras et al., 2021).

However, word production does not rely only on Broca's area, but is underpinned by a large neural network predominantly in the left hemisphere (Price, 2010, 2012). More precisely, the retrieval of word forms involves a dorsal stream encompassing the supramarginal gyrus, the premotor cortex and pre- and postcentral gyri (Duffau et al., 2014; Schwartz et al., 2012; Stefaniak et al., 2020; Vigneau et al., 2006). Recently, an fMRI (functional Magnetic Resonance Imaging) study (Hesling et al., 2019) further highlighted the involvement of motor areas in word production. Moreover, the excitability of the motor cortex could also be a predictor for aphasia recovery (Glize et al., 2018). Several studies found a contribution of phonological subscores (El Hachioui et al., 2013; Nouwens et al., 2018) or word repetition scores (Glize et al., 2017; Tábuas-Pereira et al., 2019) to predict aphasia recovery. These studies suggested that phonological and motor aspects of language could be crucial for recovery. In fact, some tDCS studies used facilitatory anodal stimulation over the left motor cortex of the lips either for PwA, finding positive effects of such a stimulation (Meinzer et al., 2016), or for people with apraxia of speech following a left brain stroke and found more speech improvement after motor cortex stimulation than after the stimulation of Broca's area (Wang et al., 2019). Another NIBS study used intermittent facilitatory Theta Burst Stimulation (TBS) over the left primary motor cortex of the hand in people with post-stroke aphasia (PwA) that induced changes in connectivity of both motor and language areas (Xu et al., 2021). Finally, a mini-review suggested a potential association between the stimulation of the motor cortex using rTMS and changes in several cognitive or language functions (Tomeh et al., 2022).

Furthermore, according to recent studies and reviews (Arheix-Parras et al., 2021; Stefaniak et al., 2022), the use of rTMS in aphasia should be more individualized, based on clinical patterns or lesion specificity. To explore the individualization of a treatment, the Single Case Experimental design (SCED) is particularly adapted to study a small number of patients while maintaining high methodological quality (Krasny-Pacini & Evans, 2018). The SCED is based

on intrasubject analysis, randomized introduction of the intervention and repeated measures (Krasny-Pacini & Evans, 2018).

Taking into account all these findings, we hypothesized that people with chronic aphasia suffering from phonological impairments could benefit from inhibitory rTMS over the right motor cortex of the lips. We hypothesized that this stimulation would allow to improve language production, and would particularly decrease phonological errors.

In the present study, we used a SCED to explore the impact of inhibitory stimulation targeting the right motor cortex of the lips in PwA.

## Method

### Participants

Three participants suffering from chronic aphasia following a single event of left hemispheric stroke (Figure 1) were recruited at Bordeaux University hospital from May to December 2022. For all patients, the lesion included parts of the LIFG and the precentral gyrus (superior part for P1, inferior part for P2 and P3, see Appendices Tables A.1 to A.6 for more details about lesion localization).

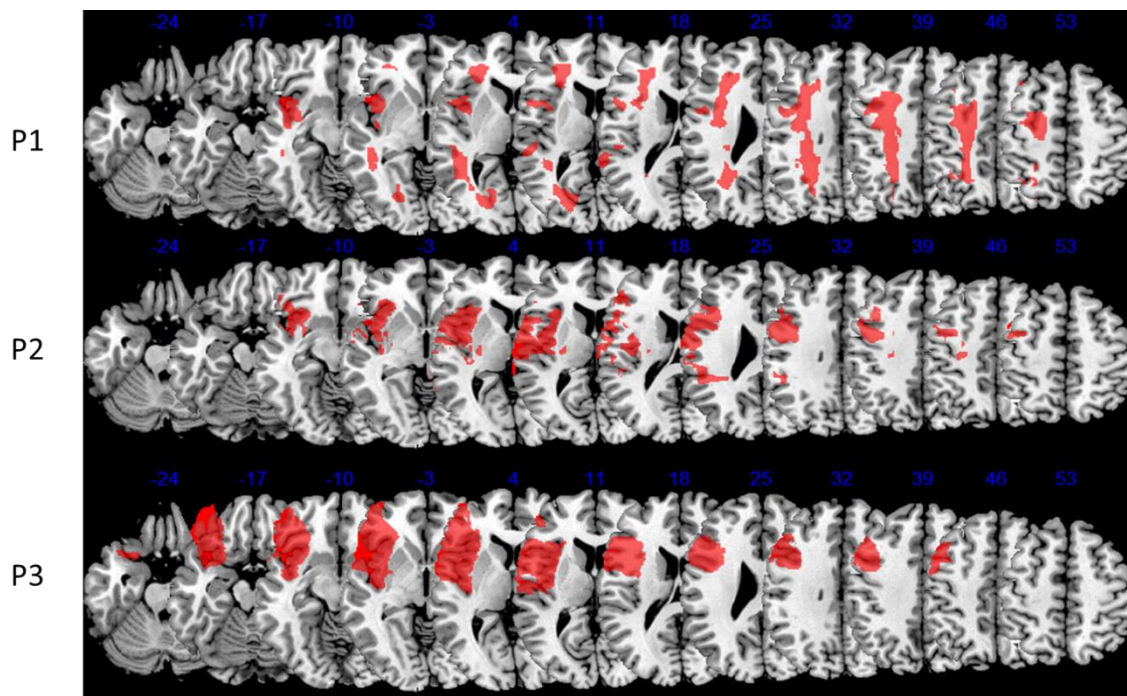


Figure 1: left hemisphere lesions of the participants in red

All participants gave a written informed consent, according to the declaration of Helsinki and this study was approved by French Ethic Committee. All patients were native French-speakers and right-handed according to the Edinburgh questionnaire (Oldfield, 1971). Table 1 regroups patients' main demographic characteristics.

Table 1: demographic and stroke data of the participants

	Gender	Age	Years of education	Time post-stroke (months)	Type of stroke
P1	F	37	14	40	Hemorrhagic
P2	M	68	8	55	Ischemic
P3	F	55	17	7	Ischemic

All participants had mild to moderate aphasia (see Table 2). They presented predominantly with a phonological deficit, i.e., mainly phonological (vs lexical-semantic) errors in spontaneous speech or picture naming tasks, and impaired non-word repetition. No participant had oral or reading comprehension impairment. Indeed, auditory comprehension was preserved for basic sentences (i.e., closed-ended questions, simple commands) and semantic processes were preserved, as shown by scores in the norm for semantic association of pictures and spoken word-picture matching.

Non-inclusion criteria were non-stabilized epilepsy, severe depression, psychiatric antecedent, illiteracy, known neurodegenerative disorder, severe uncorrected visual or hearing impairment, facial palsy.

The participants performed a cognitive and language assessment with a speech language pathologist combining different tests: e-Gebas (electronic Geneva Bedside Aphasia Scale) (Chicherio et al., 2020), subtests from the BECLA (Batterie d'Évaluation Cognitive du Langage) (Macoir et al., 2016), go/no go task from the TEA (Tests d'Évaluation de l'Attention) (Zimmermann & Fimm, 2002), TMT (Trail Making Test) (Bowie & Harvey, 2006), SPART

10/36 Test (Rao, 1990), and visuospatial working memory from the MEM-IV (Daniel, 2013). We also investigated depression and quality of life using tools adapted for PwA: the Aphasic Depression Rating Scale (ADRS) (Benaïm et al., 2004) and the Sickness Impact Profile (SIP-65) (Bénaïm et al., 2003). All scores are summarized in Table 2.

P1 suffered from fluent mild aphasia characterized by anomia and latencies in speech production, but preserved informativeness. She presented a phonological encoding deficit with impaired non-word and sentence repetition, and phonological errors in spontaneous speech. She showed sentence production deficits with syntactic errors, such as omissions of grammatical words and substitutions in verb agreements. She presented additional symptoms of apraxia of speech, such as inconsistent distortion of sounds, groping for sounds, and altered prosody. Other cognitive skills assessed (i.e., inhibition, non-verbal working and episodic memory) were preserved, except some difficulties in processing speed and flexibility.

P2 had fluent aphasia characterized by anomia, latencies and phonological errors in spontaneous speech, but relatively preserved informativeness. He suffered from a phonological encoding deficit with impaired phoneme, word, non-word and sentence repetition. He also made phonological errors in picture naming and spontaneous speech. P2 also presented symptoms of apraxia of speech, such as moderate groping for sounds and errors in rhythm (i.e., segmentation of syllables in words, inappropriate pauses during the speech). All other cognitive abilities assessed were preserved (i.e., working and episodic memory, inhibition, processing speed, flexibility).

P3 suffered from fluent aphasia characterized by anomia, latencies and phonological errors in spontaneous speech, with preserved informativeness. She presented phonological encoding impairments as shown by impaired word and non-word repetition, as well as phonological errors in picture naming. P3 suffered from sequelae of apraxia of speech (that was initially severe), such as mild groping for sounds and altered prosody. Other cognitive abilities were preserved (i.e., working and episodic memory, inhibition, flexibility). The Aphasic Depression Rating Scale (ADRS) indicated a possible depressive symptomatology.

Table 2: cognitive and language baseline pre-stimulation

	P1	P2	P3
<b>Language</b>			
<u>e-Gebas score</u>			
Spontaneous verbal expression (cut-off=10)	10/10	10/10	10/10
Automated sequences (cut-off=5)	5/5	5/5	5/5
Picture naming	10/10 z-score = 0.645	8/10 z-score=-2.85	8,5/10; z-score<-3.0
Repetition (phonemes, words, sentences)	9/10; z-score<-3.0	5/10 z-score<-3.0	8/10; z-score<-3.0
Verbal fluency	NP	6/10 z-score=-1.04	8/10; z-score=-1.94
Auditory comprehension: close-ended questions	10/10	10/10	10/10
Auditory comprehension: spoken word-picture matching and commands	10/10; z-score=0.266	9.5/10; z-score<-3.0	10/10; z-score=0.266
Written production (word and sentence dictation, word spelling, copy, first name and family name)	4.5/10; z-score<-3.0	8/10 z-score<-2.76	10/10; z-score=0
Reading (words, sentences, and spoken word-written word matching) (cut-off=10)	10/10	10/10	10/10
Temporal and spatial orientation	5/5; z-score=0.199	5/5 z-score=0.199	4.5/5; z-score<-3.0
Calculation	8/10; z-score<3.0	8/10; z-score<3.0	10/10; z-score=0.323
<u>BECLA subtests</u>			
Auditory discrimination	35/36; pc 5-25	30/36; pc 5-10	36/36; pc50-95
Semantic association of pictures	20/20; pc>50	20/20; pc 50-95	20/20; pc 50-95



Spoken word-picture matching	20/20; pc>5	20/20; pc 50-95	20/20; pc 5-95
Spoken picture naming (objects and actions)	18/20; pc>5	15/20; <pc 5	16/20; <pc 5
Word repetition	15/15; pc>10	14/15; pc 15	11/15; <pc 1
Non-word repetition	8/10; pc 1-2	6/10; pc 2-5	7/10; <pc 1
<b>Executive functions</b>			
Go/no go (TEA)			
<i>Omissions</i>	NP	1; pc 12	0; pc>62
<i>False</i>	NP	0; pc>62	0; pc>14
Trail Making Test			
<i>Part A</i>	58s; -2.41 SD	72s; -0.15 SD	28s; 0,57 SD
<i>Part B</i>	247s; <-3.0 SD	247s; -1.21 SD	84s; -0,46 SD
<b>Memory</b>			
SPART 10/36 Test			
<i>Immediate recalls</i>	14/30; -0.85 SD	15/30; -0,08 SD	26/30; 2.1 SD
<i>Delayed Recall</i>	4/10; -1.09 SD	5/10; -0,3 SD	10/10; 2.3 SD
Visuo spatial working memory (MEM-IV)			
<i>Raw score</i>	9	8	18
<i>Standard score</i>	7	8	15
<b>Psychological aspects</b>			
Aphasic Depression Rating Scale (ADRS) (cut-off=9)	4/32	3/32	11/32
Sickness Impact Profile (SIP-65)	21/61; 34%	16/65; 25%	12/61; 20%

NP: not performed; SD: standard deviation; pc: percentile

Scores in bold are considered pathological under pc5 or -2.0 for the SD/z-score

## Experimental design

This study was a randomized multiple baselines design across participants that followed SCED protocols (Krasny-Pacini & Evans, 2018) (Figure 2). Participants performed a picture naming task three times a week during six weeks (18 measures in total). The naming task was

considered as the repeated measure. A picture description task was also performed once a week in order to assess a possible generalization to connected speech. All participants received rTMS inhibiting the right motor cortex of the lips three times per week during two weeks (six stimulation sessions in total). The stimulation was off-line and no rehabilitation was performed after the stimulation. No additional SLT was performed for P2 & P3. P1 followed her usual SLT sessions in ambulatory care in a clinical routine twice a week. The duration of the baseline pre-rTMS varied pseudo-randomly across participants (6, 9, or 12 time-points). Thus, intervention started at different time points for every participant.

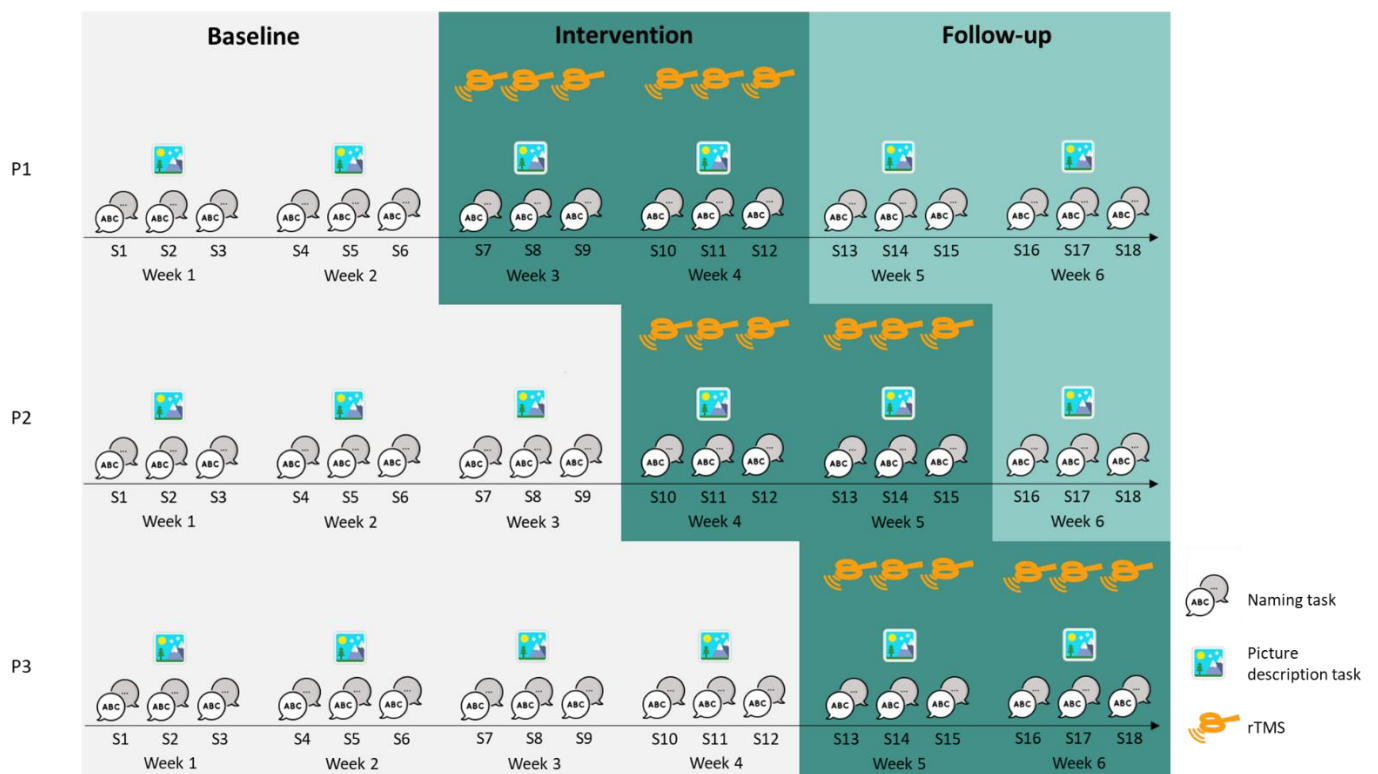


Figure 2: multiple baselines design across participants with rTMS intervention

## Material and procedure

### *Behavioral tasks*

#### Repeated measure

Participants performed a picture naming task (D120) containing 120 pictures (black line drawings on white squares) of monosyllabic (N=40), bisyllabic (N=60) and trisyllabic (N=20) words of various lexical frequency according to a French database (New et al., 2004). For more detail about the stimuli, see Laganaro et al., 2013).

Participants were tested individually and sat approximately 60cm in front of a PC screen. Trials' presentation was controlled by E-Prime 2.0 software (E-Studio). Before the experiment, all participants underwent a familiarization with all pictures and their corresponding written names. Only at this point in the experiment, the examiner gave oral feedback of the expected target word if the participant produced an error. The experimental trial had the following structure: first, a "+" sign was presented for 500 milliseconds (ms) on screen. Then, the picture appeared for 3000ms. Participants had to produce the word corresponding to the picture and the production was recorded with a Jabra® Speakerphone510. Each stimulus was launched manually by the experimenter. The 120 pictures were presented in two different orders alternatively.

Response accuracy and production latencies (reaction time in ms, i.e., the time separating the picture onset and the articulation onset of correct answers only) were analyzed with the speech analysis software CheckVocal (Protopapas, 2007). Errors were classified in four different categories: semantic (e.g., the picture of a "cube" named "square"), phonological (e.g., "broom" named "proom"), phonetic (e.g., dysfluencies, phoneme iterations or distortions) and other.

#### Generalization measure

Once a week, the participants performed a picture description task (Lemistre et al., in prep). This task consisted of an everyday scene in color, which includes 17 items from the D120, presented on a piece of paper. The instructions given to the participants were: "Describe the picture in front of you in the most precise way possible" and production was recorded using a Jabra® speakerphone. No template was provided before the protocol. This task allowed us to record the patient's semi-spontaneous speech and to measure possible generalization effects. To analyze the participants' production, we used the Correct Information Unit (CIU) analysis. This standardized rule-based scoring system calculates the amount of relevant and informative content linked to the task (Nicholas & Brookshire, 1993). Hence, we calculated the number of words per minute, the number of CIUs per minute, and the number of phonological errors per minute.

#### *rTMS*

We applied rTMS using a 75mm 8-shaped coil (Cool-B65 Butterfly Coil, MagVenture ®) connected to MagPro X100unit. The intervention consisted of three stimulations a week during two weeks using continuous TBS (600 pulses, burst frequency at 5 Hz, burst of 3 pulses at 50Hz). The coil was oriented to induce posterior-to-anterior current flow in M1. The stimulation

intensity corresponded to 90% of the Resting Motor Threshold (RMT). RMT was recorded from the left orbicularis oris muscle (OO) using standard surface EMG techniques. Recording electrodes (Neuroline, Ambu®) were placed over the OO in a belly-tendon montage and the reference electrode (Red Dot, 3M) was placed over the lateral epicondyle of the humerus. Signals were sampled at 10 kHz, amplified (1000 gain), filtered (20–1000 Hz) and stored for offline analysis using LabChart 7.3.7 software (ADInstrument). OO mapping and RMT evaluation were assessed by using standard protocols (Rossini et al., 1994). OO spot, i.e., cTBS target, was memorized using Neuronavigation with TMS Navigator Software (Localite®) based on the anatomical MRI of each participant.

### *Statistical analysis*

Statistical tests were chosen according to the SCED guidelines (Krasny-Pacini & Evans, 2018). Graphs and statistical analyses were performed using two websites (Manolov & Solanas, 2018; Tarlow, 2016). For all behavioral results (i.e., picture naming accuracy, number of errors per error type and latencies), we estimated the monotonic trend of the baseline, then we could correct the result if necessary, using Kendall's Tau rank correlation coefficient using the website from Tarlow (Tarlow, 2016). Hence, a baseline-corrected Tau-U was calculated when the baseline showed a significant positive or negative trend. The baseline-corrected or -uncorrected Tau-U calculation (Parker et al., 2011) generated effect sizes interpreted as a small change below 0.2, a moderate change between 0.2 and 0.6, a large change between 0.6 and 0.8, and a large to very large change above 0.8 (Tate & Perdices, 2018; Vannest & Ninci, 2015). For the latencies, we used the analysis of the mean and standard deviation (SD) with the same approach, but outliers were excluded (i.e., values below 3SD or above 3SD from the individual mean). Considering the sample size, we used descriptive statistics for the picture description task scores to analyze clinical changes induced by the rTMS.

## **Results**

Among the 18 sessions per patient, P1 missed session 13 (week 5, first session of the follow-up) because she was unwell. P2 was able to complete all sessions. As P3 was not feeling well after the rTMS in session 13 (week 5, first session of the intervention), she did not perform the D120 this day. Due to technical problems, latencies of the D120 in session 1 were not measurable for P1 and P2.

## Behavioral results

### *Picture naming D120: Accuracy*

Visual analysis of the percentage of accuracy during the naming task showed a positive effect during the rTMS intervention for P2 and P3, and a tendency towards improvement for P1 (Figure 3). All trends were stable in the baseline and after the beginning of the intervention, with low variability (for more detail, see Appendices Table A.7).

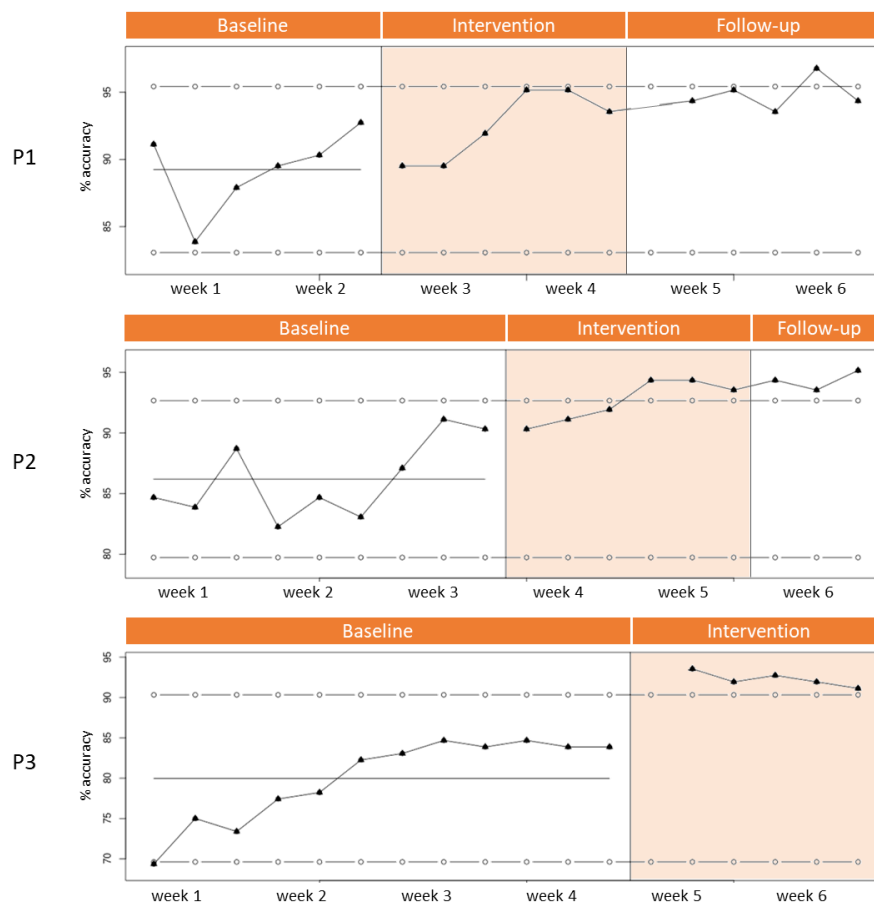


Figure 3: percentage of accuracy during the naming task, with mean solid line during the baseline and two standard deviation dashed lines

For P1, the two-week baseline was relatively stable ( $\text{Tau}=0.467$ ,  $p=0.260$ ). An improvement was observed during week 4 after three sessions of rTMS and almost reached the two standard-deviation (2SD) band. One point was above the 2SD band during the follow-up. However, there was probably a ceiling effect for this task, as P1 performed between 93.5% and 97% for the

five last sessions. Statistical analysis showed a moderate effect size of the intervention ( $\text{Tau}=0.544$ ,  $p=0.013$ ,  $\text{SE}_{\text{Tau}}=0.288$ ).

