Universitat de Girona
Facultat de Medicina

Hospital Universitari de Girona
Doctor Josep Trueta

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR LANGUAGE RECOVERY IN POST-STROKE NON-FLUENT APHASIC PATIENTS

A randomized sham-controlled clinical trial

FINAL DEGREE PROJECT

AUTHOR: Laia Rigat i Puig

CLINICAL TUTOR: Dra. Yolanda Silva Blas

METHODOLOGICAL TUTOR: Dr. Abel López Bermejo

Facultat de Medicina, Universitat de Girona
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“The limits of my language are the limits of my world”.

Ludwig Wittgenstein

1. ABBREVIATIONS

ACA: Anterior Cerebral Artery

AEMPS: Asociación Española del Medicamento y Productos Sanitarios

ASRS: Aphasia Severity Rating Scale

BA: Brodmann Area

BDAE: Boston Diagnostic Aphasia Examination

BNT: Boston Naming Test

BOLD: Blood Oxygenation Level-Dependent

CEIC: Clinical Research Ethics Committee

CT: Computerized Tomography

EMA: European Medicines Agency

EU: European Union

FDA: Food and Drug Administration

fMRI: Functional Magnetic Resonance Imagining

GABA: Gamma-Aminobutyric Acid

GLM: General Linear Model

HF-rTMS: High-Frequency repetitive Transcranial Magnetic Stimulation

IdIBGi: Institut d'Investigació Biomèdica de Girona

IHV: Intracerebral Hemorrhage Volume.

ITG: Inferior Frontal Gyrus

ITI: Inter-Train Interval

LF-rTMS: Low-Frequency repetitive Transcranial Magnetic Stimulation

LTD: Long-Term Depression

LTP: Long- Term Potentiation

MCA: Middle Cerebral Artery

MEP: Motor Evoked Potentials

NIBS: Non-Invasive Brain Stimulation

NIHSS: National Institute of Health Stroke Scale

PCA: Posterior Cerebral Artery

PET: Positron Emission Tomography

ROI: Region Of Interest

r-TPA: recombinant Tissue Plasminogen Activator

RMT: Resting Motor Threshold

rTMS: repetitive Transcranial Magnetic Stimulation

SADQ-10: Stroke Aphasic Depression Questionnaire

SAH: Subarachnoid Hemorrhage

SD: Standard Deviation

SPSS: Statistical Package for Social Sciences

SQOL-39: Stroke and Aphasia Quality of Life Scale

TBI: Traumatic Brain Injury

TMS: Transcranial Magnetic Stimulation

WAB: Western Aphasia Battery

2. ABSTRACT

Background: *Stroke is the second cause of death and a major cause of morbidity worldwide and approximately 1/3 of the patients who suffer a stroke, remain with aphasia. Aphasia is one of the most disabling sequelae of stroke, it affects the quality of life of the patients and has a huge impact on personal, social, familiar, and work-life. Nowadays, aphasia has no specific treatment, and its management is based on speech therapy which obtains limited results. Repetitive transcranial magnetic stimulation is a non-invasive, low-cost, and available technique that has shown a potential therapeutic effect on recent literature. However, the evidence is still week due to the lack of standardized stimulation protocols, the variability of the study population, and the number of resources needed to perform these studies.*

Objectives*: To assess the clinical efficacy of repetitive transcranial magnetic stimulation combined with intensive speech therapy in subacute post-stroke patients with aphasia in language rehabilitation assessed using the Boston Diagnostic Aphasia Examination. Secondary objectives include evaluating its effect on the quality of life and mood of these patients.*

Design and methods: *A randomized, double-blind (single-blinded in the stimulation session), sham-controlled clinal trial performed in Hospital Josep Trueta of Girona. It will recruit 64 patients using a consecutive non-probabilistic method. Patients recruitment will last for 1 year. Patients will be randomized in the experimental group that will receive real-rTMS or in the control group that will receive sham-rTMS following a 1:1 ratio. The randomization will be stratified by stroke type (ischemic or hemorrhagic). Patients will be administered the assigned stimulation 5 days/week for 2 weeks. The stimulation session will take 20 min and immediately after it, patients will receive a 45-minute speech and language therapy. Patients will be assessed for the measure endpoints of the study (subtests of BDAE which are BNT, fluency, repetition, and comprehension tests) before the stimulation, after the stimulation period and they will be followed-up after 6 months and 12 months. A general linear model will be performed to study the effect of the intervention on the endpoint of the study adjusting for potential confounding variables.*

Keywords: stroke; aphasia; patients with aphasia; rTMS; BDAE; BNT; HF-rTMS; LF-rTMS; fMRI; aphasia rehabilitation

3. INTRODUCTION

3.1 STROKE

Stroke is a cerebrovascular disease characterized by a sudden onset of a neurologic deficit from a vascular mechanism: 85% are ischemic and 15% are hemorrhagic (including subarachnoid and intraparenchymal). (1)

3.1.1 EPIDEMIOLOGY

Stroke is a great health problem as it is commonly disabling or lethal. In Spain, the annual incidence of stroke is 187.4 of 100.000 inhabitants per year. (2) It represents the main cause of female mortality and the second cause of male mortality. Stroke is also the leading cause of neurological sequelae in adults worldwide.

3.1.2 ETIOLOGY

Ischemic stroke results from focal cerebral ischemia caused by an insufficient blood supply associated with permanent brain infarction. According to the SSS-TOAST system, we can classify patients with acute ischemic strokes into the following etiologic categories (from the most the least common). (3)

- Large artery atherosclerosis (20%): the presence of cerebral or cervical arterial stenosis or occlusion with ≥50% diameter reduction. It is usually associated with generalized atherosclerosis and vascular risk factors
- Cardioembolic stroke (15%): the source of emboly is the heart and it is produced because of a cardiopathy such as atrial fibrillation, recent myocardial infarction, endocarditis, mechanical valvular prothesis…
- Small artery occlusion (25%): presence of a single and small infarct (less than 20 mm in the greatest diameter in TC-scan) because of the occlusion of basal or brainstem perforating arteries, the main cause of the obstruction is an intrinsic small-vessel disease.
- Stroke of rare causes (20-25%): other causes are acute or chronic meningitis, vasculitis disorders, syphilis, hypercoagulability disorders, etc.
- Undetermined strokes (5-10%) undetermined causes which can be classified into one of these groups:

- Unknown cause after a complete evaluation, also called cryptogenic stroke
- Presence of ≥2 possible causes/unclassifiable
- Cursory evaluation or absence of a complete diagnostic assessment

Hemorrhagic strokes occur when a blood vessel ruptures and bleeds into the central nervous system. We can distinguish two main types of bleeds:

- intracerebral hemorrhage when bleeding occurs in the brain parenchyma. The main causes are hypertension (if the hematoma is in the basal ganglia) or amyloid angiopathy (if the hematoma is localized in the cerebral lobes).
- subarachnoid hemorrhage (SAH) when bleeding occurs into the subarachnoid space (arachnoid and pia mater). The main cause of spontaneous SAH is a ruptured aneurysm followed by arteriovenous malformation and bleeding disorders.

3.1.3 RISK FACTORS

Stroke is a heterogeneous syndrome, but the main risk factors are common in all types of stroke. (4) They can be classified as nonmodifiable or modifiable. The main nonmodifiable risk factors of stroke are age (the risk doubles for every successive decade after the age of 55), sex (higher risk in men except in the elderly), race-ethnicity, and genetics. The modifiable ones are hypertension, current smoking, diabetes, alcohol consumption, abdominal obesity, hyperlipidemia, cardiac causes, physical inactivity, poor diet, and psychosocial stress and depression. (5) Other risk factors are the use of combined oral contraceptive pills, chronic infections, asymptomatic carotid arteriopathy. Primary prophylaxis can be helpful to reduce modifiable risk factors. Previous transient ischemic attacks or strokes are also an important risk factor to develop future strokes. Secondary prophylaxis can be useful to prevent them.

3.1.4 CLINICAL MANIFESTATIONS

The symptoms of stroke occur suddenly. Symptoms reflect the vascular territory involved. Anterior circulation usually causes unilateral deficits whereas posterior circulation can cause unilateral or bilateral deficits and could affect consciousness. The following clinical manifestations are suggestive of stroke: (6)

- Strength loss in the face, arm, and/or leg especially if the disfunction is unilateral
- Confusion

- Aphasia
- Visual disturbances in one or both eyes
- Difficulty to walk, dizziness, loss of balance or coordination
- Severe headache
- Difficulty to swallow
- Unilateral sensibility disorder

3.1.5 DIAGNOSIS

The diagnosis of stroke is suggested by the clinical manifestations of the patient. The correct diagnosis of strokes includes the following steps.

- Anamnesis and physical exploration of the patient. The main objectives are knowing the time when the symptoms started, knowing the previous degree of disability/ dependence using the RANKIN scale (see Annex 1), discard contraindications for future specific treatments, orientate the etiology of the stroke and the vascular territory involved, do a primary clinical evaluation (ABCDE) and rate stroke severity using NIHSS scale.
- Basic analytics, electrocardiogram, and chest x-ray: this complementary proves are useful to do the differential diagnosis and orientate the etiology of the stroke.
- Neuroimaging: including simple CT, multimodal CT, CT angiography, multiparametric MRI. Brain imaging allows us to confirm the diagnose, differentiate ischemic stroke from hemorrhagic stroke, determine the affected area, and decide which treatment is best for the patient. (7)

The diagnostic process must be as fast as possible because every minute we spend not treating the patient represents a significant neuron loss.

3.1.6 TREATMENT

ACUTE PHASE

The acute treatment of stroke is complex and must be applied as sooner as possible. The general treatment is common in all types of strokes which consist in hospitalize the patient, stabilize him, provide supportive care, and prevent and treat complications. Specific acute treatments vary by type of stroke.

In ischemic strokes, the following step consists of reperfusion technics which include intravenous fibrinolysis using recombinant tissue plasminogen activator (r-TPA), intra-arterial thrombolysis, and/or mechanical thrombectomy depending on the patient. (8)

In intracerebral hemorrhages, the specific treatment consists of the strict control of blood pressure, reversion of the anticoagulation/antiaggregant drugs if the patient has used them, and sometimes, it could include surgical hematoma evacuation or ventricular derivation.

In subarachnoid hemorrhages, the treatment consists of blood pressure control, prevention of vasospasm with nimodipine, and endovascular treatment or surgical intervention in the cases with a ruptured aneurism. (9)

SUBACUTE-CHRONIC PHASE

Medical interventions in the convalescence phase have three main objectives:

- Prevent potential complications of stroke including aspiration, deep venous thrombosis, pulmonary embolism, urinary tract infections, pressure ulcers, undernutrition, falls, bowel disfunction, etc. (10)
- Secondary prevention of stroke: it is necessary to identify treatable causes of stroke and to minimize stroke risk factors which include lifestyle changes, drug therapies. Secondary prevention of stroke depends on the type of stroke and every patient.
- Rehabilitation of the patient to maximize functional recovery. The rehabilitation approach should be interdisciplinary and individualized to the patient's needs. Some therapies are occupational and physical therapy, speech therapy, physiotherapy, etc. In this paperwork, I am going to focus on the rehabilitation of aphasia.

3.2 APHASIA

Aphasia is an acquired impairment in language affecting several functions such as comprehension (auditory and reading) and expression (speaking and writing) due to brain injury. (11) The damage is usually on the left hemisphere (dominant hemisphere of 96% of right-handed people and 70% of left-handed people) and mostly involves the perisylvian cortex and structures beneath it such as basal ganglia, internal capsule, and periventricular white matter. Any type of lesion situated on the language network from the dominant hemisphere can cause aphasia.

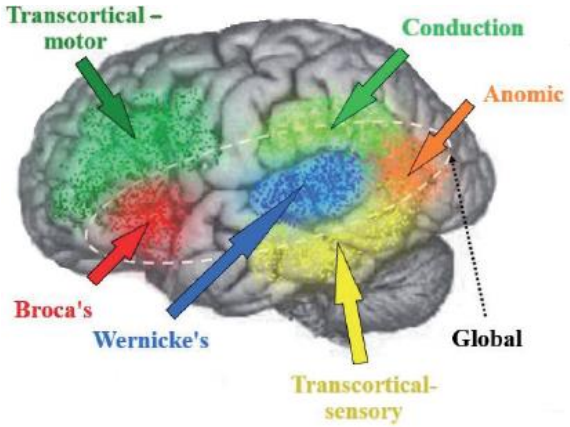


Figure 1 Anatomoclinical correlations of different types of aphasia from (12)

The main cause of aphasia is stroke, it appears in 21-38% of patients suffering a stroke. However, strokes are not the only etiology of aphasia. Aphasia can also be caused by traumatic brain injury, brain tumors, degenerative diseases, infections, multiple sclerosis, and stroke mimics (aura migraine, epilepsy). Aphasia is considered one of the most disabling sequelae after stroke. Aphasia affects the quality of life of the patients and has a huge impact on personal, social, familiar, and work-life among the patients with aphasia.

3.2.2 CLASSIFICATION OF APHASIA: APHASIA SYNDROMES

Aphasia syndromes include Broca's aphasia, Wernicke's aphasia, global aphasia, transcortical aphasia (motor, sensory and mixed), conduction aphasia, and anomic aphasia. (13) Aphasia syndromes are classified according to clinical aspects. The clinical assessment of aphasia is based on the analysis of six main language domains: fluency, comprehension, naming, repetition, writing, and reading. Fluency is the ability to produce connected speech and it evaluates the motor component of language. Comprehension is the ability to understand the given information and it evaluates the

sensitive component of language. Naming also tests the sensitive component of language. Finally, repetition evaluates both motor and sensitive components because to repeat a word first you must understand it and then, reproduce it.

Table 1 Classification of aphasias adapted from (14)

Aphasia syndrome	Fluency	Comprehension	Naming	Repetition	Damage localization	Involved artery
Broca's aphasia	Non-fluent	Preserved	Disrupted	Disrupted	Frontal	Superior branch of MCA
Wernicke's aphasia	Fluent	Disrupted	Disrupted	Disrupted	Temporal	Inferior branch of MCA
Global aphasia	Non-fluent	Disrupted	Disrupted	Disrupted	Extensive left hemisphere	The main trunk of MCA
Transcortical motor aphasia	Non-fluent	Preserved	Disrupted	Preserved	Frontal (around Broca's area)	The watershed territory of ACA and MCA
Transcortical sensory aphasia	Fluent	Disrupted	Disrupted	Preserved	Temporo-parietal (around Wernicke's area)	The watershed territory of MCA and PCA
Transcortical mixed aphasia	Non-fluent	Disrupted	Disrupted	Preserved	Frontal, temporal, and/ or parietal	The watershed territory of ACA and MCA or MCA and PCA
Conduction aphasia	Fluent	Preserved	Disrupted	Disrupted	Supramarginal parietal circumvolution, insula	Posterior branch of MCA
Anomic aphasia	Fluent	Preserved	Disrupted	Preserved	Many locations	Variable

Broca's aphasia

Broca's aphasia is a non-fluent aphasia, spontaneous language is poor and telegraphic, and the speech is often agrammatic. The patient has a good awareness of their communication deficit. Comprehension is better than spontaneous speech but is still not normal. The patient can understand simple orders but is incapable to understand complex ones. Repetition and naming are also disrupted due to their expression difficulties. Similarly, reading and writing are affected. Neurological signs associated with Broca's aphasia are apraxia of speech, dysarthria, and right hemiparesis.

The main affected area in Broca's aphasia is Broca's area (BA 44, 45) in the left posterior inferior frontal gyrus (opercular cortex). Sometimes, the lesion is much larger including the inferior frontal and insular cortex as well as deeper white matter. Broca's aphasia is produced by infarcts or hematomas in the superior branch of the left MCA.(12,15)

Wernicke's aphasia

Wernicke's aphasia is a fluent aphasia so spontaneous language is preserved and their speech rhythm and prosody are normal. However, their speech can be unintelligible because of the number of speech mistakes such as paraphasias and neologisms. The main language impairment of the patients is comprehension in all modalities. The patients are less aware of their deficits than Broca's aphasic patients. Repetition is also impaired, and it also includes paraphasias. Naming is impaired, the patient has anomia; he is no able to name the object, he describes it instead.

The main affected area in Wernicke's aphasia is Wernicke's area (BA 22) which is the left posterior superior temporal gyrus. The lesion sometimes includes inferior parietal lobes, insular-external capsule region, and anterior part of temporal gyri as well as deeper white matter. Wernicke's aphasia is produced by ischemic or hemorrhagic strokes in the territory of the inferior division of the left MCA.(12,15)

Global aphasia

Global aphasia is the most severe type of aphasia. It is usually a lesion of a large area of the left hemisphere because of the infarction in the territory of the middle cerebral artery. All aspects of speech are impaired because the entire language network is damaged. The language is not fluent; comprehension, repetition, and naming are very poor. The patient is only able to emit automatic or

stereotypic responses. The aspects of language controlled by the right hemisphere such as intonation, musical ability, and emotional expression are preserved. These patients usually have other neurologic symptoms such as right hemiplegia or hemiparesis, and hemisensory disorders.

Global aphasia is caused by extended left-hemisphere lesions which are the result of the occlusion or rupture of the main trunk of MCA. Both frontal and temporoparietal lesions can also cause global aphasia as well as subcortical extended infarct into basal ganglia.(12,15)

Transcortical aphasia

Transcortical aphasias are a group of aphasias with the following common characteristics. First, they are quite uncommon compared with other types of aphasia. Second, they are caused by lesions outside the Sylvian fissure and they are usually caused by infarction or hematoma in border zones. Third, they have a well-preserved ability to repeat despite having other important language impairments. We can distinguish three different types of transcortical aphasia: transcortical motor aphasia, transcortical sensory aphasia, and transcortical mixed aphasia.

Transcortical motor aphasia is similar to Broca's aphasia. It is characterized by the following features: difficulties in spontaneous speech production, good comprehension, impaired naming, preserved repetition, and impaired reading and writing. Lesions are situated in the watershed territory between left ACA and MCA. Less frequently, we can find lesions in the left premotor area, prefrontal regions, and subcortical frontal structures. (12,15)

Transcortical sensory aphasia is similar to Wernicke's aphasia. The patients have fluent aphasia with paraphasia and echolalia, poor comprehension, preserved repetition. Naming, reading, and writing are usually impaired. Lesions are situated in the watershed territory between left MCA and PCA. Less frequently, it is caused by subcortical lesions. (12,15)

Transcortical mixed aphasia is similar to global aphasia, but repetition is also preserved. Lesions are situated in the watershed territory between left ACA and MCA in addition to the watershed territory between left MCA and PCA. Sometimes it is also caused by subcortical lesions.(12,15)

Conduction aphasias

Conduction aphasias are a subtype of aphasia characterized by fluent speech and a well-preserved comprehension. These patients are more likely to correct their paraphrastic errors. Repetition, naming, reading, and writing are impaired.

Traditional models suggest that conduction aphasia arises from lesions to the arcuate fasciculus, the white matter tract between Broca's and Wernicke's areas. However, current evidence shows that patient's lesions are usually in the left posterior neocortex, in the inferior parietal cortex. The inferior parietal cortex is supposed to participate in working memory which could explain the repetition deficits observed in this patients' group. Conduction aphasia is produced by embolic infarcts of the inferior division of the left MCA.(12,15)

Anomic aphasias

Anomic aphasia is the mildest of the aphasias. Patients with anomic aphasia have preserved language functions except for the naming function. This group of patients has difficulties to find the appropriate word usually associated with paraphasias and circumlocutions (replacing the missing words with other information). The anatomic lesion can be anywhere in the linguistic zone. (12,15)

3.2.3 POST-STROKE APHASIA

3.2.3.1 EPIDEMIOLOGY

Stroke is among the leading causes of disability worldwide and aphasia is one of the common presentations of stroke. The frequency of aphasics among stroke patients ranges from 21-38%. There is no significant difference in the occurrence of aphasia in ischemic vs hemorrhagic stroke.

The most common type of post-stroke aphasia seen in studies including hemorrhagic and ischemic strokes is global aphasia (24-38%) followed by Broca's aphasia (20-25%), transcortical motor aphasia (10-15%), Wernicke's aphasia (10%) and anomic aphasia (5%); other aphasias are rare. 10% of post-stroke aphasia remain unclassifiable especially in patients with stroke antecedents. (12) (16)

Usually, aphasia becomes less severe in the first 3 months after stroke in one-third of patients and during the first 6 months in approximately half of them. (17) Post-stroke aphasics significantly have a lower health-related quality of life.

3.2.3.2 SPONTANEOUS RECOVERY

Post-stroke aphasic patients can recover spontaneously without treatment. Usually, aphasia becomes less severe in the first 3 months after stroke. Spontaneous recovery depends on:

- Initial aphasia severity
- Infarction site: anterior–inferior temporal lobe lesions that extended into the middle temporal gyrus were associated with worse language recovery (18)

- Infarction size: bigger infarctions have the worst prognosis (18)
- Stroke severity
- Etiology of stroke: whether it is caused by an ischemic or a hemorrhagic stroke
- Time from the onset: highest aphasia recovery rates are seen in the acute and subacute phase rather than in the chronic phase
- Brain neuroplasticity
- Age, gender, motivation, personality, and associated disorders of the patient

Physiopathology of post-stroke aphasia and spontaneous recovery

We understand the brain as a dynamic structure that responds to damage. A healthy brain has an interhemispheric balance: the activation of one hemisphere depends on the activation of the other one because of transcallous inhibition. When the brain is damaged, the interhemispheric balance is broken: the damaged hemisphere is hypoactive due to the damage suffered and is not able to inhibit the preserved hemisphere resulting in a pathological hyperactivation of the healthy hemisphere that at the same time, over-inhibits the damaged hemisphere increasing its hypoactivity. In the case of aphasic patients, the damaged hemisphere is their dominant hemisphere which is the left one in 96% of the right-handed patients, and in 70% of the left-handed; we consider the dominant hemisphere is the left hemisphere. Therefore, when patients suffer a stroke in the left hemisphere, it causes the hypoactivation of the left hemisphere and hyperactivation of the right one.

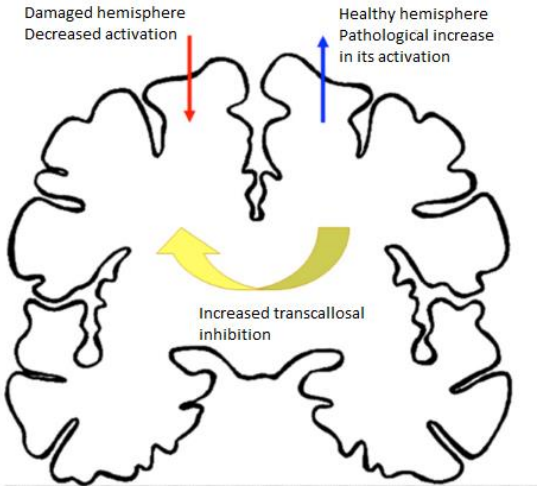


Figure 2 Representation of the effects of brain damage on neural activity according to the brain interhemispheric rivalry model adapted from (19)

The course of recovery of aphasia after stroke is highly variable. Some patients recover rapidly over the first days after onset and others never recovers from it. The spontaneous recovery of language entails at least three stages that do not have clear time limits:

- Acute phase (first few days after stroke): in ischemic strokes, language recovery depends on the reperfusion of yet-viable tissue (ischemic penumbra). Saving the cerebral area implicated in a specific language leads to a clinical improvement of the language function. In hemorrhagic strokes, the mechanisms of recovery are not well known but they are related to hematoma and edema reduction. (20)
- Subacute phase (begins within days of the stroke and continues for months). The hypoperfused area has progressed to infarction. Nonetheless, spontaneous recovery can occur thanks to neural reorganization. Recent neuroimaging and behavioral data indicate that there is a reorganization of structure and function relationships. The reorganization of brain tissue leads to the resolution of the diaschisis. The diaschisis is a concept postulated by von Monakaw (1914) and it refers to the disruption in blood flow and metabolism (and eventually, disruption in function) within a region distant to the site of lesion as a result of deafferentations of neurons (so, loss of excitation) because of axon damage caused by the stroke. The diaschisis undergoes gradual regression and when it is resolved, the affected area recover its function.
- In the chronic phase (from month to ages after the stroke), the recovery depends on the establishment of new networks to substitute the damaged ones and the acquisition of compensatory strategies to communicate more effectively.

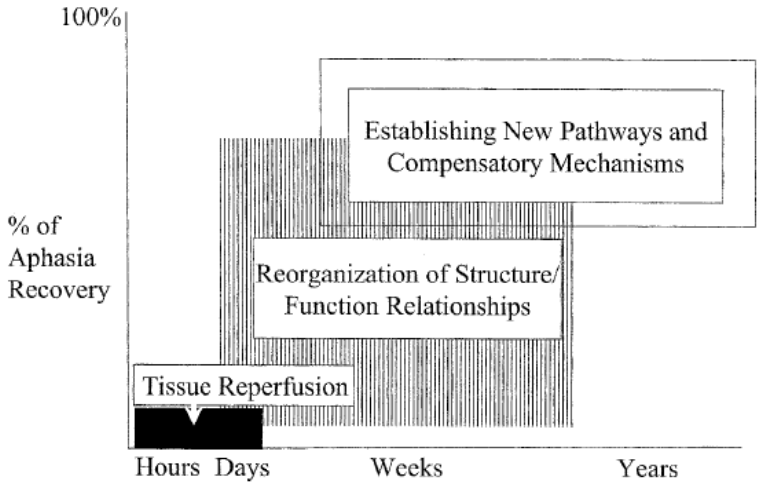


Figure 3 The three stages of functional recovery from aphasia from (21)

Current evidence suggests that three kinds of changes in neuronal activity after stroke may occur in post-stroke aphasia evolution(22):

1. Recruitment of lesioned and perilesional left hemisphere regions for language-related tasks: the mechanism of the increased perilesional activation is not well known but could be the release of inhibitory input from the infarcted cortex. There is evidence that suggests that the activation of left-hemisphere structures is related to better spontaneous language recovery.
2. Acquisition, unmasking, or refinement of language processing ability in the non-dominant right hemisphere: the activation of the right hemisphere can contribute to language recovery in some patients
3. Dysfunctional activation of the nondominant hemisphere that may interfere in language recovery: the activation of the right hemisphere is a maladaptive plastic change in neural activity that impedes the functional recovery of perilesional areas in the left hemisphere.