For P2, the three-week baseline was stable ( $\text{Tau}=0.366$ ,  $p=0.208$ ). We observed an improvement during the intervention: after three sessions of rTMS, all points were above the 2SD band. Statistical analysis showed a large effect size of the intervention ( $\text{Tau}=0.708$ ,  $p=0.001$ ,  $\text{SE}_{\text{Tau}}=0.235$ ).

For P3, the four-week baseline was not stable. We could observe an improvement during the first sessions likely corresponding to a learning effect. However, after two weeks of baseline, scores were stable for over seven sessions, ranging from 82% to 84%. From the second stimulation onwards, scores were immediately better and stable, above the 2SD band. The learning effect observed was confirmed by statistical analysis showing a baseline trend ( $\text{Tau}=0.813$ ,  $p<0.001$ ). Therefore, we could not consider the whole baseline as stable despite the stability visually observed from session 6 to session 12. Taking into account the baseline's improvement with a Baseline Corrected Tau (BC Tau), the effect in the intervention phase did not reach significance (BC Tau=0.177,  $p=0.429$ ,  $\text{SE}_{\text{Tau}}=0.338$ ). Nevertheless, P3 had the highest level of mean difference between the baseline and the intervention (12.28%, see Appendices Table A.7).

More precisely, the number of phonological errors (Figure 4) was stable during the baseline for all participants, but significantly decreased after the beginning of the stimulation, with a moderate effect size for P1 ( $\text{Tau}=-0.571$ ,  $p=0.011$ ,  $\text{SE}_{\text{tau}}=0.282$ ) and a large effect size for P2 ( $\text{Tau}=-0.701$ ,  $p=0.001$ ,  $\text{SE}_{\text{Tau}}=0.238$ ) and P3 ( $\text{Tau}=-0.690$ ,  $p=0.002$ ,  $\text{SE}_{\text{Tau}}=0.248$ ).

Semantic errors were rarely produced by P2 and P3, contrary to P1 who showed a significant decrease of semantic errors during the baseline ( $\text{Tau}=-0.828$ ,  $p=0.035$ ). However, this decrease was temporary, as the number of semantic errors significantly increased again after the stimulation for P1 (BC Tau=0.678,  $p=0.002$ ,  $\text{SE}_{\text{Tau}}=0.252$ ).

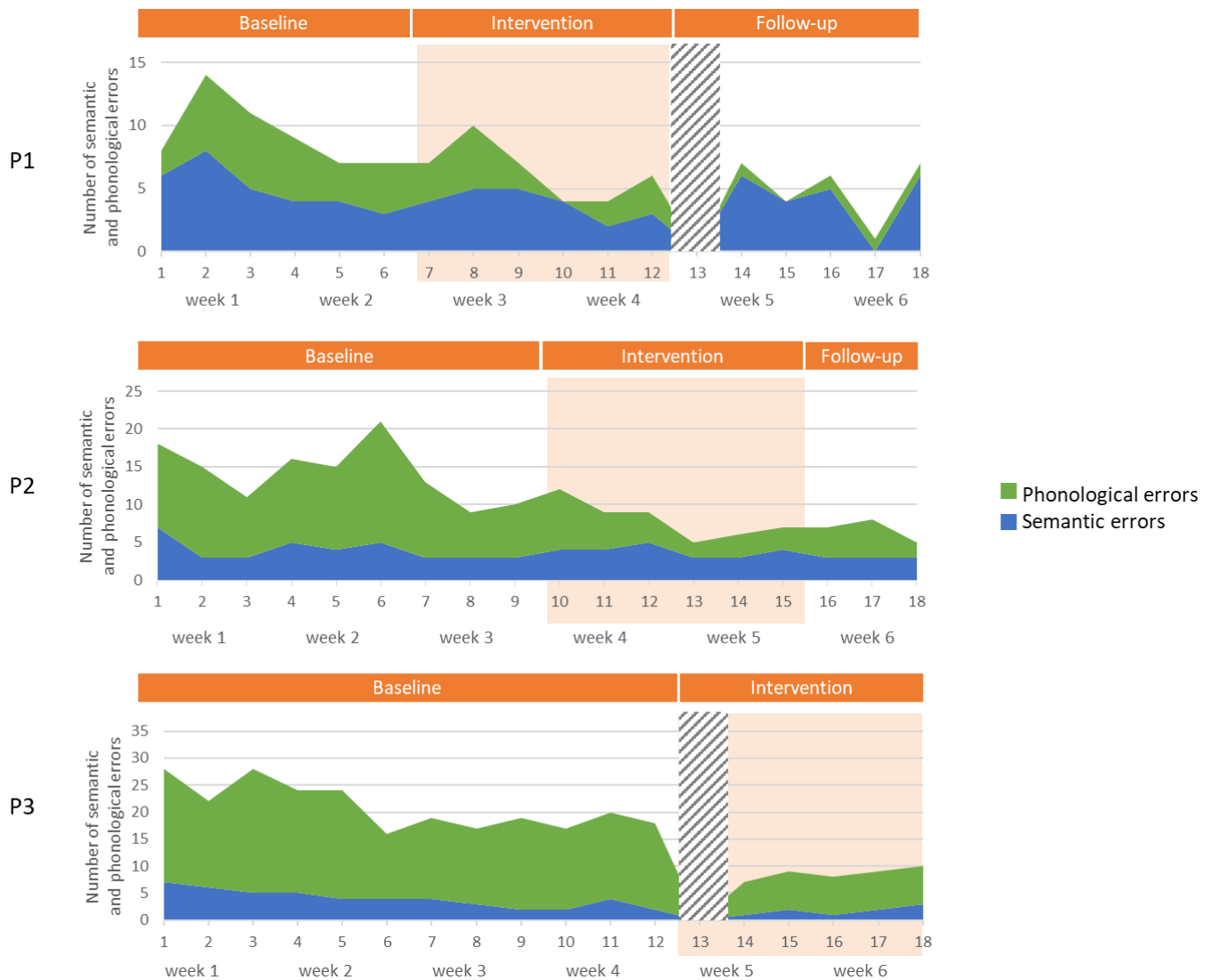


Figure 4: number of errors per category during the picture naming task D120. Incomplete data are represented in grey.

#### *Picture naming D120: Latencies*

For P1, mean latencies were stable during the baseline ( $\text{Tau}=-0.400$ ,  $p=0.462$ ), then showed a non-significant trend towards decrease during the stimulation, with 2 points under the 2SD band ( $\text{Tau}=-0.406$ ,  $p=0.070$ ,  $\text{SE}_{\text{Tau}}=0.323$ ) (Figure 5).

We observed a decrease during the baseline in mean latencies for P2 ( $\text{Tau}=-0.714$ ,  $p=0.019$ ) and in mean latencies for P3 ( $\text{Tau}=-0.745$ ,  $p=0.002$ ). However, this decrease was temporary, as the reaction time showed the opposite effect during the stimulation for P2 ( $\text{BCTau}=0.728$ ,  $p=0.001$ ,  $\text{SE}_{\text{Tau}}=0.235$ ) and P3 (mean:  $\text{BCTau}=0.466$ ,  $p=0.031$ ,  $\text{SE}_{\text{Tau}}=0.303$ ).

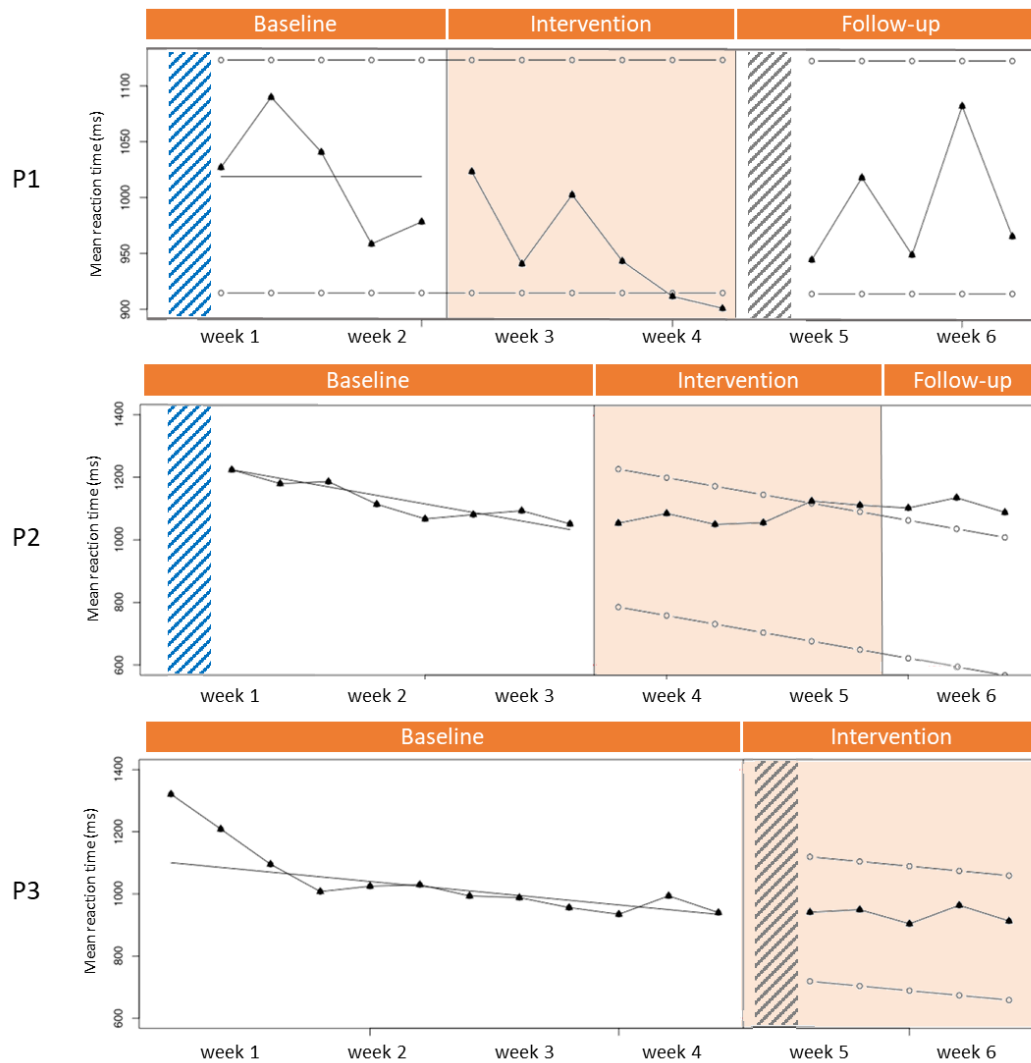


Figure 5: mean reaction time for correct answers during the naming task D120 per session.

Mean solid line during the baseline and two standard deviation dashed lines for P1. Baseline trend solid line and median-based envelop dashed lines for P2 and P3. Missing data in blue are due to data collection issues and in grey because patients did not complete the naming task.

### Picture description

Descriptively, no patient showed a substantial improvement for the number of CIUs or words per minute in picture description during/after the intervention (Figure 6). However, P1 and P2 tended to produce less phonological errors during/after the intervention (P1: baseline range 0.6-1.4%, intervention and follow-up range 0-0.8%; P2: baseline range 5.3-7.8%, intervention and follow-up range 2.6-4.4%).



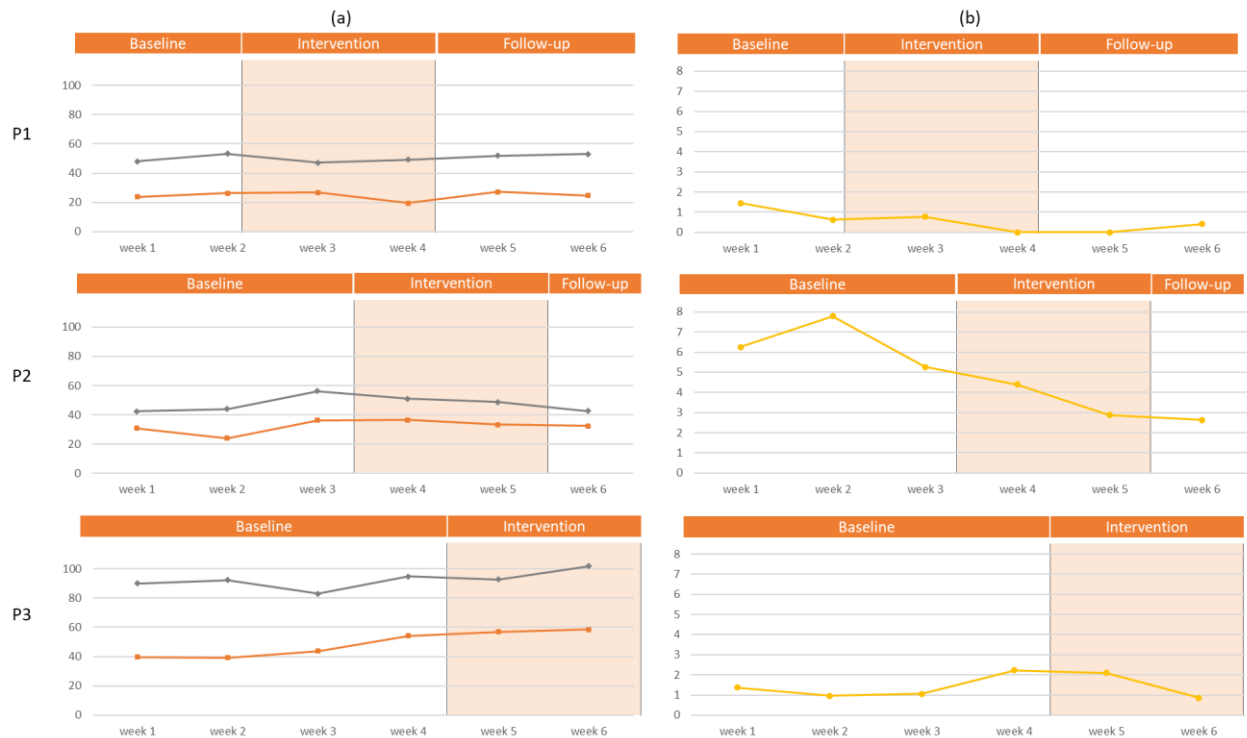


Figure 6: scores for the picture description task per week with (a) number of words per minute (grey), number of CIUs per minute (orange), and (b) percentage of phonological errors per minute (yellow)

## Discussion

This SCED study aimed to explore the effects of inhibitory rTMS on language performance, using continuous TBS that targeted the right motor cortex of the lips in PwA. We found two main positive results: i) inhibition of the right motor cortex of the lips induced improvement in picture naming accuracy, ii) this improvement concerned particularly the decrease of phonological errors.

### Language improvement

This study highlights the positive effect of rTMS on naming accuracy for all included patients with a “phonological profile”, by targeting the motor cortex of the lips, regardless of the baseline’s length. These results suggest that neuromodulating the contralesional motor cortex of the lips could have an impact on language processing. Indeed, rTMS targeting a specific area modulates other brain areas, through interhemispheric and intrahemispheric connections (Ridding & Rothwell, 2007). For example, Nicolo et al., (2016) found an association between lexical processes and the magnitude of resting-state alpha-band coherence of the stimulated

rIFG and the rest of the brain, before cTBS in neurotypical individuals. Those results highlighted the importance of pre-stimulation brain connectivity to ensure the effectiveness of rTMS. Furthermore, as described in the introduction, many findings have suggested the involvement of motor areas in language, both for prediction of post-stroke recovery and word production (Glize et al., 2018; Hesling et al., 2019). Indeed, language production recruits a large network, including the left inferior frontal gyrus (LIFG), but also pre-rolandic areas (Hesling et al., 2019; Hickok & Poeppel, 2007). Therefore, the inhibition of the right motor cortex of the lips might impact the entire left dorsal phonological pathway, via the corpus callosum, the arcuate and superior longitudinal fasciculi (Duffau et al., 2014; Stefaniak et al., 2020; Vigneau et al., 2006).

Interestingly, phonological errors in picture naming decreased after the stimulation. This brings new insights about the involvement of motor areas within language neural networks: traditionally, motor areas have been mainly associated as the final output serving articulation, but it is possible that targeting M1 with NIBS could functionally modulate associated parts of the network. Most rTMS studies have focused on people with non-fluent aphasia without describing in detail their underlying linguistic impairment (e.g., phonological or semantic) or cognitive abilities (for a review, see Arheix-Parras et al., 2021), and these specific points were rarely taken into account for randomization. Moreover, the main target remains the IFG (Arheix-Parras et al., 2021). Our findings suggest that motor areas could also be a relevant target to beneficially modulate the impaired language networks. The idea that stimulation of different targets could lead to improvements in different language processes was already explored. Ren et al., (2019) compared the effect of low-frequency rTMS targeting either the rIFG or the right posterior superior temporal gyrus (rSTG) in two groups of post-stroke patients with global aphasia. They found improvements in spontaneous speech and repetition scores after rIFG stimulation and higher performance in auditory comprehension after rSTG stimulation (Ren et al., 2019). In a longitudinal fMRI study investigating aphasia from a subacute to a chronic stage, Stefaniak et al., (2022) described that recovery of different language features (i.e., fluency, semantic/executive, phonology) was associated with specific patterns of activation in non-overlapping bilateral areas and thus networks. Hence, brain recovery trajectory could vary from one patient to another according to the language feature recovered. Based on these results, Stefaniak et al., (2022) suggested that using the same target in NIBS could induce different effects in PwA, including negative ones, according to the language impairments and trajectories of recovery. In the present study, our rationale in choosing to target

the motor cortex, considering that M1 is crucially involved in phonological processes, seems to be a promising approach, particularly for patients with phonological encoding impairments.

Many NIBS studies have used picture naming accuracy as the only outcome to evaluate their intervention (Arheix-Parras et al., 2021; Biou et al., 2019). Nevertheless, picture naming tasks do not necessarily reflect word retrieval in connected speech, and even less in daily life. In the present study, all patients improved their score in the picture naming task but none improved in the picture description task. The present study also investigated picture naming latencies and found that during the baseline, reaction times progressively decreased, probably due to repetition priming (Barry et al., 2001; Silkes et al., 2020). However, the rTMS intervention did not further decrease reaction times that possibly already reached an asymptote due to the baseline's length, as demonstrated in neurotypical subjects (Logan, 1990).

### **Perspectives**

The individualization of NIBS to improve the effect size of benefits on language performance could be an interesting perspective for further studies. Thus, SCEDs could test an intervention that is specific to a few people (e.g., aphasia following right hemispheric lesion) with high methodological quality (Howick et al., 2011; Tate et al., 2013).

Therefore, the target could be chosen using both clinical markers and imaging data. Indeed, some studies hypothesized that aphasia recovery could be predicted by white matter hyperintensities in the undamaged right hemisphere (Varkanitsa et al., 2020) or evaluating disconnections in language networks (Talozzi et al., 2023). Hence, further research could use a “disconnectome” that could highlight preserved and impaired parts of the network and allow to choose a specific area to target with NIBS (Talozzi et al., 2023).

Some rTMS studies have used fMRI to identify the best area(s) to target depending on left or right recruitment in different language tasks (Abo et al., 2012; Hara et al., 2015) or to target spared LIFG (Szaflarski et al., 2018). However, the temporal precision of fMRI is about 2-3 seconds, and processes for a language task are much faster (e.g., all planning processes in picture naming occur in less than 1 second (Indefrey, 2011)). Hence, the low temporal resolution of fMRI limits the possibility to target the best entry for NIBS. On the contrary, electroencephalography (EEG) permits a higher temporal resolution that could guide researchers to the best target for NIBS in aphasia. Indeed, in a picture naming task, Laganaro et al. correlated lexical-semantic impairments with abnormalities between 110 and 430ms after picture presentation and phonological impairments with abnormal EEG patterns between 300

and 450ms. Consequently, further work could identify specific impaired processes in Event-Related Potentials and then target the best region of interest for NIBS using source localization, especially when the clinical profile is complex or mixed (e.g., both phonological and lexical-semantic impairments) (Laganaro et al., 2009).

Overall, we believe that the individualization of the NIBS target according to personal factors (i.e., lesion location, size, language impairments, electrophysiological profile) could improve the effect size of rTMS on language recovery for PwA.

### **Limitations**

If SCED models have high methodological quality, the results of the present study need to be replicated in at least two other research teams to be confirmed (Kratochwill et al., 2013). In addition, our patients all presented apraxia of speech to various degrees, and the boundary between phonological and phonetic errors was sometimes narrow and difficult to distinguish (Laganaro, 2015). Moreover, we used only two different orders for the picture naming task, and the participants were sometimes able to predict the order of the pictures after several sessions. P1 presented mild aphasia and had a ceiling effect in the naming task. Furthermore, possible mood disorders might have participated in the instability of the baseline for P3. Finally, the generalization measure used in this study was a picture description task containing a small subset of pre-determined words of the D120. However, this measure did not reflect spontaneous speech and was maybe not sensitive enough to reflect speech improvements.

### **Conclusion**

To conclude, the present study highlighted the potential of the motor cortex as a target for rTMS to improve naming in PwA. We used an original approach to select this target, based on the clinical profile of the patients. This work opens up new perspectives for further studies about the individualization of NIBS in small groups of patients with similar characteristics (e.g., clinical profile, lesion site or size, electrophysiological profile), using an adapted SCED model. This also suggests a possible crucial role of the motor cortex in language production.