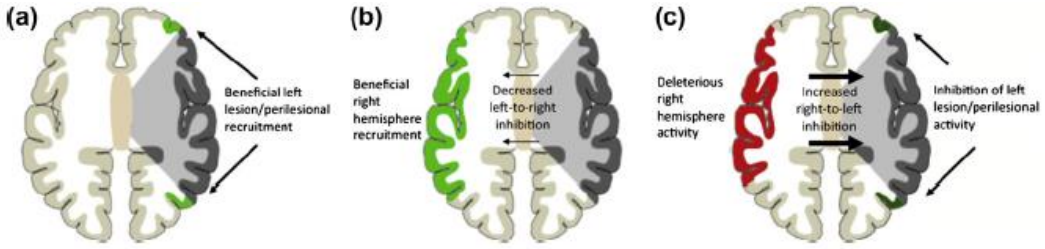


Figure 4 Differing accounts of plasticity in language systems in post-stroke aphasia (22)

These three explanations of post-stroke aphasia evolution are not mutually exclusive. Recent activation studies using functional neuroimaging (fMRI, PET) in patients with aphasia, concluded that the recovery process is a dynamic process that involves different plastic changes in both hemispheres according to the hierarchical model presented by Heiss & Thiel in 2006. The findings were supported with studies with selective disturbance of cortical areas by rTMS in healthy volunteers and patients with brain lesions (17)(23)

According to this model, recovery depends on the severity of the stroke. When lesions of the left hemisphere are small, the recovery is achieved by restoration of the normal language networks in the left hemisphere achieving excellent recovery. When lesions are a little wider, the recovery is the result of the recruitment of left perilesional areas and they compensate for damaged left hemisphere language regions achieving good recovery. Among patients with extensive left

hemisphere injury, the language functions are transferred to the right hemisphere, which can assume some language functions, but the recovery is not complete because the remodeled language network is inefficient compared to the premorbid one achieving limited recovery. The role of the right hemisphere in language recovery is controversial. Some studies expose that recruitment of the left hemisphere is beneficial and it is developed thanks to the release of trans-callous inhibition because of the damage of the left hemisphere. On the other hand, some studies say that activation of the right hemisphere is harmful because the right hemisphere can inhibit the left hemisphere and affect its recovery. (22) (24)

Some studies suggest that there is a temporal component in the reorganization of the language network after stroke. In the early phase of the recovery, there is a tendency for reallocation of language function in the right hemisphere. Over time, the language processing redistributes back to the left hemisphere coinciding with functional recovery in a great number of patients. (25)

In all hypothesis, there is an engagement of alternative language networks which can be potentiated or inhibited using non-invasive brain stimulation. Further investigations are needed to understand and clarify the role of rTMS in language recovery.

3.2.4 ASSESSMENT OF APHASIA

The assessment of aphasia is still quite difficult due to the limitations of neuroimaging techniques and the lack of qualified speech therapists. In the assessment of an aphasic patient, we can distinguish different steps.

The first approach of aphasia assessment is using a bedside neurologic test. During our neurologic exploration, we can evaluate the following language domains: spontaneous speech, naming, repetition, comprehension, reading, and writing. Our main goals are orientating the patient's aphasic syndrome and differentiating it from other possible diagnoses that interfere in communication such as dysarthria, hypoacusia, impaired vision, delirium, etc.

The following step might be evaluating patient aphasia using neuropsychologic tests. Neuropsychologic tests are useful to detect finer levers of impairment and to plan a patient's treatment. Several formal battery tests are available for aphasia assessment:

- Boston Diagnostic Aphasia Examination (BDAE)
- Western Aphasia Battery (WAB)

- Montreal-Toulouse Language Assessment Battery
- Minnesota Test for Differential Diagnosis of Aphasia
- Multilingual Aphasia Examination
- Bilingual Aphasia Test

Boston Diagnostic Aphasia Examination was developed in 1972 by Goodglass and Kaplan. The most recent edition was published in 2001 by Goodglass, Kaplan, and Barresi and contains both a shortened and extended version of the BDAE. This battery is a comprehensive assessment of verbal function. Assessments include verbal comprehension, written comprehension, writing to dictation, naming, articulation, spontaneous speech, repetition, reading, following simple and complex commands, speech fluency, and prosody. The test provides an overall severity rating score and a profile of subtest performance. (26) The main disadvantage of this battery is that the testing time is quite long. The extended version takes more than 2.5 hours, and the shortened version takes 30-40 minutes to be completed. Separate subtests can be administered independently for a more focused (and shorter) examination of specific areas of verbal function. Some used specific tests are the Boston Naming Test, Controlled Oral Word Association Test, and Sentence Repetition. In the Boston Naming Test, patients are required to name 60 objects depicted in line drawings. The objects range from simple and common objects such as a tree to complex and uncommon objects such as an abacus. If a patient is unable to name an object, the patient is given a semantic cue.

Finally, to complete aphasia assessment it is necessary to obtain brain images (CT, MRI, PET) to characterize the lesions and their etiology.

3.2.5 TREATMENT OF APHASIA

Treatment of aphasia is multidisciplinary and personalized, and it depends on the severity, the type of aphasia, the location of the lesions, and its etiology.

Speech therapy

Nowadays, the standard treatment of aphasia is speech therapy. Speech and language therapy should be typically started as soon as the patients become stable, which is generally possible in acute stroke units (in the acute/subacute stage of stroke). Studies have demonstrated that intensive speech therapy intensity has better outcomes than low-intensity speech therapy. Thus, speech therapy should be at least 1 hour per day in the first months after stroke onset. The positive outcome of speech therapy also depends on the patient's age (the younger the patient is, the better

are the results), patient's motivation, the presence/absence of concomitant complications (it is better if there are no associated complications), the etiology of the damage and the extension of it (minor deficits have the better outcome). Speech therapy has never been proven to hurt the patient and it is recommended to any aphasic patient adapting it to the patient's specific needs. (27)

The main objectives of the therapy are:

- Keep the patient verbally active: it is important to avoid the single-use of gestures, we have to communicate to patients using verbal or written language
- Relearn language
- Provide strategies to improve language
- Teach patient's family to improve communication
- Psychological support(12)

Speech therapy should be conducted by a specialized speech therapist. The speech therapy strategy should be adapted to each patient according to his/her aphasia syndrome. Unfortunately, the outcomes of speech therapy are limited, and the patients' recovery is heterogeneous. Some patients accomplish good recovery while others remain with language impairment for the rest of their lives. The rate of patients regaining the ability to communicate at 1 year and therefore, responding to speech therapy is the following. Only 1/3 of global aphasia, 40% of Broca's aphasia, 60% of Wernicke's aphasia, 70% of conduction aphasia, 60% of transcortical aphasia (including sensory, motor, and mixed), and 90% of anomic aphasia. (16) Hopefully, transcranial magnetic stimulation would increase the rate of response of these patients and help them to recover language function.

Pharmacotherapy

Pharmacotherapy for the treatment of aphasia has been studied over the last years with no good evidence of benefits. Therefore, pharmacotherapy is not regularly accepted in daily practice and it is only used on clinal trials.

The role of pharmacotherapy is based on the possibility that functional impairment of aphasia may be caused by the dysregulation of neurotransmitters release caused by neuron damage. Most studies evaluate drugs aimed at GABA-aminergic systems (piracetam), catecholamine systems (bromocriptine, dexamfetamine), and acetylcholine systems (donepezil). Recent studies suggest that piracetam, paired with speech therapy, promotes the reactivation of the damaged tissue around the infarct. Piracetam has positive effects in the acute phase but it has not been proven to

be effective in long-term use. Bromocriptine did not improve nonfluent aphasia in a randomized, double-blind, placebo-controlled clinical trial. Dexamfetamine improved subacute aphasia in a recent trial and the effects last for 6 months but it did not reach statistical significance. Donepezil has also been used in fluent aphasia obtaining moderate results. In conclusion, the efficacy of pharmacological treatments needs to be proven in chronic aphasic patients. (28)

Transcranial magnetic stimulation

TMS has been studied in recent years and it has proven positive effects in the recovery of aphasic patients. In the following chapter, I will widely discuss the effect of TMS in post-stroke aphasia.

3.3 TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulation and neuromodulation technique that delivers magnetic pulses to the brain capable of depolarizing neurons in humans. TMS uses electromagnetic induction to induce weak electric currents in the brain. TMS is considered a non-invasive brain stimulation technique (NIBS) and it has been studied as a tool to study brain function and recently, as a therapeutic tool for different psychiatric and neurologic diseases.

Figure 5 Applying rTMS to a patient using a figure-8 coil

3.3.1 FUNDAMENTALS

Transcranial magnetic stimulation is based on the principle of electromagnetic induction discovered for Michael Faraday in 1831. The principle says that every electrical field generates a perpendicular magnetic field and vice versa. In TMS, a stimulator generates an electrical current that flows within the coil and generates a transient magnetic field, which propagates in space and induces a secondary current in the brain that is capable of depolarising neurons if the coil is held over the subject's head. (29)

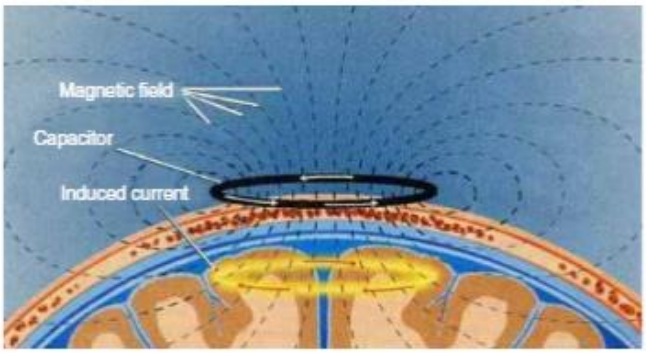


Figure 6 Electromagnetic induction from

3.3.2 MODERN TMS DEVICE

The modern TMS device has different components:

- Stimulator/computer: it generates the electrical current. We can control and establish the stimulation parameters such as the number of stimuli, strength, and duration.
- Flexible wire: it transmits the electrical current from the stimulator to the coil.
- Coil: the coil generates the magnetic field thanks to the electrical current that flows in it. There are different coil types. The most used ones are the figure-eight coil and the round coil. The round coil generates a wide magnetic field and can simultaneously stimulate both hemispheres. The figure-eight coil generates a more localized magnetic field allowing a selective neuron depolarization.

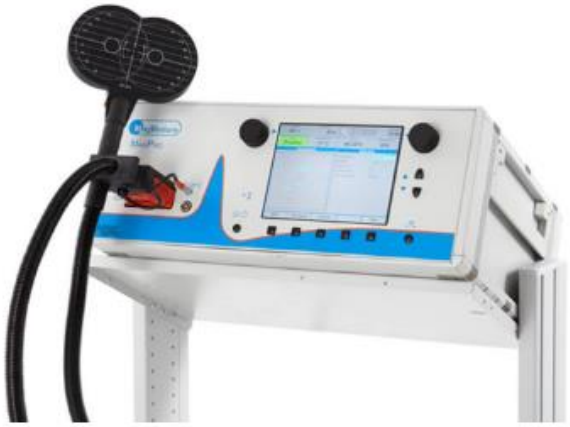


Figure 7 Modern TMS devise from (29)

3.3.3 MODALITIES OF TMS

We have different application modalities of TMS depending on the frequency and duration of the magnetic pulses:

- Single TMS: produces a single pulse that stimulates a specific cerebral area. It is used to stimulate the primary motor cortex to record Motor Evoked Potentials (MEP)
- Paired TMS: produces two stimuli. It can assess the functional integrity of intracortical facilitation and inhibition circuits. It is used to explore intracortical excitability, interhemispheric connectivity, and calculate trans callous conduction time.
- Repetitive TMS (rTMS): produces repetitive stimuli. It is demonstrated to produce long-lasting effects that persist after the stimulation.

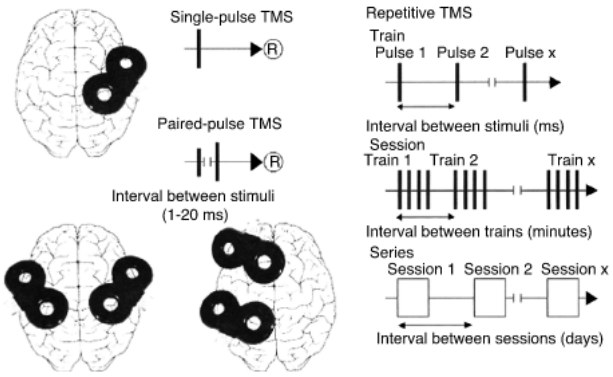


Figure 8 Different modalities of TMS from (30)

3.3.4 FACTORS DETERMINING STIMULATION PROTOCOLS

Mechanical factors and biological factors influence the effects of transcranial magnetic stimulation. The mechanical factors are the **stimulation parameters** that are adjusted for the desired outcome according to safety rules. We can determine the following stimulation parameters.

- **Intensity**: expressed as % of resting motor threshold (RMT). RMT reflects the excitability of the cortex and it is the minimum stimulus intensity capable of eliciting a motor evoked potential of at least 50mV in 5-10 consecutive stimulations. RMT is determined by placing the coil over the motor cortex which will depolarize pyramidal neurons and the stimulus will travel along the corticospinal tract generating a motor evoked potential. The motor evoked potential will be recorded in a belly-tendon montage on the skin overlying the selected muscle.

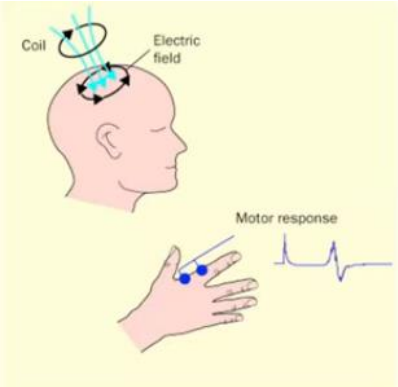


Figure 9 Determination of motor evoked potential from (31)

- **Frequency**: Frequency is the number of TMS pulses delivered per second. Depending on the frequency of the stimulation, rTMS is classified into:

    - High-frequency rTMS (>1 Hz): the most used frequencies range from 5 to 25 Hz. High-frequency stimulation may increase cortical excitability and originating long-term potentiation.
    - Low-frequency rTMS (1 Hz or lower): low-frequency rTMS may depress cortical excitability and causing long-term depression.
- **Number of trains**: a train is a set of pulses of the same intensity and frequency that last a determined range of time
- **Inter-train interval** (ITI): the time between the delivery of two consecutive trains
- **The number of pulses**: the number of pulses per train depends on the train duration and the number of pulses per session depends on the number of trains per session.
- **Coil type**: there are different coil types. The most used ones are the figure-eight coil and the round coil. The round coil generates a wide magnetic field and can simultaneously stimulate both hemispheres. The figure-eight coil generates a more localized magnetic field allowing a selective neuron depolarization which is desired for therapeutic uses.
- **The orientation of the coil**: the orientation of the coil determines the place we are stimulating. The coil is orientated facing the scalp when stimulating and not facing the scalp when administering sham stimulation.
- **Distance:** the distance between the coil and the scalp also determines the place we are stimulating. The more distance we have with the scalp, the superficial the stimulation will be.

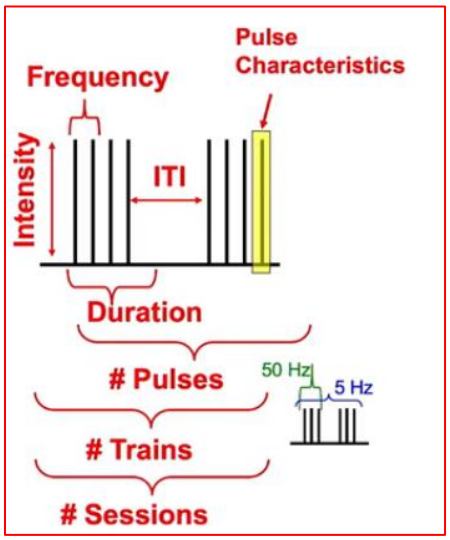


Figure 10 rTMS stimulation parameters from (31)

The biological factors that influence the effects of TMS are structural/functional architecture, target selection, and initial cortical activation state. The biological factors require prior knowledge of brain structure and function. For these reasons, to adequate stimulating protocols we need to acquire structural and if possible, functional neuroimages from patients before stimulation.

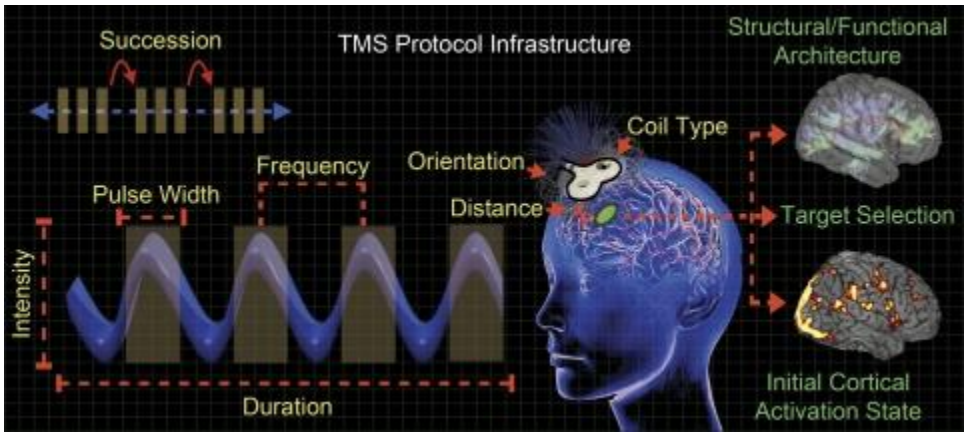


Figure 11 Factors that influence the effects of transcranial magnetic stimulation (TMS) from (32)

3.3.5 MECHANISM OF ACTION OF rTMS

Repetitive transcranial stimulation can produce long-lasting effects which is the reason it has therapeutic effects. The effects of rTMS depend on the length of stimulation: the longer the stimulation period, the longer the duration of effect. (33) The mechanism of action of rTMS is not well known. However, there is evidence that suggests that TMS excites neural tissue and induce synaptic plasticity and neuronal reorganization. In other words, TMS could induce long-term potentiation (LTP) or long-term depression (LTD) depending on the stimuli we apply to the patient. High frequency rTMS stimulation may induce LTP-like plasticity and low-frequency rTMS may induce LTD-like plasticity. (17)

rTMS could have another important effect on the physiology of neuromodulators such as dopamine, serotonin, acetylcholine, or adrenaline. Neuromodulation can induce neuron plasticity beyond the stimulation period which can justify the long-term effects of rTMS. (17)

3.3.5 CLINICAL POSSIBILITIES OF rTMS

Nowadays, rTMS is approved by the US Food and Drug Administration (FDA) for the treatment of medication-refractory major depression syndrome. Thus, refractory depression syndrome is the only approved indication for clinical use of rTMS.

However, the use of rTMS is wide in the research field because it is believed to have good therapeutical potential. Some current evidence suggests beneficial effects of rTMS for different clinical indication including neuropathic pain, complex regional pain syndrome type I, fibromyalgia, Parkinson's disease, motor stroke, hemispatial neglect, multiple sclerosis, epilepsy, Alzheimer's disease, tinnitus, depression, post-traumatic stress disorder, obsessive-compulsive disorder, schizophrenia (including auditory hallucinations and negative symptoms) and for addiction and craving. (34)

Some recommendations of rTMS efficacy have also been made for post-stroke aphasia (level B). Nonetheless, the recommendations are still weak, and we need more evidence before it is approved for using it in clinical practice.

3.3.6 CURRENT EVIDENCE ON APHASIA REHABILITATION USING rTMS

After suffering a stroke, some patients have aphasia because of the damage to the language centers and the interruption of the language networks. Some patients are capable of correctly reorganize their neuronal networks by themselves but in other patients, this capacity is suboptimal due to lack of neuroplasticity, and the problem persists and becomes chronic. rTMS can induce changes in cortical excitability, increasing the plastic capacity of the brain, and facilitating the recovery or reorganization of affected neural networks, and restoring balance in brain interhemispheric interactions. rTMS aim to improve the patient's prognosis and quality of life by promoting adaptative cortical reorganization after stroke to restore language function in post-stroke aphasic patients.

The rehabilitation of aphasic patients has two main strategies:

- Recruitment of perilesional cortical regions in the dominant hemisphere (left hemisphere)
- Development of language ability in the non-dominant hemisphere (right hemisphere)

Following the first strategy, we have two ways to recruit perilesional cortical regions in the left hemisphere using conventional rTMS:

- Using an **inhibitory protocol** (low-frequency rTMS) in the right hemisphere to reduce activity in the contralateral homologous area and reduce transcallosal inhibition of the left hemisphere. Most rTMS studies employ this protocol to obtain promising outcomes. The

site of stimulation usually is the right inferior frontal gyrus (*pars triangularis, pars opercularis, or pars orbitalis*). Other studies stimulate the primary motor cortex (ventral) or superior temporal gyrus.

- Using an **excitatory protocol** (high-frequency rTMS) in the left hemisphere (on the left inferior frontal gyrus)

Scientific research has focused on studying the efficacy of applying an inhibitory protocol in the right hemisphere. Weiduschat's group conducted the first controlled study which included 10 patients suffering subacute post-stroke aphasia. The patients received low-frequency rTMS in the right frontal gyrus compared to sham-stimulation (placebo). Performance on language tests, evaluated through the Achen Aphasia Test showed significant improvement after two weeks compared to the control group. (35) With similar intervention protocols, other studies such as ones performed by Heiss' group or Thiel's group have found similar positive results. (36,37) However, studies performed by Walsowski and Seniów have not found significant differences between both groups using the same protocol. (38,39) In an attempt to obtain better results, some groups have tried to obtain a more homogenous sample. Barwood group conducted a controlled clinical trial focusing on Broca's aphasic patients. They demonstrated that applying low-frequency rTMS in the pars triangularis of the right inferior frontal gyrus (IFG) improved language compared with the group receiving sham stimulation. They demonstrated significant improvement in accuracy and time reaction in the Picture Naming Test. (40) Promising results were also obtained by the Tsai group but the current evidence is not enough to recommend the use of rTMS on IFG for language rehabilitation in post-stroke Broca's aphasic patients. (41)

There are hardly any studies focusing on the effect that the application of an inhibitory protocol on the injured hemisphere has on the rehabilitation of aphasia. The most important studies are performed by Dammekens', Szaflarki's, and Cotelli's group. Dammekens's group published a single case study founding positive effects on different language functions. (42) Szaflarki's and Cotelli's groups also found positive results in chronic patients with an intervention protocol with excitatory rTMS on the damaged group. (43,44)

Following the second strategy, to stimulate the development of the non-dominant hemisphere we could use an excitatory protocol in the right hemisphere or an inhibitory protocol in the left hemisphere. (22)

Recently, some studies are starting to do dual-hemispheric rTMS which consists of stimulating both hemispheres targeting the same objective. For example, if we aim to recruit perilesional cortical regions in the left hemisphere, we use both protocols: an excitatory protocol in the left hemisphere and an inhibitory protocol in the right hemisphere. (17)

Despite the positive results obtained in both protocols, the empirical evidence is insufficient to be able to make recommendations on the use of rTMS in the rehabilitation of post-stroke aphasic patients. The main limitations of the current studies are:

- The heterogeneity of the patients included: including patients with different aphasia syndromes, different times after the stroke onset, etc.
- The lack of official guides about stimulation protocols. There are a variety of rTMS protocols, no one is standardized, and they are being tested. (17) In research, real stimulation is compared with sham stimulation (placebo stimulation).rTMS is conceived to be a complementary treatment for aphasic patients. For this reason, most studies use rTMS as the neoadjuvant treatment for speech and therapy. The stimulation parameters used are heterogeneous. The stimulation typically lasts for 20-40 min per session for 10-15 days. (45) The intensity of stimulation is defined with the individual patients resting motor thresholds (RMT), most studies use an intensity close to 90% of RMT.
- The number of resources needed to perform the studies. rTMS and its equipment could be expensive especially if we use functional imaging to determine the size of stimulations. For the sake of comparison, a 4-6 week rTMS treatment in depression costs approximately 10.000 dollars in the United States of America. (17)
- The variability of the stimulation site between patients and between each stimulation session in the same patient. The site of stimulation might be selected by using the 10-20 international system (based on the normative relationship between the location of the electrode and the underlying area of the cerebral cortex) but it is not faithful because there is stimulation variability due to differences in neuroanatomy seen in post-stroke patients. Therefore, other studies determine the site of stimulation using stereotactic neuronavigational systems that use patients' MRI scans to localize targets for stimulation. Moreover, to be ever more precise, we could use functional imaging modalities such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). The basis of functional neuroimaging consists of relating neuron function with increased

blood flow (used in fMRI) or metabolism (used in PET where we use regional cerebral metabolic rate of glucose). Using functional imaging we can identify areas with greater activation during language tasks and target them during stimulation. In this way, we could adapt the site of stimulation for every patient. Moreover, functional imaging helps use to visualize disturbed language networks and study reorganization after brain damage and monitor the effects of stimulation. (17)(46)

- The lack of outcome measures focusing on the improvement of quality of life of patients receiving rTMS. To assess the benefits of rTMS, scientific studies apply neuropsychological tests, but we still do not know whether an improvement in the performance of these tests would represent a significant improvement in patient's communication ability and quality of life.
- The lack of long-term outcome measures because of the lack of follow-up of the patient months after the stimulation.