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## Appendices

Table A.1: lesioned cortical areas for P1 based on standard anatomy in the AAL template (Tzourio-Mazoyer et al., 2002)

Area	Damaged volume per area in cc	Percentage of damage per area
Precentral_L	4.46	15.8
Frontal_Sup_L	0.469	1.6
Frontal_Mid_L	2.794	7.2
Frontal_Mid_Orb_L	0.002	0
Frontal_Inf_Oper_L	1.908	23.1
Frontal_Inf_Tri_L	0.778	3.9
Frontal_Inf_Orb_L	0.077	0.6
Rolandic_Oper_L	0.208	2.6
Insula_L	3.844	25.6
Calcarine_L	0.815	4.5
Cuneus_L	0.029	0.2
Lingual_L	0.85	5
Occipital_Sup_L	0.222	2.1
Occipital_Mid_L	0.64	2.5
Fusiform_L	0.073	0.4
Postcentral_L	0.178	0.6
Parietal_Sup_L	1.102	6.7
Parietal_Inf_L	0.873	4.5
Angular_L	0.087	0.9
Putamen_L	0.002	0
Temporal_Sup_L	1.956	10.7
Temporal_Pole_Sup_L	0.307	3
Temporal_Mid_L	0.975	2.5
Temporal_Inf_L	0.013	0.1
<b>Total</b>	<b>56.59</b>	<b>/</b>

Table A.2: lesioned white matter tracts for P1 on standard anatomy in the Natbrainlab template (Catani et al., 2012)

<b>White matter networks</b>	<b>Number of cc</b>	<b>Percentage of damage per network</b>
Arcuate_Anterior_Segment_Left	0.166	4.1
Long_Segment_Left	0.545	18.3
Arcuate_Posterior_Segment_Left	1.26	20.8
Cingulum_Left	0.61	1.6
Corpus_Callosum_Left	2.975	6.4
Cortico_Ponto_Cerebellum_Left	0.125	1.9
Cortico_Spinal_Left	5.961	21.4
Inferior_Longitudinal_Fasciculus_Left	1.778	12.8
Inferior_Occipito_Frontal_Fasciculus_Left	1.383	12.5
Internal_Capsule_Left	0.437	4.3
Optic_Radiations_Left	0.59	13.4
Uncinate_Left	0.249	3.4

Table A.3: lesioned cortical areas for P2 based on standard anatomy in the AAL template (Tzourio-Mazoyer et al., 2002)

<b>Area</b>	<b>Damaged volume per area in cc</b>	<b>Percentage of damage per area</b>
Precentral_L	7.9	28
Frontal_Sup_L	0.016	0.1
Frontal_Sup_Orb_L	0.053	0.7
Frontal_Mid_L	0.768	2
Frontal_Inf_Oper_L	4.206	50.9
Frontal_Inf_Tri_L	3.243	16.1
Frontal_Inf_Orb_L	1.35	9.9
Rolandic_Oper_L	3.881	48.9
Olfactory_L	0.003	0.1
Insula_L	10.292	68.5
Postcentral_L	2.804	9
SupraMarginal_L	1.568	15.8
Putamen_L	0.428	5.4

Pallidum_L	0.023	1
Heschl_L	0.73	40.5
Temporal_Sup_L	3.437	18.8
Temporal_Pole_Sup_L	0.394	3.9
Temporal_Mid_L	0.102	0.3
<b>Total</b>	<b>45.78</b>	<b>/</b>

Table A.4: lesioned white matter tracts for P2 on standard anatomy in the Natbrainlab template (Catani et al., 2012)

<b>White matter networks</b>	<b>Number of cc</b>	<b>Percentage of damage per network</b>
Anterior_Commissure_Left	0.017	0.3
Arcuate_Anterior_Segment_Left	1.044	25.5
Long_Segment_Left	0.523	17.5
Arcuate_Posterior_Segment_Left	0.363	6
Cortico_Ponto_Cerebellum_Left	0.111	1.7
Cortico_Spinal_Left	0.666	2.4
Fornix_Left	0.003	0
Inferior_Longitudinal_Fasciculus_Left	0.004	0
Inferior_Occipito_Frontal_Fasciculus_Left	0.244	2.2
Internal_Capsule_Left	0.181	1.8
Optic_Radiations_Left	0.135	3.1
Uncinate_Left	0.336	4.6

Table A.5: lesioned cortical areas for P3 based on standard anatomy in the AAL template (Tzourio-Mazoyer et al., 2002)

<b>Area</b>	<b>Damaged volume per area in cc</b>	<b>Percentage of damage per area</b>
Precentral_L	5.05	17.9
Frontal_Sup_L	0.006	0
Frontal_Sup_Orb_L	0.084	1.1
Frontal_Mid_L	3.855	10
Frontal_Mid_Orb_L	2.158	30.3
Frontal_Inf_Oper_L	7.512	90.8

Frontal_Inf_Tri_L	11.875	59.1
Frontal_Inf_Orb_L	11.24	82.7
Rolandic_Oper_L	4	50.4
Olfactory_L	0.05	2.2
Insula_L	12.682	84.4
ParaHippocampal_L	0.007	0.1
Amygdala_L	0.014	0.8
Postcentral_L	0.265	0.9
Putamen_L	0.359	4.5
Heschl_L	0.614	34
Temporal_Sup_L	2.708	14.8
Temporal_Pole_Sup_L	2.836	27.7
<b>Total</b>	<b>72.66</b>	<b>/</b>

Table A.6: lesioned white matter tracts for P3 on standard anatomy in the Natbrainlab template (Catani et al., 2012)

<b>White matter networks</b>	<b>Number of cc</b>	<b>Percentage of damage per network</b>
Arcuate_Anterior_Segment_Left	0.218	5.3
Long_Segment_Left	0.326	10.9
Cortico_Spinal_Left	0.001	0
Inferior_Longitudinal_Fasciculus_Left	0.001	0
Inferior_Occipito_Frontal_Fasciculus_Left	1.061	9.6
Optic_Radiations_Left	0.004	0.1
Uncinate_Left	0.923	12.6

Table A.7: level, trend, variability and overlap of accuracy (in percentage) in the picture naming task (based on Manolov et al., 2016)

		P1	P2	P3
Level difference (intervention – BL)	Mean	4.34	6.99	12.28
	Median	4.26	8.7	9.27
Trend	Baseline	0.81	0.89	1.28
	Intervention and follow-up	0.27	0.48	-0.4
Trend stability (80%-20% formula)	Baseline	100%	100%	100%
	Intervention and follow-up	100%	100%	100%

Catani, M., Dell’acqua, F., Bizzi, A., Forkel, S. J., Williams, S. C., Simmons, A., Murphy, D. G., & Thiebaut de Schotten, M. (2012). Beyond cortical localization in clinico-anatomical correlation. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, 48(10), 1262-1287. <https://doi.org/10.1016/j.cortex.2012.07.001>

Manolov, R., Moeyaert, M., & Evans, J. J. (2016). *Single-case data analysis*. 407.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, 15(1), 273-289. <https://doi.org/10.1006/nimg.2001.0978>

Fin de l'article n°4 :

“Neuromodulation of the motor cortex of the lips using rTMS to improve post-stroke aphasia symptoms: a Single Case Experimental Design”



#### 4. Individualisation de la rTMS pour un participant au profil atypique

Pour cette étude de cas, notre démarche s'apparente à une approche EBP. En effet, nous avons reçu au sein de notre service DT, une personne gauchère ayant présenté un AVC droit entraînant une aphasie sévère non-fluente. Face à la récupération limitée de DT à la phase chronique, nous avons souhaité lui proposer un suivi clinique en rTMS. Or, considérant son profil atypique, nous disposons de très peu d'études sur lesquelles nous appuyer.

Nous avons donc proposé à DT l'intégration à un programme de rTMS basé sur une méthodologie SCED qui a testé trois types de stimulations différentes, afin d'évaluer l'efficacité, voire la supériorité d'une stimulation sur l'autre : (1) inhibition du gyrus frontal inférieur gauche, (2) facilitation du gyrus frontal inférieur gauche, et (3) facilitation du gyrus frontal inférieur droit.

Compte tenu de la latéralité manuelle de DT et de la sévérité de son aphasie, nous avons fait l'hypothèse que l'organisation prémorbide de son langage était latéralisée à droite, contrairement à la majorité des personnes neurotypiques (Mazoyer et al., 2014; Pujol et al., 1999; Szaflarski et al., 2018). Pour la première partie de l'étude, nous avons donc appliqué un protocole de rTMS inhibitrice visant le gyrus frontal inférieur gauche (hémisphère préservé), suivant le principe de balance inter-hémisphérique (partie 1, section 1.2.3).

Considérant l'étendue de la lésion (i.e., incluant 27.6% du corps calleux droit) et la sévérité des troubles phasiques, nous avons appliqué dans un deuxième temps un protocole de stimulation facilitatrice de cette même zone. Le postulat pour cette stimulation facilitatrice ciblant l'hémisphère préservé était le même que pour l'article n°3 (aphasie sévère), c'est-à-dire une remise en question de l'applicabilité du principe de balance interhémisphérique pour les troubles phasiques sévères associés à des lésions larges ou incluant des zones cruciales pour les processus langagiers.

Enfin, la lésion de DT épargnait presque complètement la Pars Triangularis de l'IFG droit (1.9% lésé). Cette zone jouerait un rôle similaire pour la production de mots à l'IFG gauche des personnes présentant une organisation typique du langage (Tzourio-Mazoyer et al., 2015). Nous avons donc utilisé pour la troisième partie de cette étude un protocole de stimulation facilitatrice visant l'IFG droit, soit la zone périlésionnelle globalement préservée.

Cet article a été envoyé pour une publication au sein du journal « Annals of Physical and Rehabilitation Medicine » au mois de juillet 2023.

Article n°5: *Transcranial Magnetic Stimulation to improve aphasia following a right hemispheric stroke: a single case experimental design*

## **Transcranial magnetic stimulation to improve aphasia following a right hemispheric stroke: a Single Case Experimental Design**

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## **Abstract**

**Background.** Aphasia following a right hemispheric stroke is quite rare, as neural networks underpinning language processing are predominantly lateralized in the left hemisphere in right- and left-handers. The modulation of cortical activity using repetitive transcranial magnetic stimulation (rTMS) opens new perspectives for the recovery of aphasia, but rTMS has mainly been used to target the right hemisphere after a contralateral lesion.

**Objective.** We investigated the most appropriate rTMS target and parameters for a left-handed individual with aphasia following a right hemisphere lesion.

**Methods.** We included a left-handed patient with severe non-fluent chronic aphasia following a right hemispheric stroke. Using a Single-Case Experimental Design, we used 3 types of stimulations on the IFG: (1) LH inhibitory Theta Burst Stimulation, (2) LH high-frequency rTMS, and (3) RH facilitatory high frequency TMS, without additional speech therapy. We observed the clinical benefits in a picture naming task induced by every type of stimulation.

**Results.** We found that picture naming accuracy remained stable during each type of stimulation. However, the (1) left inhibition induced an increase in perseverations, while the (2) left facilitation induced a decrease in perseverations and phonological errors. The (3) right facilitation did not induce any change on the picture naming task.

**Conclusions.** These findings support the importance of taking into account the patient's characteristics, notably their dominant hemisphere for language as well as the severity of their aphasia, when using rTMS. This study on an atypical individual challenges the theory of interhemispheric imbalance used in a majority of rTMS protocols.

**Keywords:** aphasia, stroke, transcranial magnetic stimulation, right hemisphere, individualization

## ***Introduction***

Aphasia affects 7 to 77% of people after a stroke, with a high variability of incidence rates due to different approaches for the diagnosis and the timing post onset [1]. In most cases, aphasia follows a left hemispheric (LH) stroke. Nevertheless, some people suffer from aphasia following a right hemispheric (RH) lesion, due to an atypical lateralization of the language networks, which is usually associated with manual laterality [2–4]. Indeed, about 80% of left-handed people present with LH language lateralization, while ~10% have a RH language lateralization, and ~10% have a bilateral distribution [2–4]. More precisely, an fMRI study found that individuals with atypical RH language lateralization showed comparable regional patterns to people with typical LH language lateralization, i.e., a similar contralateral network activated during language tasks (e.g., activation of the right homolog of Broca's area versus Broca's area) [5].

Non-invasive brain stimulation (NIBS) such as repetitive Transcranial Magnetic Stimulation (rTMS) opens up new possibilities for aphasia recovery [6]. A majority of NIBS studies for people with post-stroke aphasia are based on the theory of transcallosal imbalance [7]. Hence, a majority of rTMS studies for aphasia rehabilitation used inhibitory stimulation targeting the right inferior frontal gyrus (rIFG), i.e., Broca's homolog, or facilitatory stimulation over the left hemisphere, particularly targeting Broca's area [6]. In crossed aphasia, two studies used inhibitory rTMS over the LH after a RH stroke in right-handed people, not combined with speech and language therapy (SLT) [8,9]. These two clinical case reports both found language improvements using inhibitory rTMS targeting left hemisphere areas, i.e., the left lateral sulcus for Jung et al. [8], and Broca and Wernicke areas for Lu et al. [9]. To our knowledge, only one study explored the effect of inhibitory rTMS targeting the left IFG and followed by SLT in two left-handed people with aphasia after a RH stroke [10]. However, the results from that study were inconclusive concerning the efficiency of that "mirror" approach [10].

For large brain lesions causing severe aphasia and damages in subcortical areas such as the corpus callosum, the theory of interhemispheric balance restoration could be questionable [11]. In this context, using inhibitory stimulation targeting the healthy hemisphere might not be beneficial [11] and facilitatory stimulation targeting the impaired hemisphere might be an alternative approach. Two NIBS studies [12,13] combined facilitatory stimulation targeting the right IFG with melodic intonation therapy for people with severe aphasia following a LH stroke. Vines et al. [13] found significant improvements in speech fluency after facilitatory (anodal) tDCS in the majority of the six individuals included. In an rTMS protocol, Al-Janabi et al. [12] reported mixed results for the two patients included, as one individual improved in verbal fluency and sentence repetition, but the other did not show any behavioral improvement. A randomized sham-controlled study [14] compared facilitatory versus inhibitory stimulation over the right IFG, combined with SLT, in people with non-fluent aphasia. Results showed that both types of stimulation induced significant language improvement compared to the control group, but inhibitory rTMS had a greater impact than facilitatory stimulation. Hu et al. [14]

related the activation/excitation of the right IFG to the possible reorganization of language networks in the contralesional hemisphere, as suggested by a study about motor recovery [15]. These NIBS studies on severe/non-fluent aphasia investigated the effect of brain stimulation on broad language scores. However, one specific behavior correlating with the severity of aphasia is the presence of perseverations [16]. Perseverations are defined by the inappropriate repetition of a previous response in the current context [17]. This phenomenon could be explained by the residual activation of a previous unrelated response (i.e., no semantical link and short temporal delay between the previous response and the perseveration) or incremental learning (i.e., semantical link and longer temporal delay between productions) [18]. Hence, an objective of using rTMS in patients with severe aphasia could be to reduce the number of perseverations, in order to improve communication skills.

To study different types of intervention on a unique patient, Single Case Experimental Design (SCED) allows high methodological quality [19,20]. This design allows for the individualization of treatment for a very specific demographic or for a person presenting an atypical profile. SCED is based on repeated measures, intrasubject analysis, and randomized beginning of the interventions, i.e., for studies with a unique participant and several interventions, the baseline's length will be randomized for each intervention.

While rTMS using facilitation targeting the LIFG or inhibition targeting the rIFG appears to be effective for aphasia recovery following a LH stroke, research about the use of rTMS in people with aphasia following a RH stroke remains poorly explored, especially for severe aphasia. We therefore propose an exploratory study that will investigate the most appropriate rTMS treatment for a left-handed participant with severe aphasia following a RH stroke, using SCED and three types of stimulation over the IFG (left or right): (1) left inhibition, (2) left facilitation, (3) right facilitation.

## ***Materials and methods***

### **Participant**

DT was recruited at Bordeaux University Hospital in January 2021. He suffered from aphasia following a large right ischemic stroke ( $\approx 283\text{cc}$ ), including 27.6% of the right corpus callosum (Figure 1; see Appendices Tables A.1 and A.2 for more detail about the lesion localization).

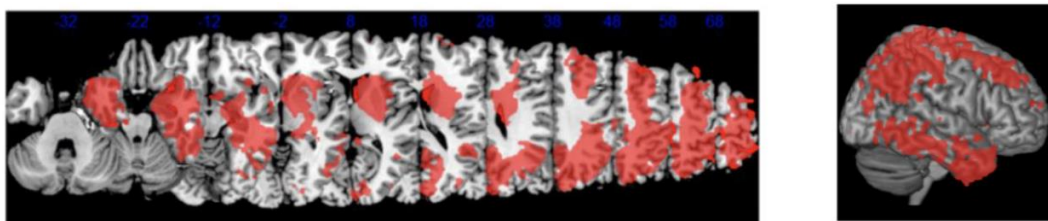


Figure 1: right hemisphere lesion of the participant in red

The present study was approved by the French Ethics Committee and the participant gave written informed consent, according to the declaration of Helsinki. DT was 76, a native French speaker and left-handed according to the Edinburgh Handedness Inventory (EHI: -60; Oldfield, 1971). He presented a single event of stroke, and was at a chronic stage ( $\approx$ 26 months post onset).

Non-inclusion criteria were (1) non-stabilized epilepsy, (2) psychiatric antecedent, (3) illiteracy, (4) known neurodegenerative disorder, (5) severe uncorrected visual or hearing impairment.

With a speech language pathologist, DT performed a cognitive and language assessment (Table 1) that combined different tests: e-Gebas (electronic Geneva Bedside Aphasia Scale) [22], subtests from the BECLA (Batterie d'Evaluation Cognitive du Langage) [23], go/no go task from the TEA (Tests d'Évaluation de l'Attention) [24], TMT (Trail Making Test) [25], visuospatial working memory from the MEM-IV [26]. We also investigated depression and quality of life using tools adapted for people with aphasia: the ADRS (Aphasic Depression Rating Scale) [27] and the SIP-65 (Sickness Impact Profile) [28].

DT suffered from severe non-fluent aphasia. In language production, his spontaneous speech was characterized by severe word finding difficulties, latencies, agrammatism, and perseverations. He was able to produce automatic sentences and isolated words. He often used non-verbal communication to express his difficulties. Anomia was also severe in picture naming, with omissions, perseverations, latencies, as well as phonetic, phonological and semantic errors. He presented with difficulties in word and non-word repetition. DT also suffered from comprehension impairments with difficulties in auditory phoneme discrimination, spoken word-picture matching and to understand complex sentences. DT was able to understand short and simple sentences, but repetition and rephrasing were sometimes needed. DT was not able to read or write any words. Non-verbal inhibition was preserved. Non-verbal memory and flexibility tests were abandoned mainly because of severe visuospatial and motor impairments. Excluding the non-verbal inhibition test, all scores were pathological: DT suffered from a severe cognitive deficit (see Table 1).

Table 1: cognitive and language baseline pre-stimulation

<b>Language</b>		
<u>e-Gebas score</u>		
Spontaneous verbal expression		<cut-off
Automated sequences		<cut-off
Picture naming		z-score < -3.0
Repetition (phonemes, words, sentences)		z-score < -3.0
Verbal fluency		NP
Auditory comprehension: close-ended questions		z-score < -3.0
Auditory comprehension: spoken word picture matching and commands		z-score < -3.0
Written production (word and sentences dictation, word spelling, written word reproduction, first name spelling and family name dictation)		NP
Reading (sentences, words and spoken word written matching) (cut-off=10)		AB
Calculation		NP
<u>BECLA subtests</u>		
Auditory discrimination		<pc 1
Semantic association of pictures		<pc 1
Spoken word-picture matching		<pc 1
Spoken picture naming (objects and actions)		<pc 1
Word repetition		<pc 1
Non-word repetition		<pc 1
<u>Executive functions</u>		
Go/no go (TEA)		
<i>Omissions</i>		pc>14
<i>Errors</i>		pc=34
Trail Making Test		
<i>Part A</i>		NP
<i>Part B</i>		NP
<u>Visuospatial memory</u>		
Visuo spatial working memory (MEM-IV)		NP
<u>Psychological aspects</u>		
Aphasic Depression Rating Scale (ADRS)		< cut-off
Sickness Impact Profile (SIP-65)		44/61; 72%

AB: abandoned; NP: not performed due to most severe deficits; pc: percentile



## Experimental design

This study was a randomized multiple baselines design across sessions that followed SCED protocols and was based on Krasny-Pacini et al. guidelines [19]. The protocol was divided into three periods, separated by wash-out periods of 4 weeks minimum. Each period of the protocol lasted 6 weeks with 3 sessions per week (total=54 sessions). The participant performed a picture naming task three times a week. This task was considered as the repeated measure.

The participant received rTMS stimulation three times per week during two weeks in each period (six stimulation sessions per period): in the first period (1), we used inhibitory stimulation targeting the left IFG, in the second period (2), we used facilitatory stimulation targeting the left IFG and in the third period (3), we used facilitatory rTMS targeting the right IFG. No SLT was performed throughout the whole study. The duration of the baseline pre-rTMS stimulation varied randomly across periods (6, 9, or 12 time-points picked at random, resulting in 9 points before the first stimulation period, 12 points before the second stimulation period, and 9 points before the third stimulation period). The study design is summarized in Figure 2.

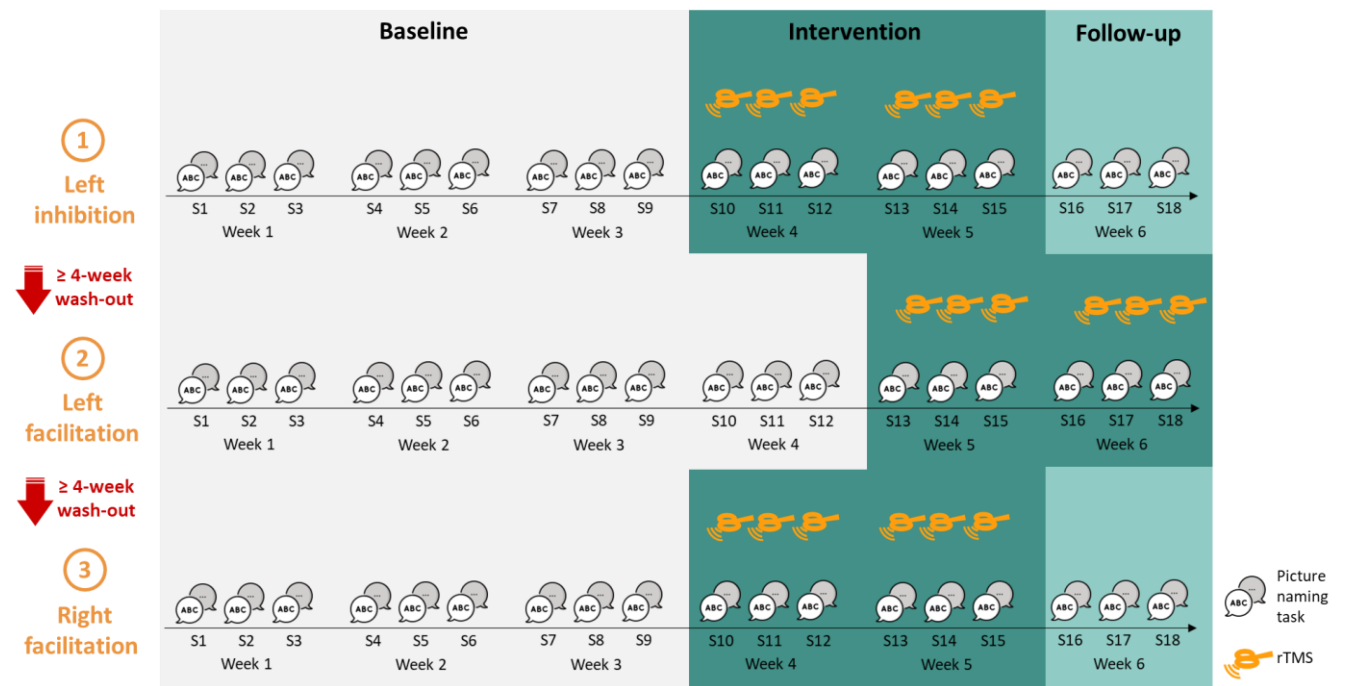


Figure 2: multiple baselines design across rTMS interventions

## **Material and procedure**

### Repeated measure: the picture naming task

DT performed a picture naming task (D120) containing 120 pictures (black line drawings on white squares) of monosyllabic (N=40), bisyllabic (N=60) and trisyllabic (N=20) words, with a lexical frequency varying from 0.13 to 227 occurrences per million words (mean=17.3) in the “French lexical database” [29]. For more detail about the task, see Laganaro et al. [30].