The outcomes of studies are diverse. rTMS is seen to be more effective in patients with non-fluent aphasia rather than other types of aphasia. rTMS has been studied in subacute and chronic patients to improve neuronal reorganization after stroke. Both subacute and chronic patients have positive results but subacute appear to be better respondents. Evidence has shown that rTMS can increase performance on a variety of language data. However, there is a need for randomized controlled clinical trials to increase evidence are eventually, introduce rTMS to the clinical practice. (17)

3.3.6 ADVERSE EFFECTS OF rTMS

TMS is a safe technique and a well-tolerated technique. The main adverse effect is local pain, headache, and neck ache due to the stimulation of superficial nerves and the contracture of local muscles. The pain is mild and can be treated with analgesia. It has been postulated that TMS increases the risk of seizure in epileptic patients and patients suffering from pro-epileptogenic conditions but there is no clear evidence of this effect in current studies. However, the use of TMS in epileptic patients is limited. (29) Other exceptional side effects are hearing loss because of the noise emitted by the stimulator and it is reduced by asking the patients to wear earplugs, psychiatric symptoms such as psychosis or mood change in patients suffering from psychiatric diseases.

3.3.7 CONTRAINDICATIONS of rTMS

The main absolute contraindications of TMS are drug-resistant epilepsy and patients wearing electrical devices (pacemakers, insulin pumps, implantable defibrillators, vagus nerve stimulators) or ferromagnetic intracranial devices or located within less than 30cm of the treatment area (plates, screws, ventriculoperitoneal shunts, stents, dental and cochlear implants). Titanium implants are safe. Other contraindications are pregnancy, lactation. The relative contraindications of TMS are current drug-abuse, the recent change in medication (especially drugs that could alter neuron's excitability), history of psychiatric disease, TBI, or cerebral tumor. (29)

4. JUSTIFICATION

Stroke is a disease of immense public health importance; it is the second cause of death worldwide with an annual rate of 5.5 million people and a major cause of morbidity worldwide resulting in more than 50% of survivors being chronically disabled. Moreover, stroke incidence is expected to increase significantly in the future so, the number of patients suffering from stroke sequelae will be even higher. (2)

Aphasia is one of the most disabling sequelae of stroke and unfortunately, it appears in 21 to 38% of patients suffering a stroke. (12) Aphasia is an acquired alteration of the capacity for language with the integrity of the neuromuscular structures producing it. Imagine for a minute that suddenly you lose the capacity to express yourself or understand others, how would you feel? You would feel isolated, powerless, sad, angry, depressed, crossed, nervous, frustrated… right? Aphasia is a disabling condition that truly affects the quality of life of the patients. It has a huge impact on personal, social, familiar, and work-life. Moreover, patients with post-stroke aphasia have greater mortality and morbidity than stroke patients without aphasia. (47) It is not strange that the loss of language has these important consequences. As Aristotle said, a human is a social creature so, the ability to communicate with others makes us humans. The importance of language is undeniable. Language is the way we interact with the world and the way the world interacts with us.

For these reasons, the rehabilitation of post-stroke aphasic patients is a priority. Some post-stroke aphasic patients spontaneously have some functional recovery during the acute phase but, residual deficits are common. Nowadays, we do not have a specific treatment for subacute-chronic post-stroke aphasic patients. Patients are sent to speech-language obtaining limited results. (16) Luckily, there is an increasing interest in studying specific treatments for post-stroke aphasic patients. One field with increasing importance for the treatment of aphasia is repetitive transcranial magnetic stimulation (rTMS). Scientific research has focused on studying the efficacy of using rTMS to potentiate the recruitment of perilesional left language areas to improve the functional recovery of aphasic patients obtaining positive results. (37,38,39,40,41,42,43,44,45,46)

However, the empirical evidence is insufficient to be able to make recommendations on the use of rTMS in the rehabilitation of post-stroke aphasic patients because of the mentioned limitations of these scientific studies and the lack of randomized, double-blinded clinical trials.

Considering the current limitations of current rTMS studies, we have designed this clinical trial that we believe will provide evidence of the beneficial effects that rTMS could have in the rehabilitation of post-stroke nonfluent aphasic patients. Hopefully, in the next years, we will be able to use rTMS in the future clinical practice to help these patients to retrieve our most precious asset: language.

5. HYPOTHESIS AND OBJECTIVES

HYPOTHESIS

This study hypothesizes that the administration of rTMS before speech therapy can facilitate language recovery when compared to the administration of sham stimulation on post-stroke subacute non-fluent aphasic patients. Moreover, the improvement of speech performance will improve the quality of life and mood of these patients.

The aim of rTMS is recruiting perilesional cortical language regions in the left hemisphere which we suppose is beneficial for the rehabilitation of aphasic patients. We believe that the recruitment of perilesional cortical language regions in the left hemisphere can be achieved by applicating an inhibitory protocol (LF-rTMS) over the right-hemispheric homolog language regions (in patients whose fMRI shows predominant activation of these areas) or applicating an excitatory protocol (HF-rTMS) over the left-hemispheric language regions (in patients whose fMRI shows predominant activation of these areas) according to the interhemispheric balance.

PRIMARY OBJECTIVES

The objective of this study was to assess the effectiveness of applying real-rTMS before speech therapy to facilitate language recovery in post-stroke subacute non-fluent aphasic patients shown by an improvement in their performance on the neuropsychological test of Boston Diagnostic Aphasia Examination (BDAE) in short-term (assessed just after the intervention) and in long-term (6 and 12 months after the intervention).

SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To study the improvement of the quality of life of these patients assessed by *Stroke and Aphasia Quality of Life Scale (SAQOL-39)* in short-term (assessed just after the intervention) and in long-term (6 and 12 months after the intervention).
- To study the improvement of mood symptoms assessed by the *Stroke Aphasic Depression Questionnaire (SADQ-10)* in short-term (assessed just after the intervention) and in long-term (6 and 12 months after the intervention).

- To study the safety of the process, the incidence of adverse effects and register the differences regarding tolerability between the different stimulation protocols (LF-rTMS, HF-rTMS, and sham-TMS)

6. METHODOLOGY

6.1 STUDY DESIGN

A randomized double-blinded (except for the stimulation procedure) sham-controlled clinical trial: patients will be randomly divided into the experimental group that will receive real-rTMS + speech therapy or into a control group that will receive sham-rTMS (placebo stimulation) + speech therapy. The clinical trial will take place at Hospital Universitari Doctor Josep Trueta (Girona).

6.1.1. RANDOMIZATION AND BLINDING METHODS

Patients will be randomly allocated to one of the groups: the experimental group receiving real-rTMS and the control group receiving sham-rTMS. They will be randomized into a 1:1 ratio and they will be stratified by stroke type (ischemic or hemorrhagic). Randomization will be performed by an independent company after the successive enrolment of participants. Patients of the experimental group will receive a stimulation protocol depending on their fMRI results: patients showing predominant activation of the left hemisphere on the fMRI will receive HF-rTMS on the left hemisphere and patients showing predominant activation of the right hemisphere on the fMRI, will receive LF-rTMS on the right hemisphere.

The clinical trial will be double-blinded except for the stimulation procedure that could only be done single-blinded due to the impossibility to blindly conduct the intervention. However, the pre-treatment and post-treatment assessments and the speech therapy will be double-blinded.

Table 2 Clinical trial description

STUDY TYPE	Interventional: clinical trial
HEALTH CARE CENTER	Single centre: Hospital Doctor Josep Trueta (Girona)
ALLOCATION	Randomized 1:1 ratio
CONTROL TYPE	Sham-stimulation (placebo)
INTERVENTION MODEL	Parallel assignment
MASKING	Double-blind (subject, investigator/examinator) * The stimulation procedure will be single-blinded due to the impossibility to blindly conduct the intervention
PRIMARY PURPOSE	Treatment

6.2 STUDY SUBJECTS

The study population of this clinical trial will be post-stroke subacute non-fluent aphasic patients. Subacute post-stroke aphasic patients are patients suffering from aphasia from 12 weeks to 52 weeks after the stroke.

6.2.1. INCLUSION CRITERIA

Our inclusion criteria are the following ones:

- Age > 18 years old
- The presence of a first-ever stroke either ischemic or hemorrhagic confirmed by CT or MRI in the left-dominant hemisphere
- Subacute stage of aphasia (from 12 weeks to 52 weeks after stroke)
- Diagnose of Broca's aphasia or transcortical motor aphasia (non-fluent aphasias) recognized in neuropsychological assessment in a patient with prior normal language function
- Right-handed patients
- Catalan or Spanish native
- Presence of at least one caregiver responsible for patients' adherence to treatment
- Written informed consent by the patient or legal tutor. (see Annex 8)

6.2.2. EXCLUSION CRITERIA

Our exclusion criteria are the following ones:

- Prior stroke
- A neurodegenerative disease that could explain language deficits such as Parkinson, dementia, motor neuron disease, etc.
- History of drug-abuse substances, depression, or other neuropsychiatric diseases
- Use of drugs that could alter neuronal excitability
- Auditory or visual deficits that might impair the evaluation of language function
- Participation in another therapeutic intervention in the same period
- Contraindications for magnetic stimulation: pregnancy or lactation, epilepsy, electrical devices (pacemaker, cardioverters, defibrillators, pumps, and cardiac lines), and ferro-metallic implants in or near the head (<30cm) according to safety guidelines. (48,49)

- Mute patient (Scoring 0 points on Aphasia Severity Rating Scale of BDAE)
- Prior use of rTMS

6.2.3 WITHDRAWAL OF THE STUDY CRITERIA

Our withdrawal criteria are the following ones:

- Revocation of the informed consent
- The occurrence of complications or adverse effects related to the assigned therapy
- Patients who do not follow the clinical trial protocol: no attending to follow up, no attending to stimulation therapy, no attending to speech therapy, etc.

6.3 SAMPLING

6.3.1. PATIENT SELECTION

We will select our patients by consecutive sampling. Stroke is an emergent and unexpected clinical situation as they are consequences such as aphasia so, we do not know our potential patients until they assist in hospital and are diagnosed with aphasia post-stroke. For this reason, we will use a non-probabilistic consecutive sampling method: any case of post-stroke subacute non-fluent aphasic patient will be considered a potential patient to be enrolled in our research clinical trial. The recruitment of the patients will be done by the neurologists at the follow-up visits of the patients. If the patient accomplishes the inclusion and exclusion criteria and the informed consent is accepted, he or she will be formally included in our study.

6.3.2. SAMPLE SIZE

We used the GRANMO free calculator available online to calculate the sample size.

We wanted to know the number of patients we need to include in our clinical trial to determine the effectiveness of using real-rTMS before language therapy in improving language function among post-stroke subacute non-fluent aphasic patients shown by an improvement in their performance on the Boston Diagnostic Aphasia Examination (BDAE). As the Boston Diagnostic Aphasia Examination includes a wide range of subtests and we were not able to calculate the sample size for each test, we have selected the 15-item Boston Naming Test as the main dependent variable.

There are no previous significant references regarding the expected performance of aphasic patients on the Boston Naming Test. However, Lansing et al. provided standard deviations of 15 item BNT when applied to a healthy population (SD ≈ 1.8) and when applied to Alzheimer's patients (SD ≈ 3.1) (50). Moreover, Naeser et al. provided a standard deviation of BNT when applied to 4 aphasic patients (SD≈ 4.69) (51). Peña-Casanova et al. provided standard deviation among healthy people from 18 to 39 (SD ≈ 3.8) and among healthy people older than 70 years (SD≈ 6.3) when using 60-item BNT. (52)

Using the information from the literature review, it has been assumed a standard deviation of 4 because we expect that acquired punctuation in 15-item BNT among aphasic patients would include a wide range of values because mild aphasic patients have high punctuations while severe aphasic patients have very low punctuations.

According to the study design, we want to determine the differences between two mean from two independent samples (experimental vs control). We will be accepting an alfa risk of 0.05 and a beta risk of 0.2 in a bilateral contrast. The ratio between the experimental size and the control size is 1 because the randomization follows a 1:1 ratio. The standard deviation we will consider is 4 and the minimum expected difference is estimated to be 3 points in Boston Naming Test. Finally, we estimated a drop-out rate of 10%.

GRANMO results show a sample size of 32 participants in each arm. Therefore, the total number of participants in our study will be 64.

6.3.4 ESTIMATED TIME OF RECRUITMENT

According to non-published data, the Hospital Universitari de Girona Doctor Josep Trueta (Girona) attends around 800 patients with stroke for a year. According to the bibliography, around 35% of patients suffering from stroke will have aphasia which means around 280 post-stroke aphasic patients for a year. However, non-fluent aphasias (Broca's aphasia and transcortical motor aphasia) represent 1/3 of the total amount aphasias which leave us with 93-94 non-fluent aphasic patients for a year.

Therefore, the approximated time of recruitment will be 1 year because the new diagnosticated cases of the non-fluent aphasic patient for a year are 92-94 and we need 64 participants for our clinical trial so, we assume we will be able to recruit the participants we need in one year.

6.4 VARIABLES

6.4.1 INDEPENDENT VARIABLE

The independent variable of the study will be the type of stimulation applied to the patient. The clinical trial will have an experimental group receiving real-rTMS + speech therapy and a control group receiving sham-rTMS (placebo) + speech therapy.