DT sat approximately 60cm in front of a PC screen. Trials’ presentation was controlled by E-Prime 2.0 software (E-Studio). Before the experiment, DT had a familiarization with all pictures and their corresponding names. The experimental trial had the following structure: first, a “+” sign was presented for 500ms on screen. Then, the picture appeared for 3000ms. The participant had to produce the word corresponding to the picture and the production was recorded with a Jabra® Speakerphone. Each stimulus was launched manually. The 120 pictures were presented in two different orders alternatively.

Response accuracy and production latencies (reaction time in ms, i.e., the time separating the picture onset and the articulation onset) were systematically analyzed with the speech analysis software CheckVocal [31]. Errors were classified in five different categories: semantic (e.g., the picture of a “dog” named “horse”), phonological (e.g., “lung” named “tung”), perseveration (i.e., repetition of a previous response in the absence of the corresponding stimulus), omission (i.e., no response given within 3 seconds) and other. Perseverations were further divided in two sub-categories: semantic perseverations (i.e., when there was a semantic relationship between the perseveration and the current stimulus) and unrelated perseverations.

### rTMS

We applied magnetic stimulations using a 75mm 8-shaped coil (Cool-B65 Butterfly Coil, MagVenture®) connected to MagPro X100unit. In each period of the study, the intervention consisted of three stimulations per week during two weeks. Three different types of stimulation were used:

- in the first period (1), the six stimulation sessions consisted of the application of continuous theta burst stimulation (cTBS: 600 pulses, burst frequency at 5 Hz, burst of 3 pulses at 50Hz) targeting the Pars triangularis of left IFG;
- in the second period (2), we used facilitatory high frequency rTMS (HF rTMS: 1000 pulses, frequency at 10 Hz, 50 pulses per train, 20 trains, at least 5 seconds interval inter-train) also targeting the Pars triangularis of left IFG;
- in the third period (3), every stimulation consisted of facilitatory high frequency rTMS (HF rTMS: 1000 pulses, frequency at 10Hz, 50 pulses by train, 20 trains, at least 5sec interval intertrain) targeting the right IFG.

The stimulation intensity corresponded to 90% of the Resting Motor Threshold (RMT). RMT was recorded from the the abductor pollicis brevis muscle of the left upper limb, using surface electrodes (Neuroline, Ambu®). Signals were sampled at 10kHz, amplified (1000gain), filtered (20–1000Hz) using LabChart7.3.7 software (ADInstrument). RMT evaluation were assessed by using standard protocols [32]. rTMS target was found on the anatomical MRI of each subject and memorized using Neuronavigation with TMS Navigator Software (Localite®).

### **Statistical analysis**

Statistical tests were chosen according to the SCED guidelines [19]. Graphs and statistical analyses were performed using two websites specialized for analyses of SCED [33,34]. Behavioral results were analyzed using a Tau-U calculation [35]. A baseline-corrected Tau-U was calculated when the baseline showed a significant trend towards change/instability. Effect-sizes generated by the Tau-U were interpreted as a small change below 0.2, a moderate change between 0.2 and 0.6, a large change between 0.6 and 0.8, and a large to very large change above 0.8 [36,37]. For visual analysis, when the baseline did not show any trend, we represented the mean during the baseline and the 2-SD (Standard deviations) envelope after the beginning of the intervention. When the baseline showed a significant trend, we illustrated the trend during the baseline and a median-based envelope after the start of the intervention [38].

## ***Results***

DT was able to complete all 54 sessions (i.e., 18 sessions per period).

### **Behavioral results**

For the accuracy of picture naming (D120), visual analyses showed no effect of the three different stimulations (Figure 3). During the first period (1), the baseline did not show any trend before left inhibition. All successive points remained within the two standard deviation intervals during and after left inhibition. Similar results were found for left and right facilitation in the second period (2) and the third period (3), although some isolated points reached two standard deviations in both cases during the baseline and after the beginning of the intervention. These points highlight a variability in DT's performance (for more detail, see Appendix Table A.3). Statistical analyses confirmed that there was no significant effect of the three different stimulations on naming accuracy (Table 2).



Figure 3: total score during the naming task in percentage of accuracy, with mean solid line during the baseline and the two standard deviation relevant dashed lines

Concerning the type of errors, the number of non-responses and semantic errors varied without any significant trend during all periods ( $p > 0.05$ ) (Figure 4). As for phonological errors, they were stable during the whole (1) left inhibition period. For the (2) left facilitation period, the number of phonological errors was stable during the four-week baseline, then significantly decreased during the two-week intervention ( $\text{Tau} = -0.602$ ;  $p = 0.005$ ;  $\text{SE}_{\text{Tau}} = 0.266$ ). In the (3) right facilitation period, the number of phonological errors was stable during the six-week protocol. Note that during this period (3) of the protocol, the number of phonological errors was already low at baseline, suggesting that the significant improvement observed during the second period was maintained at the beginning of this third period. The number of perseverations was stable during the baseline of the (1) left inhibition period, but significantly increased after the intervention ( $\text{Tau} = 0.415$ ,  $p = 0.047$ ,  $\text{SE}_{\text{Tau}} = 0.303$ ). During the (2) left facilitation period, the baseline showed a significant trend to produce more perseverations. Taking into account this baseline's trend, the number of total perseverations significantly decreased after the beginning of the intervention: all points were below the median-based envelope (Baseline Corrected  $\text{Tau} = -0.686$ ,  $p = 0.001$ ,  $\text{SE}_{\text{Tau}} = 0.243$ ). More precisely, the number of unrelated perseverations decreased (Baseline Corrected  $\text{Tau} = -0.642$ ,  $p = 0.002$ ,  $\text{SE}_{\text{Tau}} = 0.256$ ), whereas the number of semantic perseverations remained stable ( $\text{Tau} = -0.360$ ,  $p = 0.098$ ,  $\text{SE}_{\text{Tau}} = 0.311$ ). In the (3) right facilitation period,

the number of perseverations was stable during the baseline. After the intervention, we observed a non-significant trend to produce fewer perseverations (Table 2 and Figure 4).

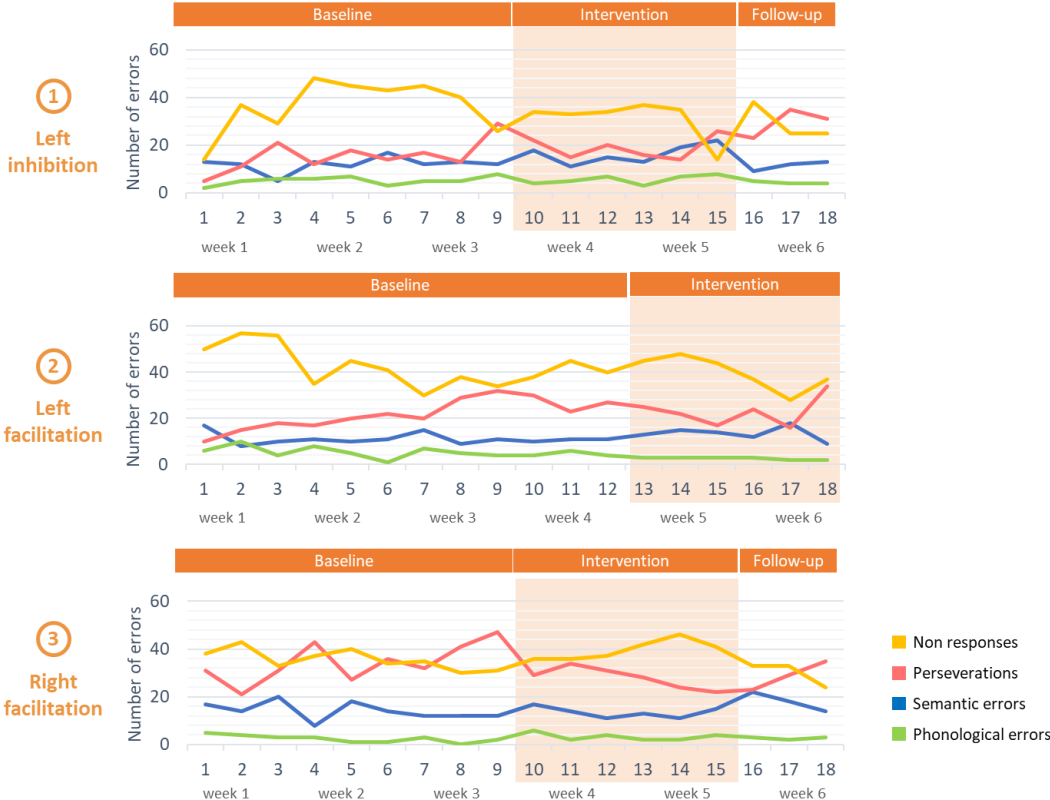


Figure 4: number of errors per error type during the picture naming task D120

Table 2: statistical analyses for the overall naming accuracy and per error type

		(1) Left inhibition	(2) Left facilitation	(3) Right facilitation
Naming accuracy	Baseline trend	No trend	No trend	No trend
	Size-effect	Tau=0.129 p=0.564 SE <sub>Tau</sub> =0.331	Tau=0.307 p=0.157 SE <sub>Tau</sub> =0.317	Tau=0.382 p=0.070 SE <sub>Tau</sub> =0.308
Non responses	Baseline trend	No trend	No trend	No trend
	Size-effect	Tau = -0.338 p = 0.111 SE <sub>Tau</sub> = 0.314	Tau = -0.099 p = 0.670 SE <sub>Tau</sub> = 0.332	Tau = -0.009 p = 1.000 SE <sub>Tau</sub> = 0.333
<i>Unrelated perseverations</i>	Baseline trend	No trend	Positive Trend Tau=0.661, p=0.006	No trend
	Size-effect	Tau=0.341 p=0.110 SE <sub>Tau</sub> =0.313	BC Tau=-0.642 p=0.002 SE <sub>Tau</sub> =0.256	Tau=-0.257 p=0.232 SE <sub>Tau</sub> =0.322
<i>Semantic perseverations</i>	Baseline trend	No trend	No trend	No trend
	Size-effect	Tau=0.38 p=0.087 SE <sub>Tau</sub> =0.308	Tau=-0.360 p=0.098 SE <sub>Tau</sub> =0.311	Tau=-0.262 p=0.252 SE <sub>Tau</sub> =0.322
Total perseverations	Baseline trend	No trend	Positive Trend Tau=0.718, p=0.002	No trend
	Size-effect	Tau=0.415 p=0.047 SE <sub>Tau</sub> =0.303	BC Tau=-0.686 p=0.001 SE <sub>Tau</sub> =0.243	Tau=-0.337 p=0.111 SE <sub>Tau</sub> =0.314
Semantic errors	Baseline trend	No trend	No trend	No trend
	Size-effect	Tau =0.275 p=0.210 SE <sub>Tau</sub> =0.320	Tau=0.361 p=0.097 SE <sub>Tau</sub> =0.311	Tau=0.084 p=0.722 SE <sub>Tau</sub> =0.332
Phonological errors	Baseline trend	No trend	No trend	No trend
	Size-effect	Tau=-0.048 p=0.858 SE <sub>Tau</sub> =0.333	Tau=-0.602 p=0.005 SE <sub>Tau</sub> =0.266	Tau=0.382 p=0.070 SE <sub>Tau</sub> =0.308

Score in bold are statistically significant

## ***Discussion***

The present study explored the possibility to individualize rTMS in a left-handed patient with severe chronic aphasia following a large RH stroke including the right corpus callosum. We aimed to improve language performance with rTMS targeting the IFG in three steps using (1) left inhibition, (2) left facilitation, and (3) right facilitation. Our clinical results showed that the (1) left inhibition induced an increase in perseverations, while the (2) left facilitation induced a decrease in perseverations and phonological errors, and the (3) right facilitation did not induce any changes in picture naming.

### **Contralesional inhibition in the case of atypical language lateralization**

Taking into account that the patient in the present study was left-handed, suffered from severe non-fluent aphasia after RH stroke and considering results from studies about language laterality in neurotypical individuals (see Introduction), we assumed a premorbid right dominant localization of language networks in DT. This hypothesis explained the choice of inhibiting first the LIFG, to boost connections in the right “dominant” hemisphere. Indeed, another study [10] analyzed the language changes induced by 10 sessions of inhibitory low-frequency (1Hz) rTMS targeting the left IFG and followed by SLT in two left-handed people with aphasia following a RH stroke. The first left-handed patient (EHI=-40) that suffered from moderate amnesic aphasia, showed improvement in language tasks compared to the sham group. On the contrary, the second left-handed patient (EHI=-100) suffering from more severe Broca’s aphasia, did not improve her results compared to the sham group [10]. The authors [10] hypothesized that the premorbid language networks could be distributed more bilaterally for the first patient, inducing both less severe aphasia and also a better response to contralesional inhibition with rTMS. For Heiss and al. (2013), the rationale for NIBS in left-handed patients should not be a simple inversion of the approach for right-handed people, as premorbid language organization might be more bilaterally distributed in left-handers than in right-handers. As a comparison, the left-handed patient in the present study (EHI=-60) presented severe non-fluent aphasia, like the second patient in Heiss and al. (2013). The inhibition of the healthy hemisphere was not efficient for both of them. One hypothesis about the absence of significant results in these two cases could be the positive contribution of the contralesional hemisphere in patients suffering from severe aphasia, even in the chronic phase. Furthermore, one study warned about a possible negative effect of inhibitory stimulation over the preserved hemisphere for people with a large brain lesion, including subcortical areas such as the corpus callosum [11]. Indeed, an unexpected result of the present study was the negative effect in terms of increased perseverations induced by the (1) left inhibition of the IFG. To our knowledge, only one study [39] reported a decrease in picture naming performance in a woman with chronic left post-stroke aphasia, after using inhibitory cTBS targeting the right IFG. As in the present study, the patient suffered from severe aphasia [39]. However, a possible publication bias could also explain that only one study reported a negative effect of rTMS. Indeed, it has been argued that the use of the same target and parameters in NIBS for different people with post-stroke aphasia could induce different effects,

including negative ones [40]. The current results highlight the importance of reporting negative effects, in order to avoid them in future individualization of the technique, and to maximize the efficacy of the stimulation.

### **Facilitation over the contralesional hemisphere and interhemispheric imbalance**

In this study, facilitatory stimulation of the LIFG induced a decrease in perseverations and phonological errors. Most studies about NIBS followed the principle of interhemispheric imbalance using inhibitory stimulation targeting the undamaged hemisphere in people with aphasia and more specifically, the right IFG in most cases, regardless of the lesion site in the LH [6,7]. However, for chronic severe aphasia, language recovery led by a return to previous processes and/or by perilesional compensation may not be possible because of the lesion size or localization (i.e., crucial areas for language) [41,42]. In such a context, language recovery could not be guided by the residual networks within the damaged hemisphere [42]. Indeed, it has been suggested that the controlateral hemisphere might play a positive role in aphasia recovery, as white matter hyperintensities in the undamaged hemisphere could predict the extent of recovery [43]. Moreover, a systematic review highlighted the increase in activation of the controlateral hemisphere after language therapy, that has been interpreted as new strategies/networks of language processing [44]. In addition, several authors questioned the transcallosal disinhibition theory, by recalling that it was not based on evidence in language studies, but as a transposition of motor studies [7,45,46]. Interestingly, the present study suggested that following the theory of interhemispheric imbalance might worsen language performance in specific cases, while facilitatory rTMS targeting the controlateral hemisphere might increase language performance. Altogether, the present results challenge this widely used theory, particularly regarding long-term aphasia recovery.

### **Cortical target and ipsilesional hemisphere stimulation**

In the present study, the patient's lesion was mostly localized in temporal and parietal areas of the right hemisphere, sparing the right IFG. However, facilitatory stimulation of the rIFG did not induce any behavioral improvement. Indeed, if the lesion spared this area, it also probably disconnected it from other intra- and inter-hemispheric areas and possibly modified its metabolism [47]. Hence, we could also question the choice to stimulate the IFG, which follows most rTMS studies for aphasia recovery [6], but also localizationist theories. The study of language network disconnections could help to predict aphasia recovery, but might also highlight the best entry for NIBS [48].

### **Limitations**

Firstly, the results of the present study are difficult to replicate because of the very specific profile of the patient included. Secondly, even with a wash-out ( $\geq 4$  weeks) between the three periods of the protocol, we cannot exclude a possible effect of the stimulations' order. Lastly, SLT was not proposed



here contrary to other studies, but adding SLT sessions after the stimulation might increase the size effect of the rTMS.

### *Conclusions*

To conclude, this SCED study calls into question the use of rTMS in severe aphasia and in patients with RH or bilateral language lateralization using the principle of transcallosal disinhibition. In the present atypical case, the most efficient stimulation was the facilitation of the undamaged LIFG. The current report also alerts on the possibility to induce adverse effects, such as a decrease in language performance. This study opens up new perspectives in the area of NIBS for aphasia recovery, based on individualization of the stimulation target and parameters taking into account laterality, clinical profile, and lesion site.

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## Appendices

Table A.1: lesioned cortical areas based on standard anatomy in the AAL template [49]

Area	Damaged volume per area in cc	Percentage of damage per area
Precentral_R	10.07	37.2
Frontal_Sup_R	12.22	38.1
Frontal_Mid_R	15.78	39.1
Frontal_Inf_Oper_R	0.98	8.8
Frontal_Inf_Tri_R	0.33	1.9
Frontal_Inf_Orb_R	0.46	3.4
Rolandic_Oper_R	0.18	1.6
Supp_Motor_Area_R	1.79	9.5
Olfactory_R	0.16	7.2
Frontal_Sup_Medial_R	0.13	0.8
Frontal_Med_Orb_R	0.02	0.3
Insula_R	3.83	27.1
Cingulum_Ant_R	0.15	1.4
Cingulum_Mid_R	1.13	6.5
Cingulum_Post_L	0.00	0.1
Cingulum_Post_R	0.89	33.3
Hippocampus_R	6.16	81
ParaHippocampal_R	5.60	62
Amygdala_R	1.79	90.8
Calcarine_L	0.42	2.3
Calcarine_R	4.49	30.2
Cuneus_L	0.58	4.8
Cuneus_R	9.06	80
Lingual_R	0.68	3.7
Occipital_Sup_R	5.18	46.4
Occipital_Mid_R	3.85	23.3
Occipital_Inf_R	0.68	8.6
Fusiform_R	10.31	51
Postcentral_R	15.83	51.6
Parietal_Sup_R	11.69	66.6
Parietal_Inf_R	8.42	78.2
SupraMarginal_R	4.83	30.6
Angular_R	10.46	74.7
Precuneus_L	0.20	0.7
Precuneus_R	15.30	58.7
Paracentral_Lobule_R	1.44	21.5
Caudate_R	7.06	88.9
Putamen_R	6.61	77.7
Pallidum_R	2.18	99.7
Thalamus_R	1.01	12
Temporal_Sup_R	1.20	4.7

Temporal_Pole_Sup_R	4.34	40.7
Temporal_Mid_R	8.99	25.3
Temporal_Pole_Mid_R	7.02	74.1
Temporal_Inf_R	16.97	59.6
Cerebelum_Crus1_R	0.06	0.3
Cerebelum_3_R	0.02	1
Cerebelum_4_5_R	0.08	1.1
Cerebelum_6_R	0.14	1
<b>Total</b>	<b>283.39</b>	<b>/</b>

Table A.2: lesioned white matter tracts for P1 on standard anatomy in the Natbrainlab template [50]

<b>White matter networks</b>	<b>Damage volume in cc</b>	<b>Percentage of damage per network</b>
Cingulum_Left	0.03	0.1
Anterior_Commissure_Right	3.93	74.1
Arcuate_Anterior_Segment_Right	0.98	11.6
Long_Segment_Right	0.05	12.5
Arcuate_Posterior_Segment_Right	2.30	27.5
Cingulum_Right	8.97	25.8
Corpus_Callosum_Right	12.50	27.6
Cortico_Ponto_Cerebellum_Right	0.29	5.7
Cortico_Spinal_Right	11.75	53.3
Fornix_Right	2.59	27.7
Inferior_Longitudinal_Fasciculus_Right	8.07	57.9
Inferior_Occipito_Frontal_Fasciculus_Right	3.91	31.1
Internal_Capsule_Right	6.78	38.8
Optic_Radiations_Right	0.84	23



Table A.3: level, trend, variability and overlap of accuracy (in percentage) in the picture naming task  
(based on Manolov et al. [38])

		(1) Left inhibition	(2) Left facilitation	(3) Right facilitation
Level difference (intervention – BL)	Mean	1.61	2.02	2.96
	Median	0	1.61	2.42
	BL	0.65	-0.13	0.24
Trend	Intervention and follow- up	-0.89	0	0.89
Trend stability (80%-20% formula)	BL	88.9%	75%	55.6%
	Intervention and follow- up	77.8%	83.3%	88.9%

BL: baseline

*Fin de l'article n°5 :*

*“Transcranial Magnetic Stimulation to improve aphasia following a right hemispheric stroke: a single case experimental design”*

Ces trois études évaluant les possibilités d'individualisation de la rTMS retrouvent des résultats hétérogènes. Néanmoins, elles permettent de mettre en avant l'intérêt et l'importance d'une telle approche, afin de mieux comprendre les facteurs à manipuler pour optimiser les paramètres et la cible corticale de la rTMS. Les perspectives et possibilités de développement de ce principe d'individualisation seront discutées dans la partie 5 (discussion générale).

Lorsque la rTMS a induit des changements comportementaux significatifs, nous nous sommes interrogés sur les modifications électrophysiologiques induites par ces stimulations, et la possibilité de mettre en évidence des biomarqueurs d'efficacité de l'intervention.

## **Partie 3. Modifications électrophysiologiques induites par les stimulations magnétiques transcrâniennes**

Cette partie constitue une approche exploratoire des changements EEG/ERPs induits par la rTMS dans une tâche de dénomination d'images auprès de personnes aphasiques post-AVC. L'approche utilisée (i.e., analyses d'amplitude et de topographie) est donc préliminaire et porte uniquement sur les trois personnes ayant reçu une stimulation inhibitrice au niveau du cortex moteur des lèvres (article n°4), étant donné que ce sont les résultats comportementaux les plus significatifs et homogènes.