Both experimental and control groups will be divided into two groups: group A and C will include patients with predominant activation of the right hemisphere in the fMRI and groups B and D will include patients with predominant activation of the left hemisphere in the fMRI.

As our goal is to activate the left hemisphere language areas using real rTMS, in the experimental group we will inhibit the activated right hemisphere language areas of the patients of Group A and we will stimulate the activated left hemisphere language areas of the patients of group B. In the control group, we have followed the same methodology, but the patient will not receive any stimulation because the coil will not be facing the patient's brain. (See Intervention).

Patients of both experimental and control groups will receive a 45-minute speech and language therapy after every stimulation session focused on the patients' linguistic symptoms delivered by a neuropsychologist.

Table 3 Main independent variables

	Experimental group= REAL rTMS		**Control group = SHAM rTMS**	
	Group A = patients with predominant activation of the **right** hemisphere in the fMRI	Group B= patients with predominant activation of the **left** hemisphere in the fMRI	Group C= patients with predominant activation of the **right** hemisphere in the fMRI	Group D= patients with predominant activation of the **left** hemisphere in the fMRI
Coil used	Figure 8 coil	Figure 8 coil	Figure 8 coil	Figure 8 coil
Site of stimulation	Most activated area of the right hemisphere	Most activated area of the left hemisphere	No side of stimulation. The coil will not be facing the brain but it will be held on the right side	No side of stimulation. The coil will not be facing the brain but it will be held on the left side
Frequency	1Hz (LF)	10 HZ (HF)	1Hz (LF)	10 HZ (HF)
Trains	Continuous train	10 trains (every train lasts 5 seconds and has 50 pulses)	Continuous train	10 trains (every train lasts 5 seconds and has 50 pulses)
Intensity	90% of RMT of the first dorsal interosseous	80% of RMT of the first dorsal interosseous	90% of RMT of the first dorsal interosseous	80% of RMT of the first dorsal interosseous
Total of pulses	1200 pulses	500 pulses	1200 pulses	500 pulses
Nº sessions	10 session (5 days/week)	10 sessions (5 days/week)	10 session (5 days/week)	10 sessions (5 days/week)
Session duration	20 min	320 seconds (5-6 min)	20 min	320 seconds (5-6 min)

6.4.2 DEPENDENT

6.4.2.1 MAIN DEPENDENT VARIABLES

The main dependent variable in our study will be an improvement in language function. The language function will be assessed using the battery test called ***Boston Diagnostic Aphasia Examination (BDAE)*** from Goodglass H, Kaplan E. This battery test includes a wide range of subtests and every subtest has its punctuation. The test will be administered by a qualified neuropsychologist with experience in aphasia assessment. The test consists of different parts. The first part consists of an informal conversation which includes seven common questions, in a free conversation about a familiar theme for the patient, and finally and in the description of the *Cookie theft picture* (see Annex 3.2). Moreover, the first part help to assess the aphasia severity using the Aphasia Severity Rating Scale (see Annex 3.1). The second part includes a set of subtests that allows us to explore the different areas of language: auditive comprehension, oral expression, repetition, naming (Boston Naming Test), lecture, scripture (see Data Collection and Annexes 3.3 and 3.4). For this study, we will focus on the severity of aphasia obtained from the Aphasia Severity Rating Scale and in the subtest that evaluates the following language domains: fluency, naming, repetition, and comprehension. (52)(53)

The main dependent variable of our clinical trial is the ***Boston Naming Test*** included in BDAE. BNT is used to assess patients' capacity to denominate. The updated version is from 2001, written by Kaplan, Goodglass, and Weintraub. We will use a shortened version consisting of 15 pictures ordered in increasing difficulty that the subject must name in a maximum time of 20 seconds for each one. If the correct answer is not given spontaneously, a semantic or phonetic clue will be given, the clues are previously preestablished. The suspension of the test will take place after 6 consecutive errors. The time of administration of the Boston Naming Test will take 5-10 minutes. The punctuation of the Boston Naming Test is obtained by adding up the correct spontaneous answers and the correct answers after the semantic clue. The maximum punctuation is 15 points. The higher is the punctuation of the patient, the better its denomination function is. However, another subtest will also be administered and assessed in our clinical trial.

The following table sums up the dependent variables obtained from **BDAE** that will be included in our clinical trial. The specific information of them is provided in Data Collection.

Table 4 Main dependent variables

Evaluated aspect	Name of subtest/variable	Punctuation range
Aphasia severity	Aphasia severity rating scale (ASRS)	From 0 to 5
Fluency	Nº of words of longest phrase obtained in the description of *Cookie Theft picture*	From 0 to (no limit of words)
Auditory comprehension	Word discrimination	From 0 to 16 points
Repetition	Word repetition	From 0 to 5 points
Naming	**Boston Naming Test**	From 0 to 16 points

6.4.2.1 SECONDARY DEPENDENT VARIABLES

- ***Stroke and Aphasia Quality of Life Scale*** *(SAQOL-39*): we will use the version published in 2009 by K. Hilari, City university (see Annex 4). This questionnaire includes 39 questions in three domains: physical, psychosocial, and communication. It has two parts: first 21 questions ask how much trouble the patient had with a specific activity during the previous week on a 5-point scale (1= Could not do it at all, 2= A lot of trouble, 3= Some trouble, 4= A little of trouble, 5= No trouble at all) and last 18 questions ask how whether the patient did or did not do a specific activity during the previous week also in a 5-point scale (5=Definitely yes, 4= Mostly yes, 3=Not sure, 2= Mostly no, 1= Definitely no). Scores from each test question are totaled and divided by the number of questions administered for a mean score indicative of the quality of life. Higher scores reflect a higher quality of life. (54)(55)
- ***Stroke Aphasic Depression Questionnaire***, we will use its Spanish version (see Annex 5). SADQ-10 is a 10-item questionnaire comprised of questions regarding the presence of depressive behavior. SADQ-10 is scored assigning corresponding numeric values to observer selections (0= not at all, 1=on 1-4 days, 2=on 4-6 days, 3=every day). Higher scores indicate more severe depression symptoms. A cut-off score of 14 out of 30 indicates the presence of depression. The administration of the test can be administered by any healthcare professional, but we recommend that the clinician has experience in a psychiatric interview. The test has to be completed by the patient's caregiver to avoid communication problems between the patients and the professional. (56)(57)

- **Side effects**: every side effect occurring during the stimulation sessions or in the following days after it will be collected. We will register how many patients experimented each adverse effect to calculate the incidence. We will register the already know adverse effects and the not-described ones. The main adverse effects of transcranial stimulation are headache and neckache. Other rare adverse effects are seizures, hearing loss, and psychiatric symptoms.

6.4.3 COVARIATES

- Age: recorded as years of age
- Gender: recorded as female (F) or male (M)
- Level of education: recorded as years of education
- Duration of stroke: recorded as days since stroke
- Type of stroke: ischaemic or hemorrhagic
- Infarct size/ ICH: recorded as infarct volume in cm^3
- Infarct location/ICH: recorded as anatomical infarct localization
- NIH Stroke Scale: this scale is performed by the neurologist to obtain a quantitative measure of stroke-related neurologic deficits and determines the stroke severity. It is made up of 11 different items that evaluate a specific ability. Every ability is scored from 0 (normal) to 1, 2, 3, or 4 (complete impairment). The higher score, the more impaired the patient is. (See Annex 2)
- Patient's motivation assessed with Multidimensional Health Locus of Control: it is an 18-item scale that contains three 6-item subscales: internality, powerful others externality, and chance externality. (see Annex 9) The patient's motivation determines how much a person believes that his recovery depends on his behavior and the external person's motivation—how a person relates his state of health to the impact of the people surrounding him. The punctuation is obtained by asking the patient's agreement on a 5-point scale with different statements related to motivation. The punctuation obtained is directly dependent on the motivation level of the patient. (58)
- Pathological antecedents: it is necessary to ask for entities that contraindicate transcranial magnetic stimulation such as epilepsy, wear of electrical or ferromagnetic devices as well as the history of headache, neckache, hearing loss, psychiatric disease, etc. his data will not be considered in statistical analysis.

- Concomitant treatments: it is necessary to ask for concomitant drugs to detect possible interactions between drugs and transcranial magnetic stimulation. This data will not be considered in statistical analysis.

6.5 INTERVENTION

Our study intervention consists of the application of repetitive transcranial magnetic stimulation according to patients' randomization as a neoadjuvant treatment for speech therapy. First, we have to considerer some general considerations common in control and experimental groups.

6.5.1 GENERAL CONSIDERATIONS

Stimulation sessions: number of sessions, place of sessions

The stimulation will take place 5 days/weeks for 2 weeks. The stimulation session will take 20 min and immediately after it, patients will receive a 45-minute speech and language therapy. The stimulation will take place in a prepared and specialized room of Hospital Doctor Josep Trueta (Girona); a skilled medical team and life-support team will be available. The stimulation will be conducted by a qualified neurophysiologist accompanied by a physician or nurse specialized in seizure management which one of the most important adverse effects of rTMS. All safety conditions will be widely specified in Safety.

Stimulation settings

The stimulation will be applied using a stimulator equipped with a figure 8 coil (each loop is 70 mm diameter) and compatible with the fMRI-navigation system. During the intervention, participants will be awake and asked to sit in a chair relaxed and they will be asked to lean their head on a headrest to ensure immobilization. Patients hear a clicking noise and feel a tapping sensation when a pulse of stimulation is given. They will wear earplugs to protect their ears.

Stimulation intensity

The stimulation intensity will be individualized for every patient according to the individual's cortical excitability. The cortical excitability of each patient will be assessed by determining their resting motor threshold (RMT). RMT is the minimum stimulus intensity capable of eliciting a motor evoked potential of at least 50mV in 5-10 consecutive stimulations. The motor evoked potential will be

recorded in a belly-tendon montage on the skin overlying the first interosseous muscle (a part of the thumb muscle) of the hand (the unaffected one if the patient's hand is paralyzed).

Site of stimulation

The site of stimulation will also be individualized for every patient according to the results of their fMRI. The fMRI allows us to identify the brain area that has maximum activation during categorical semantic evocation comparing to the resting state. The fMRI stimuli will consist of semantical categorical evocation (animal names, phonetic and word starting with *p*, *a,* or *s*). During the basal stimuli, patients will be presented with a visual stimulus consisting of 3 dots inside a square. This fMRI stimulus will be performed with the aid of a neuropsychologist.

Using fMRI (gradient ECO EPI sequence) we will obtain blood oxygenation level-dependent (BOLD) images that will be processed using specific software to finally determine the most activated area of the patient during semantic evocation (ROI). In the same session, axial and coronal conventional T1- scans were obtained to situate the activated area in its anatomic place.

Coil positioning

Once we have the site of stimulation, we need to apply a specific rTMS protocol to it. As there is no alike brain and especially in patients who have suffered from a stroke, we will use an fMRI-guided navigation system to ensure accurate and stable coil positioning at the desired site of stimulation. The fMRI-guided navigation system uses a head model in 3D (created using patients' surface anatomical landmarks for the contain and patients' fMRI for the content) as a reference. The anatomical landmarks used were the tip and the alar wings of the nose, the nibs of the tragus of both ears, and the internal angles of both eyes. This system can track coil placement on the surface of patients' scalp concerning the brain in real-time. The coil will be facing tangentially with the patients' scalp with a 45º inclination.

Speech therapy

Both experimental and control groups will receive a 45-minute speech therapy after every stimulation session focused on the individual linguistic symptoms delivered by a clinically experienced aphasia therapist.

6.5.2 EXPERIMENTAL GROUP

The experimental group will receive real-rTMS. Real-rTMS protocol will vary depending on patients' fMRI results: patients showing predominant activation of the left hemisphere on the fMRI will receive HF-rTMS (stimulatory protocol) on the left hemisphere (group A) and patients showing predominant activation of the right hemisphere on the fMRI, will receive LF-rTMS (inhibitory protocol) on the right hemisphere (group B). The main objective in both groups is the recruitment activation of perilesional language areas of the left hemisphere so, we assume that the stimulation of both groups will have this final effect. The objective of sparing them into two groups is that we want to be precise in the stimulation side according to the patient's neuroanatomy and functional cerebral activity.

Group A

In patients of group A, we will apply an inhibitory protocol over the most activated language area of the right-hemisphere because if we inhibit the over-activated right hemisphere, we will allow the activation of the left-hemisphere according to the inter-hemispheric balance hypothesis. The parameters we will use will be:

- Site of stimulation: most activated language area of the right hemisphere
- Intensity: 90% of the RMT
- Frequency: 1Hz
- Continuous train
- Total number of pulses per session: 1200 pulses
- Duration of each session: 20 min

Group B

In patients of group B, we will apply a stimulatory protocol over the most activated language area of the left-hemisphere because we want to potentiate the activation of the left hemisphere. The parameters we will use will be:

- Site of stimulation: most activated language area of the left hemisphere
- Intensity: 80% of the RMT
- Frequency: 10 Hz
- Pulses per train: 50 pulses

- Duration of trains: 5 seconds
- Total nº of trains: 10 trains
- ITI: 30 seconds
- Total number of pulses per session: 500 pulses
- Duration of each session: 320 seconds (5-6 minutes)

6.5.3 CONTROL GROUP

The control group will receive sham-rTMS (placebo-stimulation). For sham-stimulation, we will use the same stimulation parameters as the experimental group but the stimulation will not be applied facing the patient's brain so, the patient will not receive any stimulation. The coil will be held so that the edge is in contact with the head while the remainder is rotated 90° away from the scalp in the sagittal plane. We make this to reproduce the noise of the stimulation. Because patients included in our study have never received rTMS we assume that the patient will not know that the stimulation he or she is receiving sham-stimulation.

To avoid differences with the experimental group, the coil will be held on the left or the right hemisphere depending on patients' fMRI results: in patients showing predominant activation of the right hemisphere on the fMRI (group C), the coil will be held on the right side and we will use the same stimulation parameters of group A; and patients showing predominant activation of the left hemisphere on the fMRI (group D), the coil will be held on the left side and we will use the same stimulation parameters of group B.

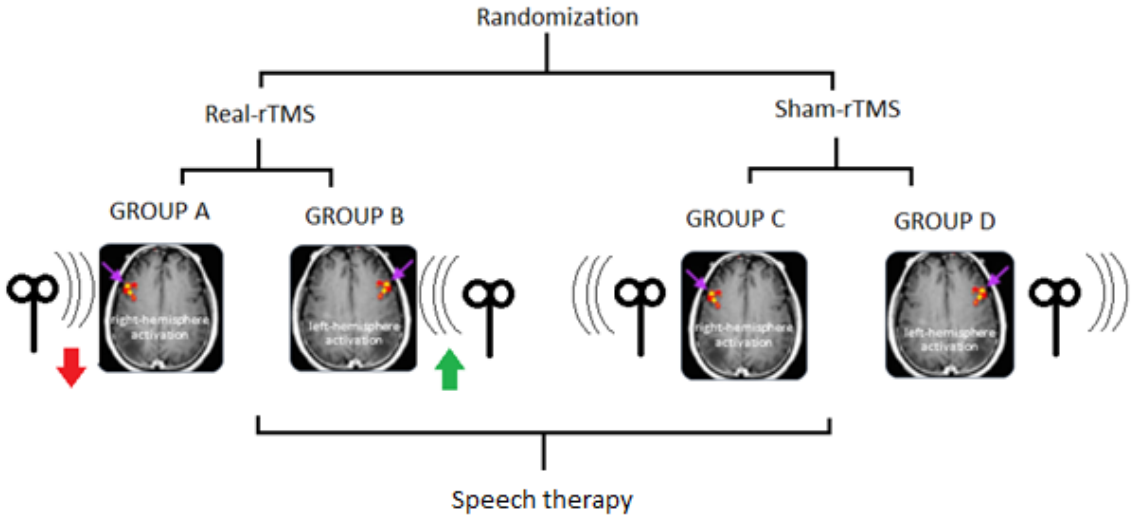


Figure 12 Review of the intervention process

6.6 SAFETY

Our clinical trial will respect and follow the safety precautions and practice recommendations established in the consensus conference held at the National Institutes of Health in June 1996 and reviewed and updated in a consensus conference held in Italy in June 2008. All safety guidelines and recommendations were summarized in Clinical Neurophysiology. (59)(60)

We declare that we will accomplish the following safety norms:

- We will individually select our patients according to a screening questionnaire that will be administered during a patient's recruitment. (see Annex 6) Every patient will be selected according to the risk/benefit ratio.
- We will use validated and approved rTMS stimulators and protection material
- We will establish stimulation protocols according to the safety limits reported in the mentioned safety guidelines.
- We will make sure that the application of rTMS is carried out by a properly trained medical assistant. All personal must be trained to recognize and manage every adverse effect that can occur during or after the stimulation session.
- We will make sure that the stimulation sessions take place in an appropriate room following the safety rules and with access to emergency medical attention.

- We will monitor patients after each rTMS session. The facultative administering rTMS will interview patients about their subjective sensations and possible side effects (headache, local pain, paresthesia). Moreover, we will evaluate the patient and monitor the patients' neurological state.
- We will communicate every adverse effect to the FDA in 24 hours and every severe adverse effect in a maxim period of 4 hours.
- We will contract Liability insurance to cover the possible adverse effects and damages that patients can suffer because of their inclusion in our clinical trial

The main safety concerns in the use of TMS are:

- Heating: it is accepted that the tissue-heating of the brain is small and cannot cause damage. However, if the patient wears conductive objects, they can heat and cause damage such as burns. For this reason, patients wearing these devices are not allowed to be included in this clinical trial.
- Forces and magnetization: the magnetic field produced by the coil can cause interactions with electrical or magnetic objects causing displacement or malfunction of them. For this reason, patients wearing these devices are not allowed to be included in this clinical trial.

Side effects of rTMS

- Hearing: the stimulation generates a noise that can reach up to 140 Db and some studies have reported mild hearing loss when they were not correctly protected. For this reason, patients must wear approved earplugs and in case they complain of hearing loss, they must be promptly reviewed by a qualified facultative. Moreover, patients with previous hearing loss or liable to it should not be included in the clinical trial.
- Seizures: seizures are the most severe rTMS adverse effect. Some seizures episodes have been reported in different studies worldwide. Seizures tend to occur during or some minutes after the stimulation. However, it is considered that the risk of seizure is very low because the number of reported seizures is low compared to the number of patients receiving rTMS. Moreover, most episodes occurred in patients sensitive to develop seizures because they were having pro-epileptic drugs, having sleep-deprivation, or brain lesions. In our study, we exclude patients with epilepsy history or having drugs affecting the nervous system. As our study includes patients with brain lesions because we study patients suffering from stroke, we will make certain that a physician or nurse assisting in the rTMS

session is skilled in seizure management and we will establish a protocol of seizure management. Moreover, our stimulation protocols are set according to the current regulations to prevent the apparition of seizures.

- Vasodepressor syncope: syncope has been reported during rTMS as an epiphenomenon, no as an adverse effect. It can occur when the patient is anxious and suffering from physical or psychological discomfort. We must distinguish between seizures and syncope. To avoid syncope, we should provide proper information to our patients, transmit confidence, and ensure the patients are sure. The nurse or facultative assisting in the rTMS sessions must know how to manage vasodepressor syncope.
- Local pain or headache: the stimulation causes a tricking sensation in the patient that can cause discomfort or pain. The patient will be warned, and painkillers will be prescribed in case they complain of pain.
- Acute psychiatric symptoms (mood change)

6.7 DATA COLLECTION

Data recorded from participants at the baseline and during the following visits will be registered and summited to the database. To preserve anonymity and keep the blind during the study, every patient will be assigned a specific identification code. The results of all the neuropsychological tests will be also physically stored labeled with patients' codes. (See Response Sheet of BDAE in Annex 16.3.5)

We will specify the data that we will collect in every period of our clinical trial.

Period 1: SCREENING AND BASELINE DATA

Screening visit (stroke follow-up visit with the neurologist): Once the neurologist makes sure the patient meets the inclusion criteria and does not meet any exclusion criteria, the study will be proposed. If the patient is interested in the clinical trial, it will be provided the study information sheet and the neurologist will explain and comment on it with the patient or with the caregiver. The patient will be assessed to determine his or her competency to make decisions. If the patient/legal tutor agrees, he/she will have to sign the informed consent and fulfill the personal data in the collection sheet. The data that we will include in our collection sheet will be:

- Informed consent

- Demographics
- Medical History
- General physical exam and neurological exam
- A safety screening questionnaire for the use of rTMS

Neuropsychology visit: the patient will be administered a neuropsychological battery test (BDAE) and psychological tests (SAQoL-39, SADQ-10).

1.1 Neuropsychological tests. The patient will be assessed using the Spanish or Catalan battery of BDAE (according to the patients' native language). As some of our patients are Catalan speakers, the test will have been previously traduced to Catalan and properly validated. We will assess aphasia severity using Aphasia Severity Rating Scale included in the BDAE and we have selected 4 subtests of this battery to evaluate the basal performance of our patient in the four main domains of language: fluency, repetition, comprehension, and nomination.

- To assess aphasia severity, we will use the **Aphasia Severity Rating Scale**. It is an ordinal scale ranging from 0 which means very severe aphasia with "no usable speech or auditory comprehension" to 5 "very slight language impairment, which is only perceived by the patient himself" (See Annex 3.1). The punctuation is assessed by the neuropsychologist based on the free conversation and the Cookie theft picture description. (Goodglass, Kaplan, & Barresi, 1996)
- To evaluate the patients' basal **fluency**, we will ask the patient to describe all he/she sees that happens on the ***Cookie theft picture*** (see Annex 3.2). The test will last 2 minutes, and it will be recorded to facilitate future transcription. We will register the **length of the patients' longest phrase (number of words)** defined as the maximum recurring number of coherent signs in an uninterrupted run. The neuropsychologist can point to neglected features of the picture and ask for elaboration if the patient's response is skimpier than his/her apparent potential. (Goodglass, Kaplan, & Barresi, 1996)
- To evaluate the patients' basal **repetition** function, we will ask the patient to repeat 5 different words. The neuropsychologist is allowed to repeat the word if the patients ask for it. To obtain punctuation, the word must be intelligible. The 5 words that the patient will need to repeat are the following Catalan words: *marró, cadira, qué, insistir, catòlic apostolic.* The maximum punctuation of this subtest will be 5 points, 1 point for every correct

repetition. The time of administration of the test will be approximately 1 minute. (Goodglass, Kaplan, & Barresi, 1996)

- To evaluate the patients' basal **auditory comprehension**, we will ask the patient to point out what we want him/her to point. First, we will ask the patient to point on his/her body to two parts named by the examiner. For the resting items, using stimulus items on cards 3 through 15 (see Annex 3.3), we will instruct the patient to point to the picture (color, letter, or number) corresponding to the spoken item. We will ask to point to the following 16 items (in Catalan): espatlla, galta, *espelma, os, cacauet, camisa, autocar, serra, formiga, tulipa, blau, marró, T, N, 4, 13*. The patient will score 1 point per item if the response is correct within 5 seconds and 0.5 points if the response is correct in more than 5 seconds. The time of administration of the test will be approximately 2 minutes. (Goodglass, Kaplan, & Barresi, 1996)
- To evaluate the basal **nomination** function, we will use the **Boston Naming Test**. We will use the short form of BNT. (See Annex 3.4) The test consists of 15 pictures ordered in increasing difficulty that the subject must name in a maximum time of 20 seconds for each one. If the correct answer is not given spontaneously, a semantic or phonetic clue will be given, the clues are previously preestablished. The suspension of the test will take place after 6 consecutive errors. The time of administration of the Boston Naming Test will take 5-10 minutes. The punctuation of the Boston Naming Test is obtained by adding up the correct spontaneous answers (1 point/each) and the correct answers after the semantic clue (0.5 points/each). The maximum punctuation is 15 points. The items that the patient must nominate are the following, the semantic clue is in parenthesis (in Catalan): *arbre (creix en el camp), rellotge (serveix per mirar l'hora), escombra (serveix per netejar), penjador (es troba a l'armari), mascara (part d'una disfressa), raqueta (s'utilitza en un esport), corona (la fan server els reis), rinoceront (un animal), xanques (s'usen per caminar més alt), escala mecànica (serveix per pujar), morrió (s'utilitza pels gossos), acordió (un instrument musical), compàs (serveix per dibuixar), papir (un document), àbac (serveix per contar).* (Goodglass, Kaplan, & Barresi, 1996)

1.2 Psychological tests. After the neuropsychological assessment of the patient, the neuropsychologist will administer the test *Stroke and Aphasia Quality of Life Scale* to the patient. In case the patient is not able to express himself or herself properly (which is completely expected in non-fluent aphasic patients) some visual support will be provided to the patient (see Annex 4.2).

Moreover, the neuropsychologist will administer the *Stroke Aphasic Depression Questionnaire* to the patient's caregiver on behalf of the patient.

- *Stroke and Aphasia Quality of Life Scale (SAQOL-39*): we will use the version published in 2009 by K. Hilari, City university (see Annex 4). This questionnaire includes 39 questions in three domains: physical, psychosocial, and communication. It has two parts: first 21 questions ask the patient how much trouble he/she had with a specific activity during the previous week on a 5-point scale (1= Could not do it at all, 2= A lot of trouble, 3= Some trouble, 4= A little of trouble, 5= No trouble at all) and last 18 questions ask to the patient whether he/she did or did not do a specific activity during the previous week also in a 5-point scale (5=Definitely yes, 4= Mostly yes, 3=Not sure, 2= Mostly no, 1= Definitely no). Scores from each test question are totaled and divided by the number of questions administered for a mean score indicative of the quality of life. Higher scores reflect a higher quality of life. The maximum score is 195 points. (54)(55)
- *Stroke Aphasic Depression Questionnaire*, we will use its Spanish version (see Annex 5). SADQ-10 is a 10-item questionnaire comprised of questions regarding the presence of observable behaviors thought to be associated with depressed mood. SADQ-10 is scored assigning corresponding numeric values to observer selections (0= not at all, 1=on 1-4 days, 2=on 4-6 days, 3=every day). Higher scores indicate more severe depression symptoms. A cut-off score of 14 out of 30 indicates the presence of depressive behavior. (56)(57)

Functional radiology visit: We will obtain patients' fMRI (see Intervention). The radiologist in charge of performing and informing the fMRI will complete a sheet that will be provided to the neurophysiologist to provide the data they need to perform the rTMS.