### **1. Introduction**

Les mécanismes de plasticité neuronale induits par la rTMS sont encore peu explorés, particulièrement en électrophysiologie (pour une revue, voir Arheix-Parras et al., 2023). Les potentiels évoqués reliés (ERP : Event Related Potentials) peuvent être associés à des tâches linguistiques pour identifier les changements induits dans des composantes spécifiques (e.g., P200 dans les tâches de production, N400 en compréhension), ou encore au sein de topographies. Ces changements peuvent également être mis en relation avec des améliorations comportementales (Arheix-Parras et al., 2023). En considérant la production de mots, les modèles psycholinguistiques suggèrent que différents processus de planification prennent place lors de différentes fenêtres temporelles. Par exemple, Indefrey (2011) décrit différentes étapes lors de la dénomination d'images : les processus lexico-sémantiques précoces débutant approximativement à 175-200ms après la présentation de l'image, l'encodage phonologique débutant approximativement après 275ms et se situant avant les processus articulatoires. Basé sur ce modèle, Laganaro et al. (2009) ont montré que le type de trouble chez les personnes aphasiques était relié aux différences ERPs entre personnes aphasique et neurotypique au sein de fenêtres temporelles spécifiques (i.e., changements dans des fenêtres temporelles précoces liés à des erreurs lexico-sémantiques, versus des fenêtres temporelles plus tardives reliés à des erreurs phonologiques en production de mots). Au cours de la revue présentée dans l'article n°2, nous avons relevé trois études analysant les changements ERPs induits par la rTMS auprès de personnes aphasiques post-AVC (Barwood et al., 2011; Barwood, et al., 2012; Chantsoulis et al., 2016), dont deux provenant de la même équipe, et évaluant le même groupe de participants (Barwood et al., 2011; Barwood, et al., 2012). Barwood et al. ont proposé un protocole de rTMS inhibitrice ciblant l'IFG droit et évalué les changements langagiers et ERP induits via une tâche de jugement sémantique de mots écrits/images. Les auteurs retrouvent une augmentation de la négativité de la N400 suite à la

stimulation, allant jusqu'à une normalisation du tracé, associé à une amélioration comportementale (Barwood et al., 2011; Barwood, et al., 2012). Une étude en cas unique auprès d'une personne présentant une aphasie croisée à la suite d'un AVC droit rapporte une réduction de la P200 tendant vers une normalisation du tracé, au cours d'une tâche de go/no go non verbal et suivant l'application d'un protocole de rTMS ciblant à la fois l'hémisphère gauche en basse fréquence et le lobe temporal droit en haute fréquence (pas d'information plus précise concernant les cibles corticales) (Chantsoulis et al., 2016). Cependant, à notre connaissance, aucune étude n'a exploré les effets de la rTMS ciblant le cortex moteur sur les tracés ERP dans une tâche de dénomination d'images. De plus, nous n'avons pas retrouvé d'étude proposant des analyses topographiques des changements induits par la stimulation. En effet, la majorité des études ERPs visant à évaluer les changements induits par une thérapie (médicamenteuse, orthophonique, ou stimulations cérébrales non invasives) n'ont utilisé qu'une analyse de changement d'amplitude basée sur des composantes spécifiques (Arheix-Parras et al., 2023). Cette approche réductrice pourrait ainsi occulter une partie des changements induits par la rTMS.

De plus, en termes méthodologiques, de possibles variations électrophysiologiques hors intervention sont envisageables, même lors de la phase chronique, questionnant la fiabilité de certaines études ne présentant qu'un point de ligne de base et ne disposant pas d'un groupe contrôle (Arheix-Parras et al., 2023).

Prenant en considération ces éléments, nous avons souhaité investiguer les modifications des ERPs induites par la rTMS dans une tâche de dénomination d'images auprès de personnes présentant une aphasie chronique post-AVC, en proposant une analyse d'amplitude et de topographie, et en vérifiant au préalable la stabilité de la ligne de base.

## 2. Matériel et méthode

### 2.1. Participants

Les trois participants ont été victimes d'un AVC hémisphérique gauche (Figure 2) ayant entraîné une aphasie chronique (Tableau 2). L'ensemble des participants présentaient une aphasie fluente légère à modérée avec des troubles d'encodage phonologique au premier plan, se manifestant en dénomination, en répétition et dans le discours (pour plus de détail concernant le profil des participants, voir l'article n°4, partie 2.1).

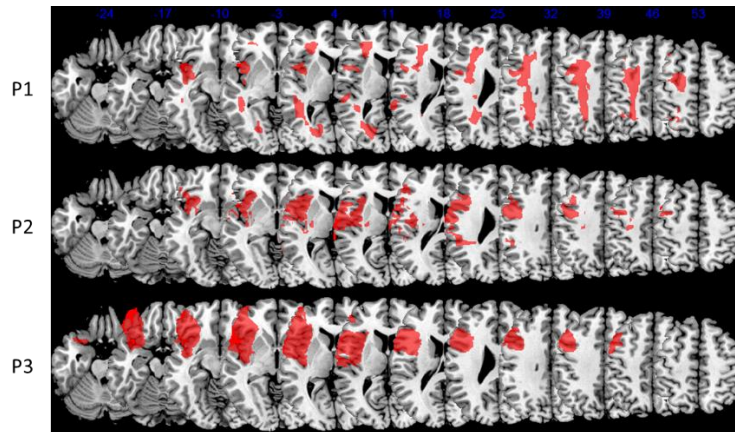


Figure 3 : Lésions hémisphériques gauches des trois participants en rouge

Tableau 2 : Données démographiques et de l'AVC

	Genre	Age	Temps post-AVC (mois)	Type d'AVC
P1	F	37	40	Hémorragique
P2	M	68	55	Ischémique
P3	F	55	7	Ischémique

## 2.2. Plan experimental

Les participants suivis avaient été inclus dans l'étude SCED de l'article n°4. Ils ont donc été suivis sur une durée de six semaines, comprenant une ligne de base, une période d'intervention de deux semaines et une période de suivi pour P1 et P2. La durée de la ligne de base variait selon les participants (i.e., deux, trois ou quatre semaines de ligne de base), en fonction de contraintes SCED (voir article n°4). Tous les participants ont reçu des stimulations rTMS trois fois par semaine pendant deux semaines (6 stimulations au total). Ils ont réalisé un enregistrement EEG par semaine pendant six semaines, selon le plan expérimental de l'article n°4 (i.e., à la fin de chaque semaine de la ligne de base : deux EEG pour P1, trois EEG pour P2, quatre EEG pour P3 ; à la fin de chaque semaine d'intervention : deux EEG pour chaque participant ; à la fin de chaque semaine de follow-up : deux EEG pour P1, un EEG pour P2, pas d'enregistrement pour P3). L'ensemble des enregistrements EEG ont été réalisés au cours d'une tâche de dénomination d'image (D120). Dans un souci d'uniformisation, nous avons fait le choix d'analyser trois enregistrements EEG par participant,

à savoir les deux derniers enregistrements EEG de la ligne de base (E1 et E2) et l'enregistrement EEG réalisé à la fin de la période de rTMS (E3) (Figure 4).

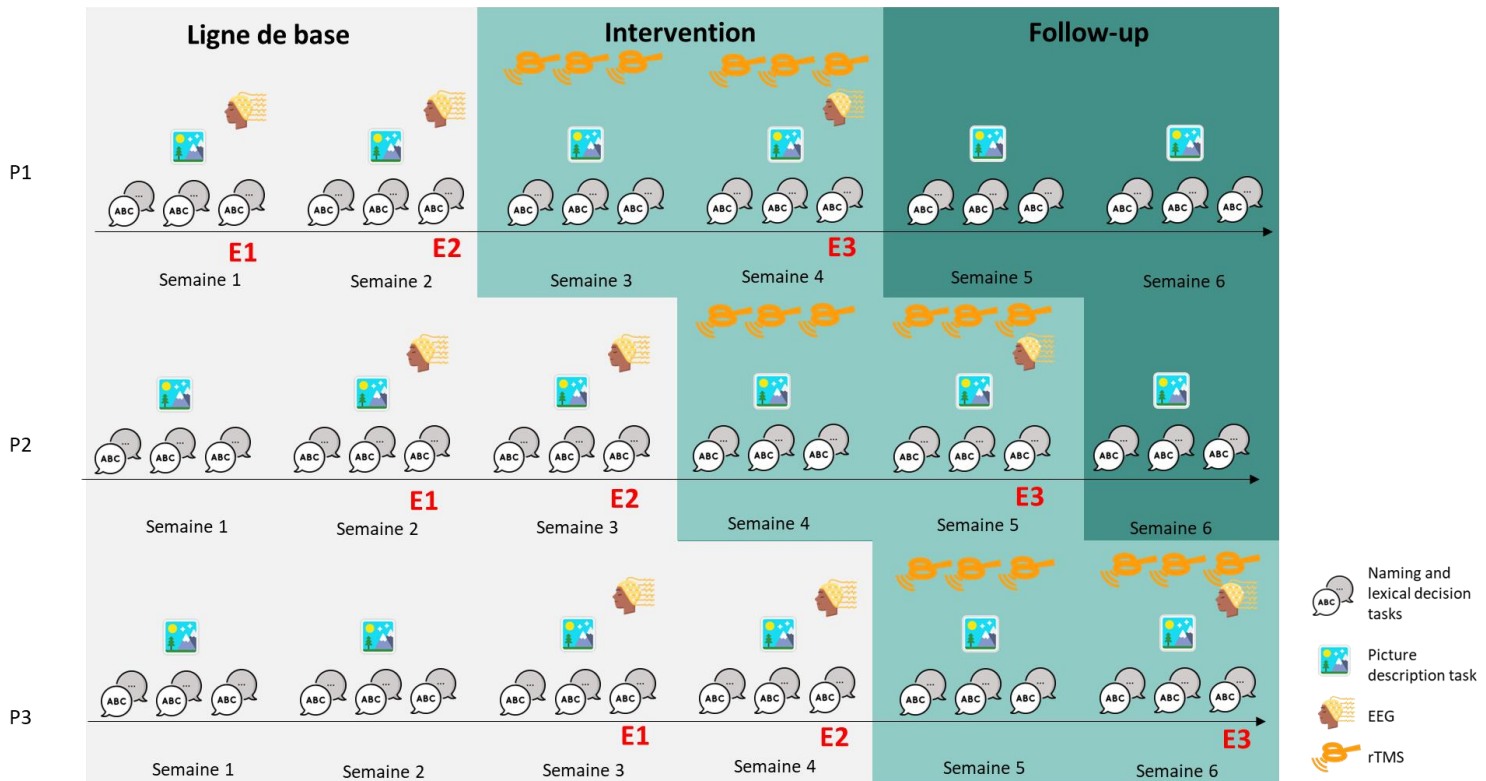


Figure 4 : Plan expérimental

## 2.3. Matériel et procédure

### 2.3.1. Tâche de dénomination d'images

Durant les enregistrements EEG, les participants ont réalisé une tâche de dénomination d'images (D120) contenant 120 dessins (pour plus de détail concernant les items, voir l'article n°4, partie « *Method, Repeated measure* »). Avant l'expérimentation, les participants ont bénéficié d'une familiarisation avec toutes les images et leurs noms correspondants. La structure expérimentale était la suivante : tout d'abord un signe « + » apparaissait à l'écran pour 500ms. Puis, une image apparaissait pour 3000ms. Le participant devait produire le mot correspondant à l'image et la production était enregistrée via un haut-parleur Jabra 510 ®. Chaque stimulus était lancé manuellement par l'expérimentatrice.

### 2.3.2. rTMS

Nous avons appliqué des stimulations magnétiques transcrâniennes en utilisant une bobine en 8 de 75mm (Cool-B65 Butterfly Coil, MagVenture ®) connectée à MagPro X100unit.

L'intervention consistait en trois séances de rTMS par semaine durant deux semaines (6 stimulations au total).

Les participants ont reçu des stimulations inhibitrices thêta burst continue (600 impulsions, fréquence des « bursts » at 5 Hz, « burst » de trois impulsions à 50Hz) visant le cortex moteur des lèvres à droite.

La stimulation a été délivrée à 90% du seuil moteur de repos (en anglais Resting Motor Threshold, RMT). Le RMT a été calculé à partir du muscle orbiculaire des lèvres gauche (Orbicularis Oris) en utilisant l'électromyogramme de surface. Les électrodes d'enregistrement ((Neuroline, Ambu®) étaient placées sur l'OO et l'électrode de référence (Red Dot, 3M) a été placée au-dessus de l'épicondyle latéral de l'humérus. Les signaux ont été échantillonnés à 10kHz, amplifiés (1000 gains), filtrés (20-1000Hz) et stockés pour des analyses hors ligne en utilisant le logiciel LabChart 7.3.7 (ADInstrument). La cartographie de OO et l'évaluation du RMT ont été analysés via des protocoles standards (Rossini et al., 1994). Le hot spot de l'OO, c'est-à-dire, la cible corticale pour la stimulation a été mémorisée en utilisant la neuronavigation avec le logiciel de navigation de TMS (Localite®) basé sur les IRM anatomiques de chaque personne.

### 2.3.3. EEG

Les enregistrements électrophysiologiques ont été réalisés avec un EEG 128 voies (Active-Two Biosemi EEG system, Amsterdam, Netherlands) couvrant l'ensemble du scalp. Le signal a été échantillonné à 512Hz avec un filtre en ligne à 0.16-100Hz. Hors ligne, les ERPs ont été filtrés à 1-30Hz. Tous les essais ont été conservés pour la tâche de dénomination d'images, y compris les essais échoués afin d'obtenir au minimum 40 époques, c'est-à-dire 40 essais. Toutes les pré-analyses ont été réalisées à partir du logiciel Cartool 3.80 (Brunet et al., 2011). Chaque essai a été analysé visuellement pour rejeter les époques contenant des artefacts (i.e., clignements oculaires, mouvements musculaires, ou autres interférences). Un minimum de 48 époques par personne et par session pu être retenu pour les analyses ERPs (moyenne : 51.2 ; écart-type : 3.4). Pour la tâche de dénomination d'images, les analyses ont été réalisées en s'alignant sur l'apparition du stimulus pour une durée de 682ms.

Les électrodes présentant un signal bruité ont été interpolées en utilisant l'interpolation 3D Spline (Perrin et al., 1987). Nous avons recalculé les époques sur la moyenne de référence et appliqué un filtre spatial.

Nous avons ensuite équilibré les époques entre les sessions (E1, E2 et E3), afin d'obtenir le même nombre d'essais par session pour un même participant. Notre critère de sélection pour cet équilibrage s'est basé sur la conservation d'un maximum de stimuli similaires de la tâche de dénomination d'images entre les sessions.

A partir de ces époques équilibrées, nous avons calculé des grandes moyennes par session et par participant.

#### 2.3.4. Statistiques

Nous avons comparé les tracés ERP de la ligne de base (E1 et E2), afin d'en établir la stabilité, puis nous avons comparé le dernier enregistrement de la ligne de base avec l'enregistrement réalisé juste après la dernière stimulation de rTMS (E2 et E3). Toutes les analyses ont été effectuées en intra-participant.

Nous avons exploré les différences d'amplitudes sur toutes les électrodes par le biais d'analyses statistiques TFCE (Threshold Free Cluster Enhancement) réalisées à partir des époques équilibrées de chaque session (nombre de computations = 4000) (pour un détail sur les analyses statistiques, voir Smith & Nichols, 2009).

Concernant les analyses topographiques, des segmentations spatiotemporelles ont été réalisées via Cartool 3.80 (Brunet et al., 2011), à partir des ERPs moyennés et équilibrés. Ces analyses correspondent à la puissance de champ global (en anglais GFP, Global Field Power) des ERPs. Nous avons extrait les topographies demeurant stables sur une période de plus de 30ms. Afin de déterminer des périodes correspondant à des différences significatives au sein des topographies d'une session à l'autre, nous avons calculé des tANOVA, correspondant à l'analyse topographique de la variance, à partir des époques équilibrées grâce au logiciel Ragu (Koenig et al., 2011). De plus, nous avons proposé des analyses statistiques (test non paramétrique de Kruskal-Wallis) via le « fitting » des différences significatives au sein de chaque carte topographique en termes de durée moyenne et de variance globale expliquée (en anglais Global explained variance, Gev) entre les différentes sessions EEG, et correspondant aux fenêtres temporelles de différences signalées par la tANOVA.

### 3. Résultats

Pour rappel, les changements comportementaux induits par la rTMS lors de la tâche de dénomination d'images étaient les suivants :

- Amélioration de la précision lexicale, avec une diminution significative du nombre de paraphrasies phonologiques pour les trois participants ;
- Diminution des temps de réaction pour P2 et P3 lors de la ligne de base, puis stabilisation à partir de la phase d'intervention ; tendance non significative à la diminution des temps de réaction pour P1 après le début de l'intervention.



### 3.1. Stabilité de la ligne de base

Nous avons rencontré un problème d'enregistrement lors de la première session EEG de P1 et n'avons donc pas pu analyser les données pour cette session. Comme nous ne disposons que d'un seul enregistrement EEG durant la ligne de base pour P1, nous ne pouvons pas évaluer la stabilité électrophysiologique de P1 durant cette période.

Pour P2, la comparaison entre E1 et E2 ne montre pas de différence significative, ce qui suggère que la ligne de base est stable en amplitude et en topographie (Figure 5 et 6). En effet, les différences observées sur la Figure 5 (a) sont considérées comme négligeables car ne concernent qu'un groupe de quatre électrodes contigües.

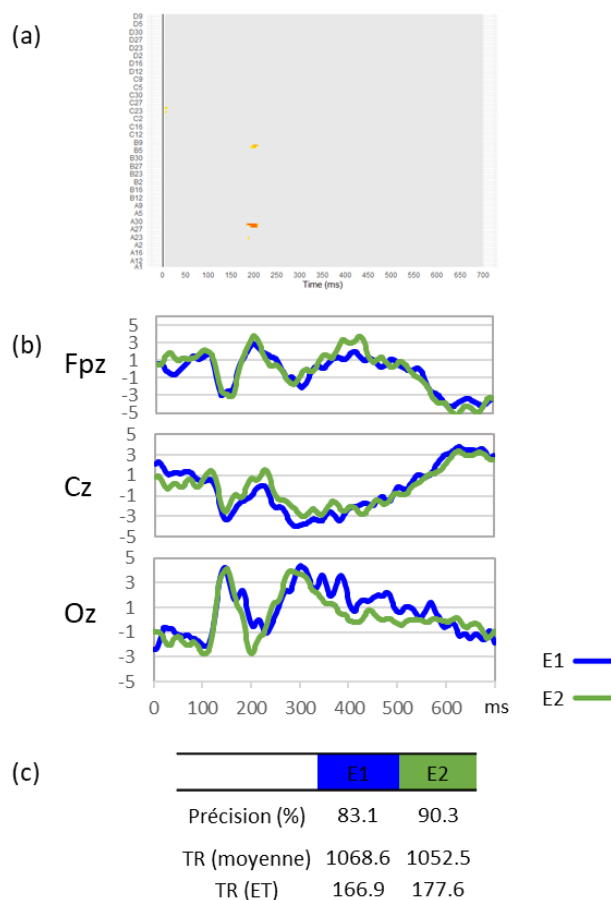
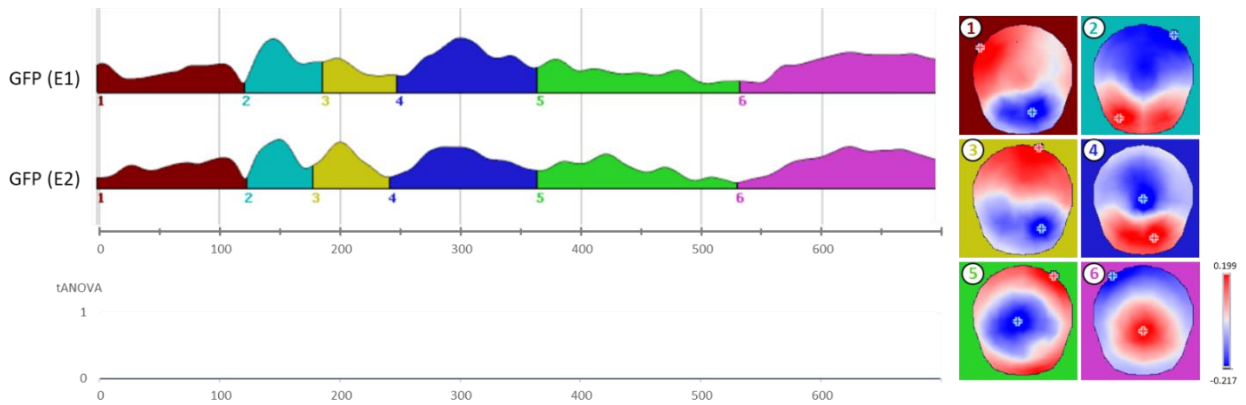


Figure 5 : Comparaison des tracés de la ligne de base (E1 et E2) pour P2 avec (a) les différences significatives d'amplitude à partir du TFCE sur chaque électrode en fonction du temps (orange :  $p < 0.01$ , jaune :  $p < 0.05$ ), (b) la représentation des électrodes Fpz, Cz et Oz, (c) un rappel des scores cliniques observés (précision lexicale et temps de réaction en dénomination orale) / TR : temps de réaction, ET : écart-type



*Figure 6 : (a) Analyses topographiques à partir des grandes moyennes des époques équilibrées et (b) analyses statistiques via la tANOVA lors de la comparaison des deux EEG de ligne de base (E1 et E2) pour P2*

Concernant P3, nous ne retrouvons pas de changement d'amplitude lors de la comparaison des tracés de la ligne de base (E1 et E2). Cependant, nous observons des différences entre les sessions selon la tANOVA entre 10 et 30ms. Ces différences se situent lors de la carte 1 et ne sont pas significatives en termes de Gev ( $p > 0.01$ ). Les tracés électrophysiologiques sont stables (Figure 7 et 8).

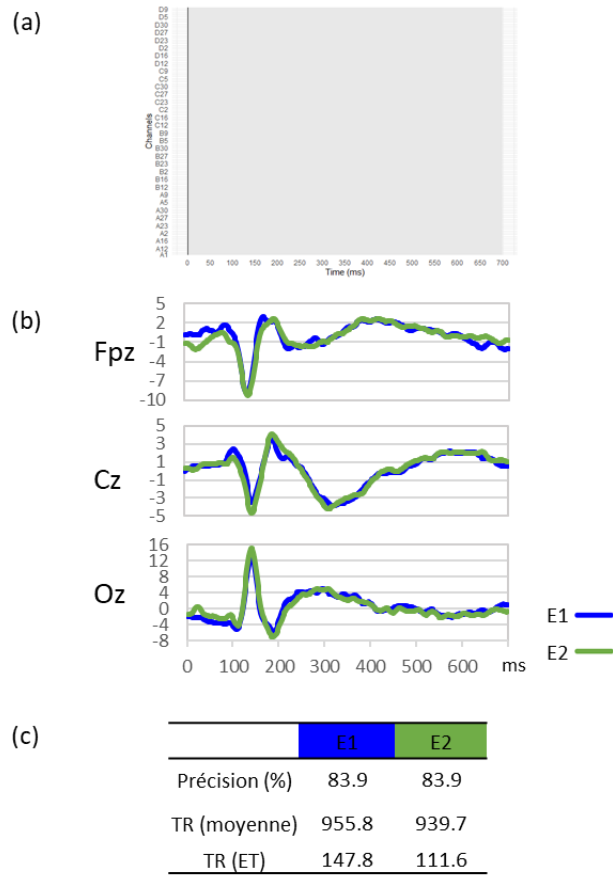


Figure 7 : Comparaison des tracés de la ligne de base (E1 et E2) pour P3 avec (a) les différences significatives d'amplitude à partir du TFCE sur chaque électrode en fonction du temps (orange :  $p < 0.01$ , jaune :  $p < 0.05$ ), (b) la représentation des électrodes Fpz, Cz et Oz, (c) un rappel des scores cliniques observés (précision lexicale et temps de réaction en dénomination orale) / TR : temps de réaction, ET : écart-type

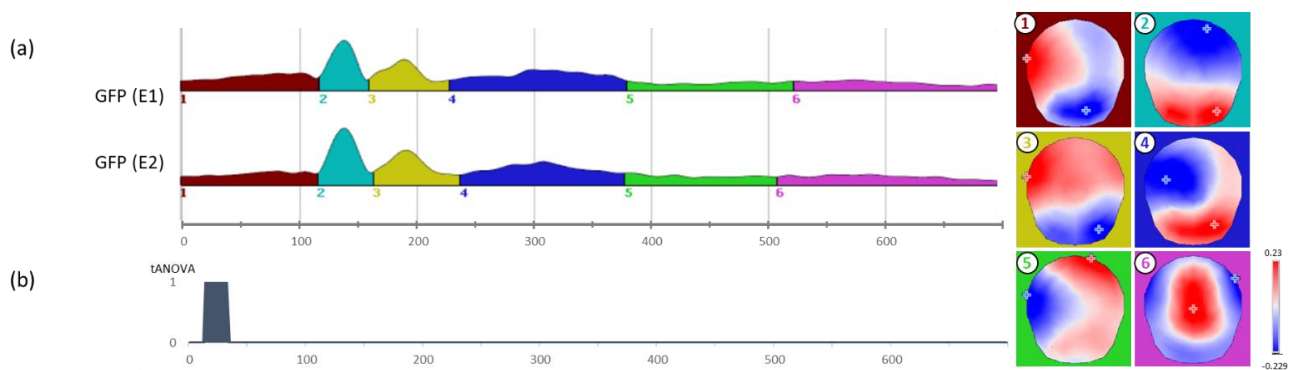


Figure 8 : (a) Analyses topographiques à partir des grandes moyennes des époques équilibrées et (b) analyses statistiques via la tANOVA lors de la comparaison des deux EEG de ligne de base (E1 et E2) pour P3

### 3.2. Changements EEG induits par la rTMS

P1 présente des changements d'amplitude en comparant le dernier enregistrement de la ligne de base (E2) et l'enregistrement effectué immédiatement post-rTMS (E3) (Figure 9). Ces changements sont situés entre 50 et 70ms, puis sur une large fenêtre temporelle débutant à 300ms après la présentation de l'image. Nous retrouvons notamment une augmentation de la positivité sur des électrodes postérieures et de la négativité dans les zones frontales aux alentours de 600ms (Figure 9 (b)).

Lors de l'analyse topographique (Figure 10), nous retrouvons des différences à partir de la tANOVA situées dans les fenêtres temporelles suivantes :

- 40-80ms : correspondant à la carte 1 ; toutefois le « fitting » ne révèle pas de différence significative en termes de durée ( $p > 0.01$ ) et de Gev ( $p > 0.01$ ) entre les conditions (E2 et E3);
- 150-170ms : correspondant aux cartes 2 et 3 ; le « fitting » ne démontre pas de différence significative en termes de durée ( $p > 0.01$ ) et de Gev ( $p > 0.01$ ) pour les deux cartes entre les conditions (E2 et E3);
- 300-330ms : correspondant aux cartes 4 et 5 ; le « fitting » révèle des différences sur la carte 4 en termes de durée ( $p < 0.01$ ) et de Gev ( $p < 0.01$ ), contrairement à la carte 5 qui ne montre pas de différence significative (durée :  $p > 0.01$  ; Gev :  $p > 0.01$ ) entre les conditions (E2 et E3);
- $> 470$ ms et correspondant aux cartes topographiques 6, 7 et 8 ; le « fitting » ne retrouve pas de différence significative pour la carte 6 (Gev :  $p > 0.01$  ; durée moyenne :  $p > 0.01$ ), mais met à jour des différences significatives pour chacune des deux cartes 7 et 8 en termes de durée ( $p < 0.01$ ) et de Gev ( $p < 0.01$ ).

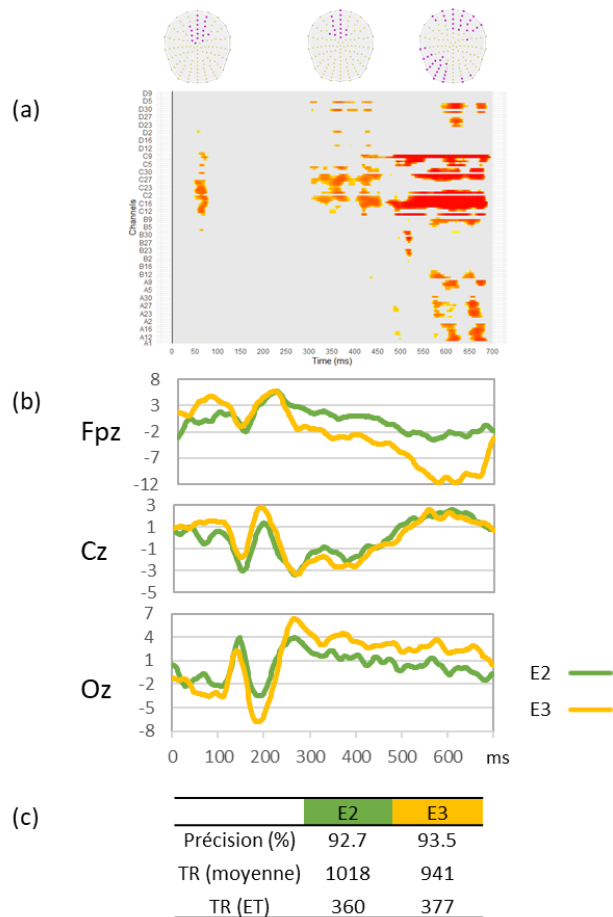


Figure 9 : Comparaison pré-post rTMS (E2 et E3) pour P1 avec (a) les différences significatives d'amplitude à partir du TFCE sur chaque électrode en fonction du temps (orange :  $p < 0.01$ , jaune :  $p < 0.05$ ), (b) la représentation des électrodes Fpz, Cz et Oz, (c) un rappel des scores cliniques observés (précision lexicale et temps de réaction en dénomination orale) / TR : temps de réaction, ET : écart-type

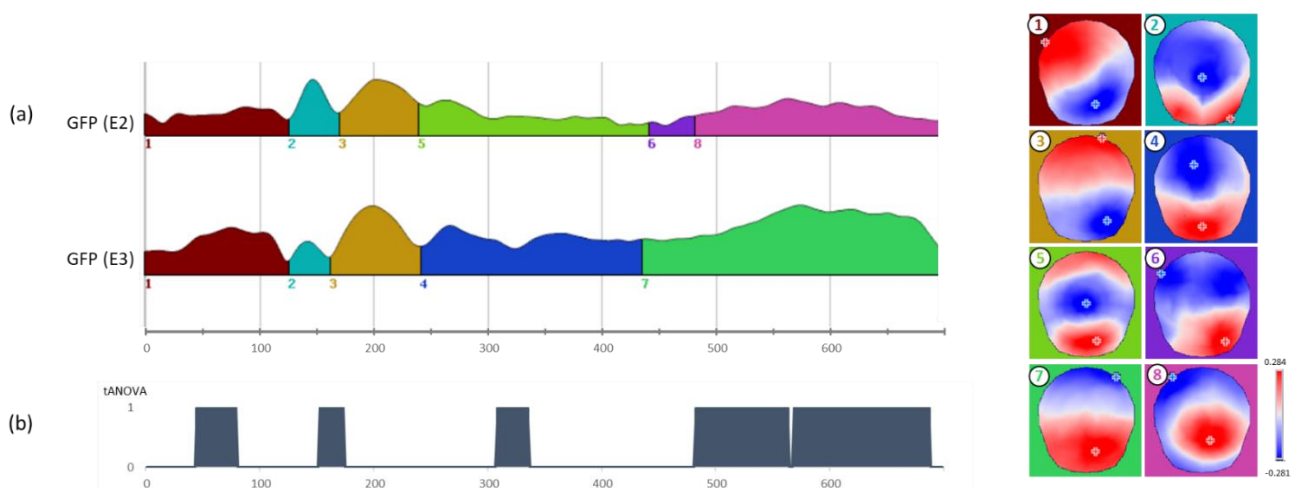


Figure 10 : (a) Analyses topographiques à partir des grandes moyennes des époques équilibrées et (b) analyses statistiques via la tANOVA, comparant les tracés pré-post-rTMS (E2-E3) pour P1

P2 ne présente aucun changement d'amplitude ou de topographie induit par la rTMS en comparant le dernier enregistrement de la ligne de base (E2) à l'enregistrement réalisé après la dernière session de rTMS (E3) (Figures 11 et 12).

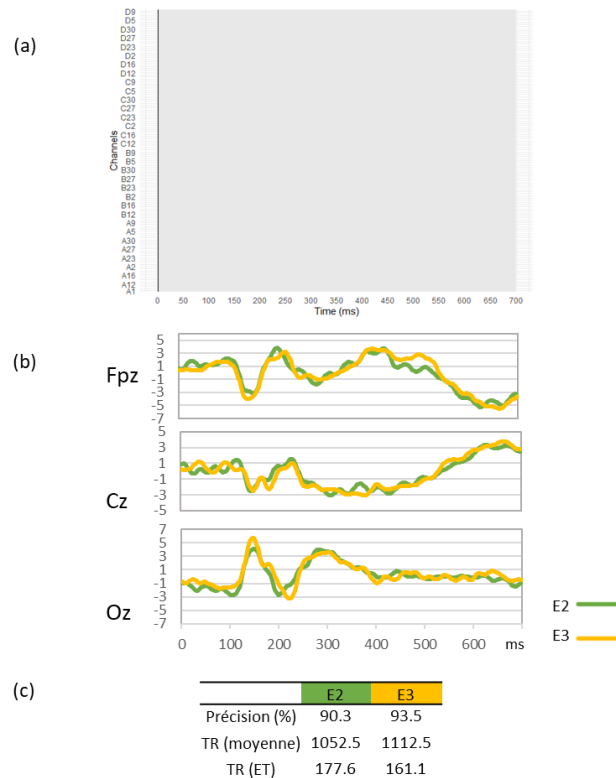


Figure 11 : Comparaison pré-post rTMS (E2 et E3) pour P2 avec (a) les différences significatives d'amplitude à partir du TFCE sur chaque électrode en fonction du temps (orange :  $p < 0.01$ , jaune :  $p < 0.05$ ), (b) la représentation des électrodes Fpz, Cz et Oz, (c) un rappel des scores cliniques observés (précision lexicale et temps de réaction en dénomination orale) / TR : temps de réaction, ET : écart-type

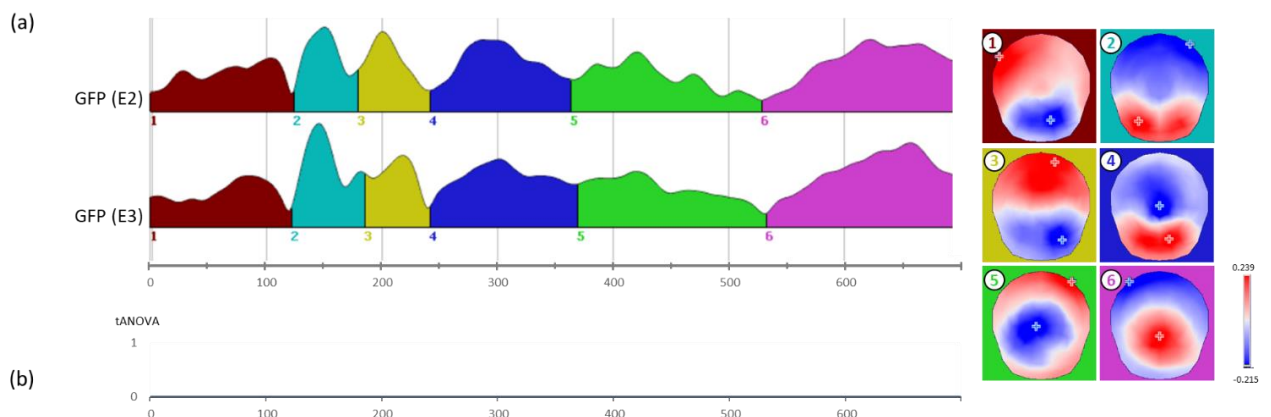


Figure 12 : (a) Analyses topographiques à partir des grandes moyennes des époques équilibrées et (b) analyses statistiques via la tANOVA, comparant les tracés pré-post-rTMS (E2-E3) pour P2

P3 ne présente pas de changement d'amplitude induit par la rTMS (Figure 13). On retrouve cependant un bref changement de topographie sur la tANOVA entre 220 et 240ms situé sur les cartes 3 et 4. Concernant la carte 4, le « fitting » révèle des différences significatives de durée moyenne ( $p < 0.01$ ), dans le sens d'un allongement en post-rTMS, sans différence au niveau de la Gev (comparaison E2 et E3). Aucune différence de Gev ou de durée moyenne n'est retrouvée pour la carte 3 (Figure 14) entre les sessions pré et post-rTMS.

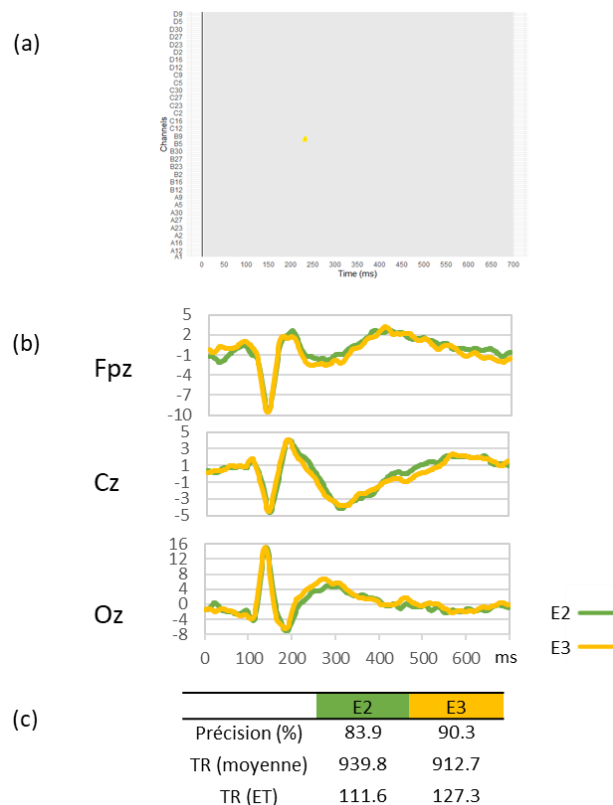


Figure 13 : Comparaison pré-post rTMS (E2 et E3) pour P3 avec (a) les différences significatives d'amplitude à partir du TFCE sur chaque électrode en fonction du temps (orange :  $p < 0.01$ , jaune :  $p < 0.05$ ), (b) la représentation des électrodes Fpz, Cz et Oz, (c) un rappel des scores cliniques observés (précision lexicale et temps de réaction en dénomination orale) / TR : temps de réaction, ET : écart-type

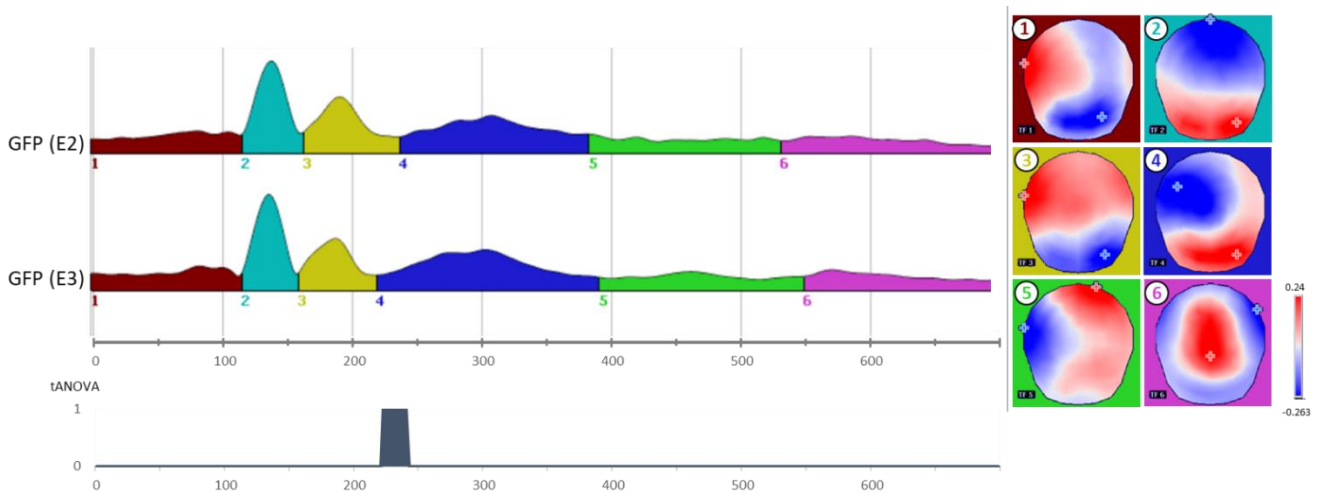


Figure 14 : (a) Analyses topographiques à partir des grandes moyennes des époques équilibrées et (b) analyses statistiques via la tANOVA, comparant les tracés pré-post-rTMS (E2-E3) pour P3

## 4. Discussion

Notre objectif était d'explorer les changements ERP induits par la rTMS au cours d'une tâche de dénomination d'images. Nous avons confirmé la stabilité de la ligne de base pour P2 et P3. En termes de changements d'amplitude induits par la rTMS, nous retrouvons des différences significatives uniquement pour P1 situées entre 50 et 70ms avec une augmentation de la positivité au niveau de l'électrode Fpz, puis entre 300 et 680ms avec une augmentation de la négativité pour l'électrode Fpz et une augmentation de la positivité pour l'électrode Oz. Concernant les analyses topographiques, nous observons via le « fitting » :

- Des différences situées après 300ms pour P1 avec des changements de cartes topographiques, rendant l'origine du signal plus postérieure et symétrique ;
- Des différences situées entre 220 et 240ms pour P3 et correspondant à des changements de durée de cartes, mais aussi d'origine du signal ;
- Aucun changement de topographie pour P2.

### 4.1. Changements électrophysiologiques induits par la rTMS

Tout d'abord, notre hypothèse initiale était que la rTMS entraînerait des changements comportementaux qui se reflèteraient au niveau de changements électrophysiologiques, plus spécifiquement dans des fenêtres cruciales pour les processus langagiers au cours de la tâche de dénomination d'image (i.e., processus précoces autour de 175-200ms après la présentation de l'image pour les aspects lexico-sémantiques, et plus tardifs pour l'encodage phonologique débutant approximativement après 275ms selon les estimations de Indefrey, (2011)). Deux



études longitudinales évaluant les changements ERPs induits par un protocole de rééducation orthophonique en tâche de dénomination d'images avaient retrouvé des changements d'amplitude, de topographie ou de localisation de source dans des fenêtres temporelles spécifiquement liées aux améliorations langagières (Cornelissen et al., 2003; Laganaro et al., 2008). Ainsi, les participants ayant bénéficié d'une amélioration de leurs troubles lexico-sémantiques présentaient des changements durant les 300 premières millisecondes après la présentation de l'image (Laganaro et al., 2008), tandis que les changements plus tardifs, i.e., 250ms post-stimulus, étaient liés aux améliorations des troubles phonologiques (Cornelissen et al., 2003; Laganaro et al., 2008). Au sein de la présente étude, tous les participants inclus présentaient des troubles phonologiques, particulièrement en production (e.g., présence de paraphasies phonologiques en discours spontané et en dénomination, difficultés de répétition de mots et de non-mots). Après l'introduction de la rTMS, ils se sont tous améliorés comportementalement, notamment par une diminution statistiquement significative du nombre de paraphasies phonologiques durant la tâche de dénomination d'images. Or, seul P1 a présenté de francs changements électrophysiologiques comparables aux études de Cornelissen et al. (2003) et Laganaro et al. (2008), avec des changements d'amplitude et de topographie, majoritairement situés dans une fenêtre temporelle tardive, correspondant probablement aux processus phonologiques (Indefrey, 2011). Nous pouvons également noter que les changements perdurant jusqu'à la fin de la fenêtre temporelle d'intérêt (682ms) pour P1 pourraient être en partie liés à la tendance (non-significative) à la diminution de la moyenne des temps de réaction pour ce participant (pré-rTMS : 1018ms  $\pm$ 360 ; post-rTMS : 941ms,  $\pm$ 377). En effet, ces changements pourraient être en lien avec une augmentation de la rapidité de l'encodage phonologique. Concernant P3, les changements de topographies se situaient entre 220-240ms, fenêtre temporelle qui correspondrait plutôt à des processus lexico-sémantiques (Indefrey, 2011). Ces changements ne peuvent ainsi pas être mis en lien avec le profil clinique initial ou la diminution du nombre de paraphasies phonologiques, mais possiblement avec l'amélioration de la précision lexicale du participant au cours de cette tâche. Ceci suggère que les modifications ERPs induites par la rTMS pourraient être moins ciblées sur les processus langagiers déficitaires ou améliorés par la stimulation, mais induire des changements au sein de processus différents.

Comparativement aux changements d'amplitude retrouvés pour P1, Barwood et al., (2011; 2012) retrouvent une augmentation de l'amplitude lors d'une tâche de jugement sémantique de mots écrits/images, après un protocole de rTMS ayant induit des améliorations comportementales. De même, dans différentes tâches d'écoute passive ou active de syllabes, de sons ou de mots, une augmentation de l'amplitude de la P300, de la N200 (Becker & Reinvang, 2007) et de la N400 (Aerts et al., 2015) après rééducation orthophonique, était en lien avec des améliorations cliniques (i.e., amélioration de la compréhension auditive pour

Becker & Reinvang (2007), de la discrimination de phonèmes, de la décision lexicale et de la répétition de pseudomots pour Aerts et al. (2015)). Cependant, ces deux dernières études ont réalisé des comparaisons de personnes aphasiques versus de personnes neurotypiques, contrairement à la présente étude qui n'a proposé que des comparaisons intra-participant. De plus, les changements comportementaux et électrophysiologiques attendus post-rTMS sont moins importants que ceux attendus post-rééducation orthophonique, qui reste le traitement de référence (Brady et al., 2022). Ensuite, si les modifications EEG/ERPs induites par de la rééducation orthophonique peuvent être visibles dès les premières mesures de fin de protocole (Aerts et al., 2015; Becker & Reinvang, 2007), il est envisageable que les effets induits par la rTMS puissent être uniquement visibles à plus long terme. En effet, l'absence de changement d'amplitude et de topographie pour P2 et les changements brefs visibles uniquement en topographie pour P3, malgré des améliorations cliniques pour ces deux participants, peuvent nous questionner sur la possibilité d'un délai nécessaire à l'observation de changements électrophysiologiques induits par les stimulations, et donc d'un décalage clinico-physiologique. Ainsi, Barwood et al. (2011) ne retrouvaient pas de modifications ERPs une semaine après leur protocole, mais des modifications d'amplitude de la N400 deux mois plus tard et jusqu'à un an post-rTMS (Barwood et al., 2011, 2012). Par ailleurs, les améliorations comportementales de la rTMS sur les troubles phasiques post-AVC pourraient également apparaître plusieurs mois après les stimulations selon plusieurs études (Barwood et al., 2013; Martin et al., 2009; Naeser et al., 2010).

#### **4.2. Changements de connectivité fonctionnelle induits par la rTMS**

En parallèle des articles en EEG, quelques études en IRMf se sont centrées sur les liens entre améliorations langagières et changements de connectivité fonctionnelle induits par la rTMS auprès de personnes aphasiques post-AVC. Trois études contrôlées randomisées ont ainsi proposé l'évaluation des différences de connectivité fonctionnelle de repos après un protocole de rTMS inhibitrice (basse fréquence : 1Hz) ciblant l'IFG droit et ayant entraîné des améliorations langagières (Bai et al., 2022; Lee et al., 2022; Lin et al., 2022). D'une part, deux premières études mettent en avant une diminution de la connectivité fonctionnelle au sein de l'hémisphère droit et une augmentation des connexions de l'hémisphère gauche post-rTMS, illustrant ainsi le principe de rééquilibrage de la balance interhémisphérique (Bai et al., 2022; Lin et al., 2022). D'autre part, la troisième étude retrouve une augmentation de certaines connexions au sein de l'hémisphère droit (cortex frontotemporal, insulaire, noyau caudé), mais aussi une diminution de la connectivité du thalamus droit et du cortex pariétal supérieur gauche (Lee et al., 2022). Ainsi, cette absence de consensus parmi les études évaluant les modifications de connectivité fonctionnelle de repos induit par la rTMS pourrait s'expliquer par

une éventuelle non-homogénéité des profils cliniques inclus dans les études citées, mettant à jour des trajectoires de récupérations différentes entre les participants (Stefaniak et al., 2022). Par ailleurs, une étude (Yang et al., 2023) utilisant de la rTMS facilitatrice ciblant le cortex moteur (M1) à gauche auprès de personnes présentant une aphasie, rapporte que les stimulations induisaient une réorganisation de la connectivité de l'hémisphère gauche en IRMf, plus précisément au sein des réseaux sémantiques (réseaux reconstruits à partir des études de Alkadhi et al. (2002) et Binder et al. (2009)), et de zones homologues situées dans l'hémisphère droit (e.g., IFG pars orbitalis gauche et droit, gyrus angulaire gauche et droit, gyrus temporal moyen gauche et droit). Ainsi, ces changements de connectivité fonctionnelle de repos pourraient être mis en lien avec les résultats retrouvés pour un des participants de l'étude présentée (P3). Nous retrouvons pour ce participant de brefs changements topographiques au sein de la fenêtre temporelle qui correspondraient aux processus sémantiques (Indefrey, 2011). Ces éléments soulignent la possibilité que l'utilisation de rTMS ciblant le cortex moteur pourrait également induire des changements au sein des réseaux sémantiques du langage. Cependant, cette hypothèse n'est pas soutenue par les changements langagiers de l'étude présentée, qui retrouvait une amélioration spécifique des troubles phonologiques, ni par ceux de l'étude de Yang et al. (2023), qui ne retrouvait pas de corrélation entre changements langagiers et d'IRMf.

### **4.3. Perspectives**

L'approche présentée ci-dessus consistait à évaluer les changements électrophysiologiques induits par la rTMS en termes d'amplitude et de topographie. Ces méthodes d'analyse n'ont pas permis de mettre en évidence des biomarqueurs d'efficacité du traitement qui soient stables entre les trois participants inclus, et ce malgré la proximité de leur profil clinique et les progrès similaires comportementaux induits. Cependant, les analyses n'ont porté que sur trois des dix participants inclus dans cette thèse.

Une perspective d'analyses complémentaires pourrait consister à comparer les tracés ERPs des participants inclus à ceux de personnes neurotypiques, afin d'observer si les données électrophysiologiques des participants ont tendance à se rapprocher du fonctionnement typique ou de s'en éloigner au fil de l'intervention (Laganaro et al., 2008, 2011).

De plus, une approche ERP en temps-fréquence pourrait permettre de détecter des changements de rythme d'ondes non reliés à la tâche (Im, 2018). Ainsi, Dammekens et al., (2014) retrouvent une augmentation des rythmes d'ondes après application d'un protocole de rTMS et Shah-Basak et al., (2020) mettent en évidence une diminution des ondes lentes après un protocole tDCS, ces changements étant tous deux liés à des améliorations langagières des personnes aphasiques incluses. Aussi pouvons-nous faire l'hypothèse que la

rTMS induirait des changements plus globaux au niveau des signaux électrophysiologiques, pouvant être explorés via ce type d'analyse.

#### **4.4. Limites**

Cette étude portant sur les changements électrophysiologiques induits par la rTMS chez trois personnes avec une aphasie comporte plusieurs limites. Tout d'abord, un problème d'enregistrement lors du premier EEG de P1 ne nous a pas permis d'établir la stabilité de la ligne de base dans son cas. Nous ne pouvons ainsi pas conclure avec certitude sur l'origine des changements ERPs retrouvés, qui pourraient également être le reflet d'une instabilité électrophysiologique possible à la phase chronique. De plus, les explorations EEG ont été réalisées en parallèle d'un protocole SCED évaluant l'efficacité de la rTMS au niveau langagier/comportemental. Par conséquent, les participants de l'étude n'ont pas tous reçu le même nombre de présentations de la tâche de dénomination D120. En outre, cette tâche était présentée de très nombreuses fois, en accord avec les critères du SCED, pouvant induire un effet d'apprentissage, voire un effet de prédiction des images après plusieurs sessions, pouvant impacter les tracés EEG. Ensuite, l'ajout d'une mesure EEG complémentaire à distance du protocole, comme dans l'étude de Barwood et al. (2012), aurait peut-être pu mettre en évidence des résultats ERPs plus homogènes entre les participants. Enfin, une limite plus générale à l'analyse et à l'interprétation des études ERPs concerne le fait que nous ne disposons pas, à notre connaissance, de lignes directrices internationales et consensuelles concernant les paramètres méthodologiques choisis (e.g., paramètres de filtre hors-ligne, nombre minimum d'époques pour les grandes moyennes, temps minimum pour une carte topographique, choix du nombre de cartes topographiques), et ce contrairement aux études en IRMf (e.g., Meinzer et al., 2013). Même si la méthodologie a progressé, ces divers paramètres peuvent amener à des changements dans les résultats, et peuvent influencer de manière non négligeable leur interprétation.

#### **5. Conclusion**

Nous avons mis en évidence des changements électrophysiologiques induits par la rTMS auprès de deux sur trois participants inclus. Ces changements ne concernaient pas la même fenêtre temporelle d'intérêt pour ces deux participants, soulignant la possibilité que la rTMS ait impacté des processus langagiers différents (i.e., fenêtre temporelle précoce qui correspondraient aux processus sémantiques ou fenêtre temporelle tardive correspondant aux processus phonologiques), malgré des améliorations langagières similaires (i.e., diminution

spécifique du nombre de paraphasies phonologiques). Ainsi, les changements électrophysiologiques, mais également de connectivité fonctionnelle en IRMf, induits par la rTMS sont encore mal compris et toujours assez peu explorés. De nouvelles études sont nécessaires dans ces deux domaines afin de mieux comprendre et maîtriser les changements induits par la rTMS sur la plasticité cérébrale.

## **Partie 4. Discussion générale**

### **1. Commentaire critique de principes utilisés en rTMS**

Au cours de ce travail de thèse, nous avons mis en évidence plusieurs limites à des principes largement utilisés dans la majorité des études proposant des protocoles de rTMS dans le cadre de l'aphasie post-AVC. Nous soulignons ici l'importance de comprendre les mécanismes de ces principes, souvent simplement appliqués sur le modèle d'études précédentes.

#### **1.1. La balance inter-hémisphérique**

Le questionnement à l'origine de l'article n°3 constituait une remise en question de la théorie de la balance interhémisphérique, ou compétition interhémisphérique, dont le principe a été développé précédemment (partie 1, section 1.2.3). Comme évoqué dans les articles n°3 et n°5, nos résultats suggèrent que ce principe puisse être discuté, notamment dans le cadre de troubles phasiques sévères, puisque certains participants ne semblaient pas tirer bénéfice de l'inhibition de l'hémisphère préservé. Dans ce contexte, cette théorie semble apporter une réponse très binaire dans une réalité bien plus complexe quant au rôle de l'hémisphère indemne dans le champ de la récupération de l'aphasie post-AVC (Hope et al., 2017).

Ce principe d'inhibition transcallosale est issu d'études à propos du cortex moteur, et a été généralisé aux fonctions cognitives, parallèle de plus en plus remis en question par la littérature scientifique (Carson, 2020; Gerges et al., 2022; Siebner et al., 2022).

Nous postulons ici que l'application stricte du principe de balance interhémisphérique dans le champ des NIBS pourrait induire une inefficacité du traitement pour certaines personnes, voire même entraîner des effets négatifs sur les fonctions langagières dans certains cas.

#### **1.2. Le choix de la cible corticale**

Nous avons mis en avant au cours de la revue réalisée à propos de la rTMS dans l'aphasie post-AVC (article n°1), que la très grande majorité des études incluses choisissaient de cibler l'IFG (i.e., Broca à gauche ou son homologue à droite), afin d'améliorer les compétences langagières des personnes aphasiques. Or, les études scientifiques s'accordent sur le fait que l'organisation des réseaux du langage est complexe, et ne se centre pas sur une seule zone (Duffau et al., 2014). L'application de la rTMS quasi exclusivement sur cette zone semble découler des anciens modèles localisationnistes (Finger, 2009), et ne pas suivre l'évolution

des modèles connexionnistes plus récents (Duffau et al., 2014). De plus, le critère de jugement de l'efficacité de la rTMS majoritairement utilisé dans les études est la dénomination d'images (Arheix-Parras et al., 2021). Or, par le biais d'études mettant en relation les lésions et les symptômes, une revue systématique et méta-analyse a mis en évidence que l'IFG gauche ne faisait pas partie des clusters en lien avec les difficultés de dénomination chez des personnes aphasiques post-AVC (Piai & Eikelboom, 2023). L'étude présentée dans l'article n°4, qui a choisi de cibler le cortex moteur des lèvres dans le cadre de troubles phonologiques post-AVC, a mis en avant la possibilité et la pertinence de choisir d'autres cibles corticales, plus en lien avec les symptômes cliniques des personnes aphasiques, et prenant compte l'organisation en réseaux du langage. Ceci est en accord avec l'étude présentée par Stefaniak et al. (2022) qui recommande une individualisation de la cible corticale pour l'utilisation des NIBS. Les auteurs évoquent la possibilité d'une inefficacité des NIBS, voire l'apparition d'effets négatifs, en utilisant la même cible corticale pour toutes les personnes aphasiques, quel que soit leur type de troubles langagiers (Stefaniak et al., 2022). D'autres méthodes telles que l'analyse des dysconnexions (« disconnectome ») pourraient être pertinentes dans ce choix de la cible corticale de la rTMS (Talozzi et al., 2023).

### **1.3. Potentialisation à long terme : inhibition ou facilitation**

Le dernier principe remis en question au cours de cette thèse constitue les paramètres de stimulation et les effets induits, i.e., inhibition ou facilitation des zones corticales ciblées. Au cours de la revue de rTMS réalisée, nous avons questionné ces paramètres de stimulation suite à la lecture de l'étude de Hu et al. (2018). Tout comme dans l'essai clinique de Hu et al., (2018), l'étude n°3 a mis en évidence la possibilité d'induire des effets comportementaux similaires par l'utilisation de stimulations supposées antagonistes, inhibitrices et facilitatrices, ciblant la même zone corticale. Ceci nous interroge donc sur les paramètres que nous utilisons pour la rTMS dans le cadre de troubles cognitifs post-AVC. Ces paramètres sont encore une fois issus d'études sur le cortex moteur (Berardelli et al., 1998; Chen et al., 1997; Huang et al., 2005; Quartarone et al., 2006), et nous pouvons ainsi questionner la validité de cette transposition, notamment de par le caractère unique de l'organisation du cortex moteur dont les connexions sont basées sur les neurones pyramidaux (Siebner et al., 2022).

De plus, l'utilisation de rTMS inhibitrice ciblant une zone cérébrale n'induit pas nécessairement l'inhibition des zones interconnectées au sein du même hémisphère. Ainsi, après application d'un protocole de rTMS inhibitrice visant la Pars Triangularis de l'IFG droit, Lee et al. (2022) retrouvent à la fois une augmentation de la connectivité au sein de zones de

l'hémisphère droit (cortex fronto-temporal, cortex insulaire, noyau caudé), ainsi qu'une diminution de la connectivité avec le thalamus droit et le cortex pariétal supérieur gauche.

Ces trois principes ont ainsi été remis en question à travers les études présentées. Celles-ci ont démontré la possibilité et la pertinence d'individualiser la cible corticale et les paramètres de la rTMS en fonction du profil clinique, de l'organisation pré-morbide du langage et de la localisation lésionnelle des participants.

## 2. L'individualisation de la rTMS dans l'aphasie post-AVC

### 2.1. Application en recherche

Les trois études SCED présentées ont évalué la possibilité et la pertinence de l'individualisation de la rTMS en fonction du profil clinique de la personne aphasique et/ou de la localisation lésionnelle (i.e., troubles phasiques sévères pour l'article n°3, troubles phonologiques pour l'article n°4, troubles phasiques sévères dans le cadre d'une lésion droite pour l'article n°5). Les résultats de ces études sont hétérogènes.

En effet, l'utilisation de l'individualisation lorsqu'elle se base sur un trouble langagier spécifique, tels que les troubles phonologiques (article n°4), a démontré des résultats probants. Au sein de cette étude, nous avons utilisé une stimulation inhibitrice ciblant le cortex moteur des lèvres de l'hémisphère droit. Nos résultats ont démontré une amélioration de la précision lexicale en tâche de dénomination d'images, notamment par la diminution du nombre de paraphasies phonologiques, pour les trois participants inclus. Afin de soutenir l'intérêt d'une telle approche et son aspect spécifique, il serait intéressant de développer une étude comparant les améliorations langagières induites par la rTMS inhibitrice visant le cortex moteur des lèvres à droite versus l'IFG droit, cible utilisée dans la majorité des études en rTMS pour l'aphasie post-AVC (Arheix-Parras et al., 2021). Ceci permettrait d'objectiver si la cible idéale permettant de moduler les réseaux phonologiques est nécessairement l'homologue de l'aire de Broca.

Par ailleurs, si ce principe d'individualisation a démontré un effet pertinent pour l'étude suscitée, nous avons également mis en avant les limites d'une telle approche lors des études des articles n°3 et n°5, voire une limite des possibilités d'effets bénéfiques de la rTMS pour des personnes présentant des troubles langagiers sévères. L'étude n°3 a comparé l'utilisation de la rTMS inhibitrice versus facilitatrice ciblant l'IFG droit auprès de personnes aphasiques



présentant un profil clinique sévère. Notre hypothèse était que les personnes aphasiques sévères pourraient davantage tirer bénéfice d'une stimulation facilitatrice plutôt qu'inhibitrice de l'hémisphère droit dans le cadre de troubles phasiques sévères, pouvant résulter d'une lésion large ou située dans des zones cruciales pour les réseaux langagiers (Price, 2010; Watila & Balarabe, 2015). Pour cette étude, notre critère clinique d'individualisation s'est donc essentiellement basé sur la sévérité de l'aphasie. Dans ce cadre, nous avons inclus des participants présentant des troubles langagiers sévères mais divers (e.g., aphasies fluente ou non fluente, présence de stéréotypie, jargon), issus de lésions cérébrales très hétérogènes (aire variant de 25.65 à 332.25cm<sup>3</sup>, incluant l'IFG pour cinq personnes sur six, mais en proportion très variable (AAL template, Tzourio-Mazoyer et al., 2002), pour plus de détail, voir le « Supplementary material » de l'article n°3). Les résultats obtenus ont été très hétérogènes : amélioration ou régression langagière pour les deux types de stimulation, amélioration pour un type de stimulation uniquement, aucun changement clinique pour les deux types de stimulation.

Avant de questionner le principe d'individualisation de la rTMS, déjà défendu dans la littérature (Stefaniak et al., 2022), nous pourrions émettre une critique concernant le critère de sélection des participants, qui a permis l'inclusion de personnes aphasiques aux profils langagier et lésionnel divers. Ainsi, les trajectoires de récupération de ces personnes pourraient être différentes, expliquant l'hétérogénéité de nos résultats (Stefaniak et al., 2022). Comme discuté à la fin de l'article n°3, il pourrait être pertinent de choisir des critères langagiers plus spécifiques pour de futures études investiguant l'individualisation de la rTMS ou utiliser des données issues de l'imagerie. En effet, l'utilisation du « disconnectome » (Talozzi et al., 2023) pourrait permettre d'avoir une meilleure idée de la trajectoire de récupération attendue, et utiliser cette prédiction pour le choix de la cible corticale de stimulation. D'autres méthodes telles que l'IRMf ont déjà été utilisées afin de choisir la cible corticale la plus pertinente en fonction du recrutement pré-stimulation de l'hémisphère droit ou gauche durant une tâche de répétition de mots (Hara et al., 2015).

Enfin, nous proposons pour de futures études l'utilisation d'une combinaison de facteurs afin de déterminer la meilleure cible corticale et les paramètres de stimulation à appliquer pour les personnes souffrant d'une aphasie post-AVC. Cette perspective de recherche sera développée dans la section 4.1 de cette discussion.

## **2.2. Perspectives cliniques**

Comme évoqué précédemment, la Haute Autorité de Santé a récemment recommandé la rTMS comme niveau de preuve A pour la prise en charge de l'aphasie post-AVC, au même

titre que la rééducation orthophonique intensive (HAS, 2022). La France devient alors, à notre connaissance, le premier pays à recommander ces stimulations cérébrales non invasives en pratique clinique courante pour la récupération de l'aphasie post-AVC ; les autres pays ou associations ne faisant pas mention des NIBS, ou considérant le niveau de preuve d'efficacité insuffisant (Organisation Mondiale de la santé, American Stroke Association, Aphasie Suisse, Brésil, Royaume-Uni et Irlande) (Intercollegiate Stroke Working Party, 2023; Mead et al., 2023; Minelli et al., 2022; Winstein et al., 2016). Bien que ne disposant pas encore d'une cotation en termes d'actes médicaux, cette validation ouvre de nouvelles perspectives cliniques pour le traitement des personnes présentant une aphasie post-AVC, notamment au sein des centres de rééducation et hôpitaux disposant de ce matériel et de personnel formé à cet outil.

Cette validation fait suite à un consensus de la littérature (issu de revues systématiques et méta-analyses, voir Arheix-Parras et al., 2021) démontrant pour la grande majorité des études, une efficacité de la rTMS inhibitrice visant l'IFG droit dans l'aphasie post-AVC, aux phases subaiguë et chronique de l'atteinte. Le seul point de nuance apporté par quelques études était une petite taille d'effet, voire dans certains cas une possible inefficacité de ce traitement. En effet, dans l'ensemble des études incluses dans la revue réalisée (Arheix-Parras et al., 2021), seule une étude de cas (n=2) et un abstract de congrès scientifique font mention de la possibilité d'effets négatifs induits par la rTMS (Georgiou et al., 2019; Heiss et al., 2007), et ce comparativement aux 23 essais cliniques contrôlés randomisés incluant 526 personnes aphasiques au total.

Ainsi, les résultats ambivalents des études présentées dans cette thèse nous questionnent sur un possible biais de publication d'études retrouvant un effet négatif de la rTMS (i.e., études négatives non publiées, biais d'inclusion de mêmes groupes de personnes dans des études différentes augmentant artificiellement le nombre d'études/de personnes). Nous nous interrogeons d'autant plus concernant l'utilisation de ces stimulations en pratique clinique courante, et plus particulièrement pour les patients présentant une aphasie sévère.

Si l'inclusion de la rTMS comme moyen thérapeutique clinique de récupération de l'aphasie post-AVC constitue une avancée et une grande opportunité pour nos patients, il semble important de recommander que son utilisation soit réalisée en suivant une démarche rigoureuse EBP (Robey et al., 2004). L'inclusion d'une personne dans un protocole clinique de récupération de l'aphasie devra fonder son approche à partir de données issues de la littérature (i.e., choix de la cible corticale et des paramètres de stimulation), liées à l'expertise du praticien (e.g., maîtrise des contre-indications et gestion des possibles effets secondaires). La personne aphasique devra être informé des effets bénéfiques attendus, mais également du fait que ces stimulations ne sont pas toujours efficaces. Le point clef de cette utilisation en pratique courante sera d'utiliser des critères d'évaluation clinique fiables (i.e., mise en place de ligne de base comme lors de l'évaluation des protocoles de rééducation orthophonique).

Des précautions seront d'autant plus importantes à prendre en compte lors de l'inclusion d'une personne présentant une aphasie sévère (e.g. comme les patients inclus dans l'article n°3), ou un profil atypique (e.g., comme la personne incluse dans l'article n°5).

L'arrêt des stimulations devra être décidé en cas de non progrès à l'issue d'une première phase d'évaluation clinique, en tenant compte du possible délai entre la stimulation et les effets cliniques induits (e.g., en proposant une évaluation à la fin du protocole mais aussi après un délai d'un mois post-stimulation) (Barwood et al., 2013).

### 3. Biomarqueurs EEG et rTMS

L'utilisation de biomarqueurs électroencéphalographiques dans le cadre de la rTMS pour le traitement de l'aphasie post-AVC pourrait à la fois permettre de déterminer l'efficacité du traitement et de proposer une intervention de TMS en temps réel. Ces éléments pourraient être réalisés à partir des données récoltées au cours de cette thèse, en proposant d'autres méthodes d'analyse.

Par ailleurs, la mise en évidence de tels biomarqueurs en pré-stimulation pourrait éventuellement permettre de guider le choix de la cible corticale pour la rTMS, perspective développée dans la partie 4.1.

#### 3.1. Biomarqueur d'efficacité de la rTMS

L'objectif principal de l'exploration EEG réalisée au cours de cette thèse était d'observer les changements EEG/ERPs induits par la rTMS, voire de mettre en évidence des biomarqueurs d'efficacité de l'intervention. En effet, au cours de la revue réalisée dans l'article n°2, nous avons retrouvé des biomarqueurs, notamment ERP, liés à l'efficacité du traitement, et donc à l'amélioration clinique (Arheix-Parras et al., 2023).

Les investigations menées dans la partie 3 ne nous ont pas encore permis de trouver un biomarqueur fiable d'efficacité du traitement par rTMS. Cependant, nous pensons que les pistes de recherche proposées dans cette partie pourraient permettre de retrouver des biomarqueurs d'efficacité, notamment en ajoutant des mesures de suivi plus à distance des protocoles de rTMS comme évoqué dans les limites de la partie 3 (*Modifications électrophysiologiques induites par les stimulations magnétiques transcrâniennes*).

A partir de la mesure de la connectivité pré-stimulation, il serait possible de mettre en évidence des biomarqueurs d'efficacité durant la ligne de base, pouvant permettre de prédire si le participant inclus sera un bon ou un mauvais répondeur au traitement par rTMS (Nicolo et al., 2016). Ainsi, plusieurs études mettent en évidence l'intérêt de mesures de repos (en anglais,

« resting state ») en EEG ou en MEG pré-stimulation pour évaluer les changements induits par les stimulations cérébrales non invasives auprès de sujets neurotypiques (Nicolo et al., 2016), mais également de patients aphasiques (Shah-Basak et al., 2020). Considérant les données récoltées dans cette thèse, nous ne disposons pas de mesure EEG de repos, mais pourrions reconsidérer l'analyse de nos données en proposant une approche en temps-fréquence, permettant de mettre à jour des changements ERP plus globaux et non reliés à la tâche (Im, 2018).

Par ailleurs, ces biomarqueurs d'efficacité pourraient être pertinent à rechercher auprès de participants présentant des aphasies sévères, et pour lesquels le critère de jugement langagier d'efficacité ne permet pas toujours de mettre en évidence les changements opérés, bien que ressentis sur le plan clinique. Par exemple, au cours de l'article n°3, nous nous sommes ainsi confrontés à cette difficulté : nous observons des changements cliniques (i.e., apparition de productions automatiques) pour une personne aphasique ne produisant initialement qu'une suite de syllabes uniques et stéréotypées, ceci ne pouvant pas être mis en évidence de manière fiable et objective.

### **3.2. Guide pour la TMS en temps réel**

Une autre perspective issue de ce travail pourrait être l'analyse des tracés EEG permettant de guider les stimulations. En effet, la mise en évidence de biomarqueurs en EEG lors de la production de mots en fonction de la réponse (e.g., réponses correctes, paraphasies phonologiques, paraphasies sémantiques, non-réponse, persévération) pourrait permettre de guider la stimulation. Singh et al., (2018) ont ainsi mis en évidence auprès de deux personnes aphasiques des différences ERPs entre les réponses correctes et incorrectes produites en tâche de dénomination d'image (i.e., cartes topographiques et localisation de source).

En réalisant le même type d'analyses intra-patient, nous souhaiterions mettre en évidence ces différences d'ERPs entre production erronée et correcte chez un participant issu de cette thèse, en réanalysant les différents enregistrements de la ligne de base et en triant les époques en fonction de la précision lexicale.

Nous pourrions ensuite proposer une approche TMS/EEG en temps réel (Hernandez-Pavon et al., 2023) permettant de lancer une stimulation ou un feedback à des fins d'auto-entraînement (priming, entraînement, etc.) lorsque le biomarqueur de réponse incorrecte est repéré (e.g., envoi d'une stimulation lors de la production d'un item incorrect).

## 4. Perspectives de recherche

Plusieurs perspectives de recherche sont proposées, répondant à différents objectifs : poursuivre et développer l'individualisation de la rTMS afin d'améliorer les effets induits sur le langage, quel que soit le profil du participant inclus (section 4.1) ; proposer une approche individualisée en tDCS pouvant éventuellement permettre de mieux maîtriser les changements induits (section 4.2); apporter une nouvelle piste de recherche par l'utilisation des stimulations transcrâniennes à courant alternatif, approche innovante très peu développée dans le domaine de l'aphasie post-AVC (section 4.3).

### 4.1. Une combinaison de facteurs

L'idée d'une approche plus individualisée pour l'utilisation de la rTMS dans le champ de l'aphasie post-AVC est en accord avec les recommandations concernant la rééducation orthophonique des troubles du langage post-AVC. En effet, il est recommandé d'apporter une approche EBP pour le traitement des troubles phasiques post-AVC, qui par définition sera centrée sur le patient et ciblée sur les troubles spécifiques dont il souffre (Robey et al., 2004). Ainsi, il est recommandé un diagnostic précis de ses troubles mettant en évidence les fonctions atteintes et les mécanismes explicatifs des troubles, à la lumière des modèles neuropsychologiques du langage dont nous disposons (e.g., la batterie d'évaluation des troubles lexicaux (Tran & Godefroy, 2011) basée sur le modèle de Hillis & Caramazza (1991)). Après ce bilan exhaustif, l'orthophoniste fixera des objectifs de travail en fonction des possibilités et des besoins du patient, en utilisant les outils à sa disposition, dans le meilleur des cas par le biais de thérapies validées scientifiquement (e.g., rééducation de l'anomie par l'approche Semantic Feature Analysis (Quique et al., 2019)).

Nous avons donc appliqué cette approche au traitement par rTMS et nous proposons de l'améliorer en utilisant une combinaison de facteurs précis (i.e., personnels, cliniques, IRM et EEG), permettant de choisir les paramètres et la cible corticale optimaux pour chaque personne présentant une aphasie sur une base individuelle (Figure 15). Nous proposons ici une perspective de recherche permettant de poursuivre la même dynamique que ce travail déjà engagé.

Tout d'abord, il semble important de prendre en compte les différents facteurs personnels qui pourraient influencer sur l'organisation prémorbide du langage (Figure 15, encadré 1). Comme illustré dans l'article n°5, la latéralité du langage est un facteur important à prendre en compte lors de l'inclusion du participant dans un protocole de rTMS. En effet, parmi les personnes gauchères, environ 10% auront une latéralisation langagière à droite (en miroir des personnes

présentant une latéralisation plus typique à gauche), et 10% auront une distribution bilatérale du langage (Mazoyer et al., 2014; Pujol et al., 1999; Szaflarski et al., 2018). D'autres facteurs tels que la langue première pourraient également influencer sur l'organisation prémorbide du langage. Par exemple, en comparant deux langues très différentes que sont l'arabe et l'allemand, une étude récente a mis en évidence que l'organisation cérébrale de l'allemand nécessiterait des connexions intra-hémisphériques plus importantes que l'arabe, qui au contraire demanderait des connexions interhémisphériques plus fortes (Wei et al., 2023). Ainsi, la notion de langue première, notamment dans le cadre de langue très différentes telles que présentées, mais également la présence d'un bilinguisme (Dupuis & Guinel, 2022), pourraient constituer des facteurs importants à intégrer dans le choix de la meilleure approche en rTMS

Ensuite, les aspects cliniques du trouble (Figure 15, encadré 2), pouvant prédire les trajectoires de récupération cérébrale selon une étude en IRMf (Stefaniak et al., 2022), devront être pris en compte de manière prioritaire. A la lumière de nos études SCEDs, il semble important que ce critère ne se base pas uniquement sur le degré de sévérité de l'atteinte, mais prenne en compte des facteurs plus précis (e.g., troubles phonologiques, troubles syntaxiques).

En outre, nous proposons de prendre en compte les données d'imagerie (Figure 15, encadré 3), à partir de l'étude du disconnectome induit par la lésion (Talozzi et al., 2023). Ainsi, si par leur atlas Talozzi et al. (2023) proposent la prédiction des troubles neuropsychologiques à 1 an post-AVC à partir des faisceaux de substance blanche déconnectés, il serait possible de mettre en évidence la déconnexion d'une voie d'accès du langage (e.g., la voie dorsale) et un chemin possible de compensation à favoriser (e.g., la voie ventrale). Ceci permettrait de mieux visualiser les trajectoires de récupération possible (Price, 2010), et donc les meilleures zones cérébrales à cibler pour la stimulation.

Enfin, un dernier facteur très exploratoire que nous proposons de prendre en compte sont les données issues de l'EEG (Figure 15, encadré 4). En prenant pour base le modèle d'Indefrey (2011), les troubles langagiers que présentent les personnes aphasiques post-AVC pourraient être liés aux différences ERP retrouvées comparativement à des personnes neurotypiques dans une tâche de dénomination d'images : différences dans des fenêtres temporelles précoces (<300ms) liées aux troubles lexico-sémantiques, différences dans des fenêtres temporelles plus tardives liées à des troubles phonologiques (Laganaro et al., 2009). Ainsi, si l'identification de différences dans des fenêtres temporelles qui seraient reliées à des processus langagiers spécifiques pourrait permettre de faciliter le diagnostic lorsque le profil clinique apparait mixte (i.e., troubles concomitants) (Laganaro et al., 2009), il pourrait également permettre de déterminer l'approche à adopter pour l'individualisation de la stimulation, en choisissant la cible corticale en fonction des troubles détectés par les

différences observées en ERPs. Une même approche pourrait être proposée pour les troubles de la compréhension (Gillis et al., 2021). De manière plus générale, l'analyse de la connectivité de repos en EEG pourrait permettre de déterminer la possibilité d'induire l'inhibition ou la facilitation attendue par les paramètres de stimulation choisis (Nicolo et al., 2016). Nicolo et al. (2016) mettaient ainsi en évidence la possibilité de prédire les changements de connectivité induits par l'utilisation de rTMS inhibitrice à partir de la connectivité de repos pré-stimulation auprès de personnes neurotypiques.

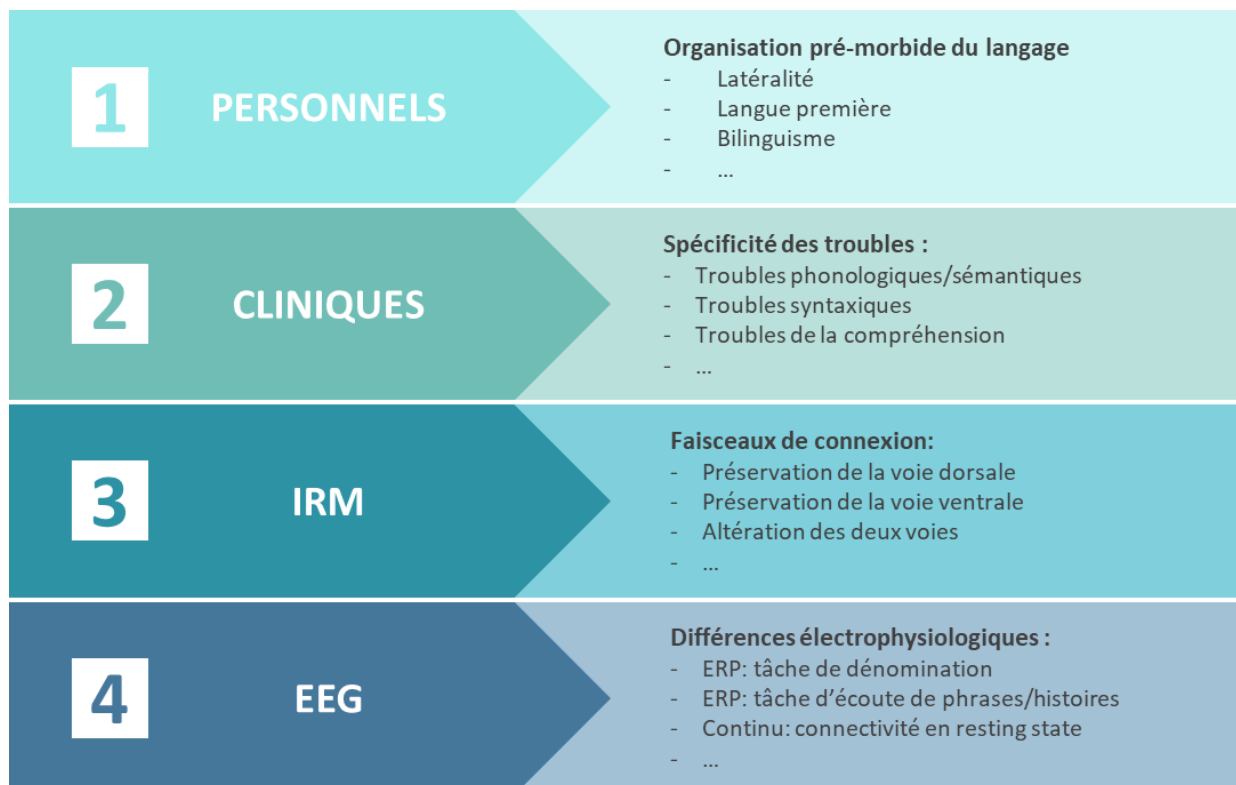


Figure 15 : Pistes de facteurs d'individualisation de la rTMS

#### 4.2. tDCS : stimulation de réseau(x) spécifique(s) ?

Si l'approche en rTMS et en tDCS induisent des modifications d'activation de zones corticales sous-jacentes et des faisceaux associés, ces deux stimulations ont des principes physiopathologiques différents. Comme décrit dans la partie concernant le contexte clinique et scientifique (partie 1, section 1.2.1), la rTMS va induire une dépolarisation neuronale pouvant entraîner une contraction involontaire du muscle, en fonction du seuil moteur de repos (Lefaucheur et al., 2014; Ridling & Rothwell, 2007), tandis que la tDCS va entraîner une modification du seuil de repos membranaire des neurones qui pourront être plus ou moins

aptes à déclencher un potentiel d'action (Lefaucheur et al., 2017; Nitsche et al., 2003). Ceci pourrait expliquer le fait que la rTMS induise des effets sans traitement orthophonique ou stimulation langagière, contrairement à la tDCS qui ne serait efficace que lorsqu'elle serait appliquée en mode « on-line », c'est-à-dire liée à une activité langagière (Arheix-Parras et al., 2021; Biou et al., 2019).

Cependant, compte tenu de cette efficacité « off-line » de la rTMS, les effets induits pourraient être moins maîtrisables et agir sur d'autres aspects que ceux visés par la stimulation. Ainsi, la tDCS pourrait permettre de mieux sélectionner les réseaux cibles, en proposant des tâches spécifiques durant cette stimulation. Par exemple, les aspects réceptifs pourraient être spécifiquement stimulés en proposant des tâches perceptives (e.g., écoute de mots, de non-mots, appariement sémantique), associés à la stimulation d'une zone particulièrement impliquée dans le traitement sémantique du langage (Binder et al., 2009; Duffau et al., 2014).

### **4.3. Les stimulations transcrâniennes à courant alternatif : nouvelle approche pour les personnes présentant des troubles sévères ?**

Une dernière approche pouvant constituer une piste de recherche intéressante à la suite de cette thèse est l'utilisation des stimulations transcrâniennes à courant alternatif (tACS, en anglais : transcranial Alternating Current Stimulation).

Le principe de la tACS est l'envoi de courant alternatif à des fréquences données, respectant les oscillations cérébrales et ciblant différentes zones du cerveau (Elyamany et al., 2021). La tACS permettrait de coupler ou de découpler deux zones interconnectées en modifiant les oscillations synchronisant ces zones. Auprès de personnes neurotypiques, il a été démontré qu'il était possible d'augmenter la puissance des ondes alpha par le biais de la tACS (pour une revue, voir De Koninck et al., 2023). Une méta-analyse a également mis en évidence la possibilité d'induire des améliorations modérées de différentes fonctions cognitives (e.g., mémoire de travail, contrôle exécutif) auprès de personnes neurotypiques, âgées ou présentant des troubles neuropsychiatriques (e.g., épilepsie, troubles Parkinsoniens, troubles cognitifs légers, troubles dépressifs majeurs, schizophrénie, trouble de l'attention avec hyperactivité) (Grover et al., 2023). Concernant l'évaluation des effets de la tACS sur le langage, les études auprès de personnes neurotypiques sont moins nombreuses, mais laissent entrevoir la possibilité d'améliorer certains aspects langagiers (i.e., décision phonologique de mots, discrimination auditive bruit/discours, fluence phonémique) (Keshavarzi et al., 2020; Moliadze et al., 2019, 2021; Sun et al., 2022). A l'heure actuelle, nous ne disposons à notre connaissance que d'une étude ayant évalué l'efficacité de la tACS dans le traitement de l'aphasie post-AVC (Xie et al., 2022). Les auteurs ont proposé des stimulations



theta (6Hz) visant l'aire motrice supplémentaire associées à un traitement orthophonique (on-line) et à de la rééducation orthophonique après la stimulation. Après deux semaines de traitement (14 sessions), les participants présentaient des améliorations langagières dans différents domaines (compréhension verbale auditive, discours spontané, répétition, dénomination), qui se maintenaient un mois post-tACS pour 72% d'entre eux (Xie et al., 2022). La tACS ouvre ainsi de nouvelles perspectives pour le traitement des personnes cérébrolésées, et plus particulièrement souffrant d'une aphasie post-AVC. Cette méthode prometteuse pourrait également permettrait de moduler de manière simultanée la connectivité de plusieurs zones corticales, et donc d'un réseau spécifique. Cette approche serait donc en accord avec les théories actuelles d'organisation du langage en réseaux (Duffau et al., 2014). De plus, la présence d'ondes lentes, connues pour être à la fois biomarqueur de troubles sévères, mais aussi source d'un mauvais pronostic de récupération (Arheix-Parras et al., 2023), pourrait être modifiée. Ceci constitue une perspective novatrice dans la recherche de l'amélioration des troubles phasiques post-AVC, notamment pour les personnes présentant des troubles sévères.

## Conclusion générale

La recherche menée au cours de cette thèse a tenté de mettre au maximum les personnes présentant une aphasie au centre des études, afin de souligner la possibilité de mener une recherche clinique rigoureuse et documentée, tout en étant au plus près de la personne présentant une aphasie.

La première partie de cette thèse a permis d'asseoir un socle théorique à ce travail, à la fois dans le cadre du traitement par rTMS et pour l'évaluation des changements EEG dans l'aphasie post-AVC.

D'une part, nous avons choisi de proposer une approche individualisée de la rTMS, qui s'avère pertinente lorsque l'on étudie des troubles aussi variés que les atteintes langagières post-AVC. Ce travail ouvre des perspectives encourageantes concernant la possibilité d'individualiser la rTMS, et le traitement par NIBS en général, afin d'améliorer la taille d'effet attendue, mais aussi pour prévenir d'éventuels effets négatifs. D'autres recherches sont nécessaires afin d'étayer cette approche, notamment en utilisant une combinaison de facteurs (e.g., clinique, imagerie). Au décours de cette thèse, nous avons pu remettre en question plusieurs principes fondamentaux largement utilisés (balance interhémisphérique, choix de la cible corticale, paramètres d'inhibition ou de facilitation), à la lumière de la complexité des processus de récupération en jeu dans le cadre de l'aphasie.

D'autre part, nous avons tenté de comprendre les effets induits par la rTMS au niveau de la plasticité cérébrale en ERP/EEG. De nouvelles analyses et d'autres recherches sont nécessaires afin de mieux comprendre les mécanismes neurophysiologiques de la rTMS, et des NIBS en général, voire de mettre en évidence des biomarqueurs d'efficacité du traitement. Enfin, cette thèse ouvre de nombreuses perspectives de recherche, notamment sur la possibilité, ou non, d'améliorer les troubles du langage pour les personnes présentant les troubles les plus sévères. Au cours de ce travail, nous avons mis en avant la nécessité grandissante de proposer des approches individualisées dans le champ des stimulations cérébrales non invasives, afin d'améliorer et de mieux maîtriser les effets induits dans le domaine de la récupération de l'aphasie post-AVC.

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## **Stimulations magnétiques transcrâniennes et aphasie chronique post-AVC : individualisation et modifications électrophysiologiques induites**

**Résumé.** Si le traitement de référence pour la récupération de l'aphasie post-AVC (Accident Vasculaire Cérébral) est l'orthophonie, les stimulations cérébrales non invasives, telles que les stimulations magnétiques transcrâniennes répétées (rTMS), constituent de nouvelles pistes pour sa récupération. La majorité des études dans ce domaine utilisent des stimulations inhibitrices ciblant le gyrus frontal inférieur (IFG) droit, avec pour objectif de réduire l'effet possiblement délétère l'hémisphère contralésionnel. Or, ce principe, issu de la théorie de la balance interhémisphérique, minimise le rôle complexe de l'hémisphère droit, notamment son rôle prépondérant dans le cadre de troubles sévères post-AVC. De plus, la cible corticale majoritairement choisie en rTMS est le gyrus frontal inférieur droit (i.e., homologue de Broca), ceci quel que soit le type de troubles langagiers que présente la personne aphasique. Cependant, ce choix de stimuler principalement cette zone corticale est réducteur de l'organisation complexe des réseaux langagiers. Notre première interrogation s'est donc centrée sur les possibilités et la pertinence d'individualiser la rTMS (cible corticale et paramètres), afin d'en améliorer l'impact langagier pour les personnes aphasiques.

Par ailleurs, l'exploration des mécanismes neurobiologiques sous-tendus par la rTMS est encore peu développée, notamment en électroencéphalographie (EEG). Or, les études via EEG, et plus particulièrement l'analyse de potentiels évoqués reliés (ERP), sont des approches pertinentes pour explorer les processus se déroulant lors de tâches langagières, grâce à leur grande précision temporelle. De manière exploratoire, nous nous sommes alors interrogés sur les modifications EEG induites par la rTMS au niveau de tracés ERPs dans des tâches de dénomination d'images auprès de patients aphasiques post-AVC.

Nous avons développé trois études expérimentales au modèle Single Case Experimental Design (SCED), afin d'analyser les possibilités d'individualisation de la rTMS. La première étude a proposé la comparaison de stimulations facilitatrices versus inhibitrice de l'IFG droit pour les patients présentant une aphasie sévère à la phase chronique (n=6). Les résultats retrouvés ont été hétérogènes, permettant une remise en question de la balance interhémisphérique et mettant en avant l'importance de l'hémisphère droit dans la récupération. Dans une deuxième étude, nous avons proposé de choisir la cible corticale en fonction de la spécificité des troubles présentés par la personne aphasique : nous avons alors utilisé un protocole de rTMS visant le cortex moteur des lèvres pour des personnes présentant des troubles de type phonologique (n=3). Les résultats comportementaux ont été positifs, soulignant la pertinence de choisir la cible corticale en fonction de la spécificité des troubles langagiers. La troisième étude s'est centrée sur un participant gaucher souffrant d'une aphasie sévère à la suite d'un AVC droit. Nous avons adopté pour cette dernière étude une démarche très individualisée afin de déterminer la stimulation la plus efficace pour ce participant au profil atypique. Ces trois études ont permis de mettre en avant la pertinence de proposer une approche plus individualisée de la rTMS.

En parallèle de ces résultats comportementaux, nous avons exploré les différences de tracés ERPs en tâche de dénomination des participants avant et après application des protocoles de rTMS. Ces analyses n'ont pas encore permis d'établir un biomarqueur électrophysiologique d'efficacité de la rTMS, mais de nombreuses pistes d'analyses sont proposées (i.e., analyses en temps fréquence, comparaison à des groupes de personnes neurotypiques), ainsi que des perspectives pour de futures recherches, proposant notamment des analyses ERPs plus à distance du protocole.

**Mots clés :** aphasie, AVC, stimulation magnétique transcrânienne, potentiel évoqué relié, EEG

## **Transcranial magnetic stimulations and chronic post-stroke aphasia: individualization and electrophysiological changes**

**Abstract.** Speech and language therapy is the gold standard for the recovery of post-stroke aphasia. However, non-invasive brain stimulations, such as repetitive transcranial magnetic stimulation (rTMS), offers new avenues for recovery. The majority of studies use inhibitory rTMS targeting the right inferior frontal gyrus (IFG), to reduce the deleterious effect of the undamaged hemisphere. However, this principle, based on the interhemispheric balance theory, downplays the complex role of the right hemisphere, particularly its predominant role in severe post-stroke language impairments. Furthermore, the right IFG (i.e., Broca's homolog) is the most used cortical target in rTMS, regardless of the language feature impairments of the person with aphasia. Thus, the choice to stimulate this cortical area reduces the complex organization of language networks. Therefore, our first question focused on the possibilities of individualizing rTMS (cortical target and parameters) to improve its impact on language for post-stroke aphasia.

In addition, the exploration of the neurobiological mechanisms underlying rTMS is still underdeveloped, particularly in electroencephalography (EEG). However, EEG studies, and more specifically the analysis of Event-Related Potentials (ERPs), are relevant approaches for exploring the processes taking place during language tasks, thanks to their high temporal accuracy. As an exploratory approach, we investigated EEG changes induced by rTMS in people with post-stroke aphasia, using ERPs in picture naming tasks.

We developed three experimental studies based on the SCED (Single Case Experimental Design), to analyze the individualization potential of rTMS. The first study compared facilitatory versus inhibitory stimulations of the right IFG in persons with severe chronic aphasia (n=6). The results were heterogeneous, allowing us to question the interhemispheric balance and the importance of the damaged hemisphere for aphasia recovery. In a second study, we proposed to choose the cortical target according to the specificity of the language impairments presented by the participants: we used an rTMS protocol targeting the right motor cortex of the lips for people with phonological impairments (n=3). The behavioral results were positive, underlining the possibility and relevance of choosing the cortical target according to language impairments. The third study focused on a left-handed participant with severe aphasia following a right hemispheric stroke. In this last study, we adopted a highly individualized approach to determine the most effective stimulation for this participant with an atypical profile. Together, these three studies highlighted the relevance of proposing a more individualized approach for rTMS in post-stroke aphasia.

In parallel with these behavioral results, we explored the differences in participants' ERPs in the naming task before and after rTMS. These analyses have not yet established an electrophysiological biomarker of rTMS efficacy, but many avenues of analysis are suggested (i.e., time-frequency analyses, comparison with groups of neurotypical individuals), as well as perspectives for future research, particularly the long-term effect of rTMS in ERPs.

**Keywords:** aphasia, stroke, transcranial magnetic stimulation, event-related potential, EEG

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