Period 2: RANDOMIZATION AND ASSIGNMENT OF THE PATIENT TO ONE OF THE STUDY ARMS

In this period, the patient will be randomly assigned to the experimental or the control arm. The randomization will be done by an external company.

Period 3: INTERVENTION PERIOD

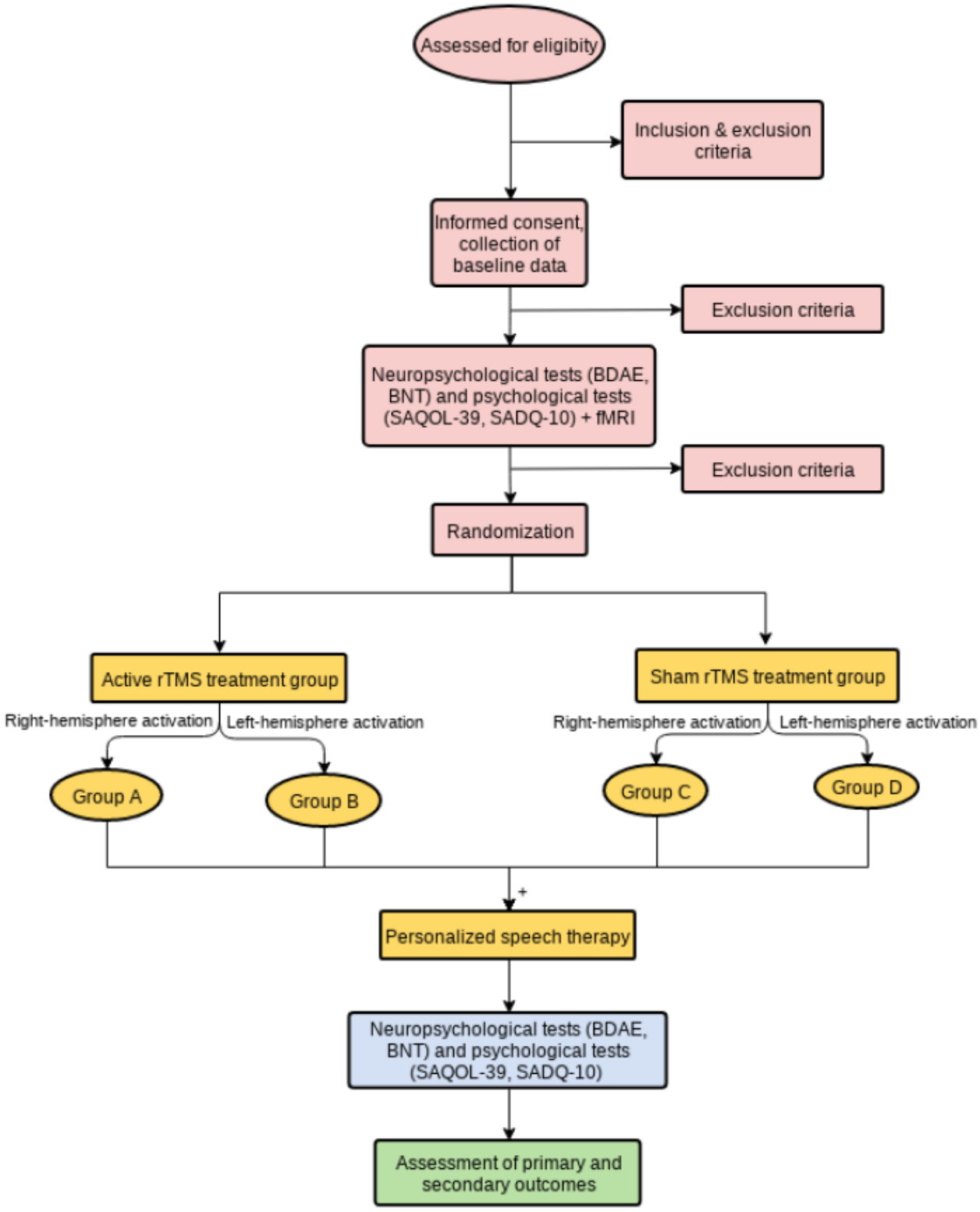
For 2 weeks, participants will receive 1 session/day only on working days (5 sessions/week). Depending on the assigned group, the patient will receive real or sham rTMS and then, they both will receive personalized speech therapy (see Intervention). After every session, the possible side effects will be collected and reported by the neurophysiologist.

After these 2 weeks, at the end of the stimulation period, all the neuropsychological and psychological tests previously performed will be administered following the same structure used in the previous neuropsychology visit.

Period 4: FOLLOW-UP

To assess the long-term intervention effect and the maintenance of the effect, 2 visits will be scheduled with the neuropsychologist: one visit 6 months after the intervention and the other one after 1 year of the intervention. The patient will be asked to assist in his/her visits with his/her main caregiver. On this visit, the neuropsychological and psychological tests previously performed will be administered following the same structure used in the first visit with neuropsychology.

6.8 FLOW CHART



7. STATISTICAL ANALYSIS

Statistical analysis will be performed using IBM Statistical Package for Social Sciences (SPSS) available for the Windows program.

For all analyses, a p-value of <0.05 will be defined as statistically significant and <0.001 highly significant. Confident intervals will be expressed as 95%.

Variable definition

To perform the statistical analysis of the data, the variable will be defined as qualitative (categorical) or quantitative (numeric).

- Independent variable: the type of stimulation is considered a nominal qualitative variable (real-TMS or sham-rTMS)
- Primary dependent variables: the outcomes of BDAE performance being the punctuation obtained in the Boston Naming Test the main dependent variable. All the following variables obtained from BDAE are considered quantitative variables.
    - Boston naming test: punctuation from 0 to 15
    - Aphasia Severity Rating Test: from 0 to 5
    - Fluency test: length of the patients' longest phrase (in number of words)
    - Repetition test: punctuation from 0 to 5 points
    - Auditive comprehension test: punctuation from 0 to 16 points
- Secondary dependent variables: the secondary variables of the clinical trial are all considered quantitative variables.
    - Stroke and Aphasia Quality of Life Scale: punctuation from 39 to 195
    - Stroke Aphasic Depression Questionnaire: from punctuation from 0 to 30
    - Side effects: nº of side effects and incidence of them
- Covariables
    - Sex: nominal qualitative variable
    - Age: discrete quantitative variable
    - Level of education: discrete quantitative variable
    - Duration of stroke: discrete quantitative variable
    - Type of stroke: nominal qualitative variable
    - Infarct size: continuous quantitative variable

- Infarct location: nominal qualitative variable
- NIHSS: discrete quantitative variable
- Patient's motivation using Multidimensional Health Locus of Control scale: continuous quantitative variable

Univariant analysis

The univariate analysis will be performed to describe the sample.

Results for variables with a normal distribution will be expressed as mean and SD and those variables without a normal distribution will be expressed as median and IQR. Non-parametric variables will be mathematically transformed to improve symmetry. Results will be expressed as frequencies (nº) and/or percentages (%) for categorical variables. The quantitative variables will be shown as box-plot charts and qualitative variables with bar charts.

Bivariant analysis

The bivariant analysis will be performed to assess the homogeneity of the different study arms and to assess the impact of our intervention on dependent variables (score obtained in the different BDAE subtests). We will use a parametric test because our dependent variable is quantitative and our sample size is superior to 30.

To assess the homogeneity of the different study arms, a comparison of results for major variables at baseline will be performed using t Student test for means. This analysis will help us to ensure that the randomization process yields comparable treatment groups.

To assess the impact of both intervention on dependent and secondary variables, a bivariate analysis will be performed with data obtained before the stimulation, after the stimulation, 6-months, and 1-year from the start of the stimulation. We will use the ANOVA test to assess homogeneity between the different study arms and if present, detect the difference between both groups. The variables included are the ones described in the Data Collection section.

Moreover, we also want to compare the data obtained in four points (before the stimulation, after the intervention, 6 months after the stimulation and 12 months after the stimulation) in the same group to assess the evolution in the performance of the patient on the different BDAE subtest. The comparison of results for major variables will be performed using the ANOVA test for repeated measures.

Multivariant analysis

The analysis of response to treatment for endpoint variables (aphasia severity, patients' fluency, patients' nomination, patients' repetition, and patients' comprehension) between the experimental group and control group will be performed by the general linear model (GLM) for repeated measures. Models will be adjusted for potential confounders (age, gender, level of education, duration of a stroke, infarct size/ICH, stroke severity, patients' motivation).

Intention-to-treat analysis and per-protocol analysis will both be performed. Imputation of missing values for endpoints variables will be performed using the latest observed values for each variable subject.

8. LIMITATIONS OF THE STUDY

This clinical trial has some limitations that should be considered, especially potential bias and methodological and logistical limitations.

Selection bias

As this clinical trial is using a non-probabilistic sampling method, the subjects of the study do not have the same chance to be selected which could lead to a bias of selection and therefore, to obtain a non-representative sample. However, the consecutive method has been chosen because is one of the non-probabilistic methods that induce less bias.

As all neurologists of Hospital Josep Trueta are asked to recruit patients for our clinical trial, we could generate selection bias because of criteria differences between professionals. However, a research team meeting will be conducted to agree on inclusion and exclusion criteria and reach criteria consensus.

Neuropsychological tests and fMRI obtention require minimal language emission so, mute patients (ASRS= 0 points) have been excluded from the patients. This fact could make our sample less representative of the post-stroke subacute aphasic population because the most severe patients will be excluded. We assume this limitation to avoid inducing data collection mistakes from neuropsychological tests and to avoid the inability to obtain the fMRI and therefore, to participate in the study.

As our study requires to assist in 5 sessions/week for 2 weeks and long-term follow-up after the intervention, we could have some patients lost and generate bias in our clinical trial results because patients who withdraw are likely to have suffered adverse effects and fewer clinical benefits. To avoid this bias, it will be necessary that the patient has the main caregiver who is compromised with the study and ensures that the patient will be able to assist in the required visits. Moreover, the sample size has been calculated assuming a 10% of patient drop-out to ensure that if we lost some patients, our results will still be faithful.

Information bias

As the stimulation procedure will be single-blinded because of the impossibility to blindly conduct the intervention, we could generate some observatory bias. However, the pre-treatment and post-

treatment assessments and the speech therapy will be double-blinded. Therefore, we assume that the collection of dependent variables will not be biased except for the side effects that could be biased because it is collected single-blinded by the neurophysiologist.

Confounding bias

As our trial accepts the possible existence of confounding factors that could influence the study outcome, we have tried to minimize them by randomizing the patients in each group and excluding some potentially confounding factors. The randomization will be stratified by type of stroke (ischemic or hemorrhagic stroke) to ensure both groups have the same number of patients suffering from each type of stroke and avoid this potential confounding factor. Moreover, we will practice a multivariate analysis including potential confounders such as age, gender, level of education, patient's motivation, stroke severity, type of stroke, infarct size and location, etc.

Other limitations

Methodological limitations

There is a lack of consensus regarding stimulation parameters that must be used for aphasia rehabilitation. Previous studies study different stimulation parameters and there is no established protocol available. In this clinical trial, we have determined the stimulation parameters according to the safety guidelines and the previous evidence, but we assume that the selected stimulation applied to the patient might be less effective (infra-therapeutical) than the ideal one, but we wanted to ensure that it was completely safe. More rTMS studies are needed comparing different stimulation protocols in aphasia rehabilitation.

The neuropsychological tests (BDAE, BNT, SAQL-39, SADQ-10) that will be used to assess the aphasic patients in our clinical trial are only available in the Spanish version for BDAE, BNT, and SADQ-10, and the English version for SAQL-39. As the patients included in our clinical trial are Catalan-native and we want to assess them in Catalan, we will traduce the tests to Catalan and they will have to follow a process of validation previous to the start of the clinical trial.

Research team limitations

The two neurophysiologists that participate in our research team have no previous experience in administrating rTMS to aphasic patients as it is not a standard treatment commonly used in clinical practice. This fact could generate procedure differences between the different neurophysiologists

and between stimulations performed by the same neurophysiologist. Moreover, the lack of experience could lead to serious mistakes in the administration of rTMS that could influence the stimulation efficacy. To avoid these limitations, neurophysiologists will be asked to assist in a mandatory rTMS training course.

The two neuropsychologists that will participate in our clinical trial have experience in assessing aphasic patients using BDAE (and BNT) because it is commonly used in the clinical practice, but they are not experienced in performing the other required test of SAQL-39 and SADQ-10 because they are less used. For this reason, neuropsychologists will be asked to assist in a mandatory training course.

The radiologist specialized in fMRI has plenty of experience in obtaining fMRI, but he/she might not have experience in obtaining fMRI of aphasic patients in coordination with a neurophysiologist responsible for stimuli generation. To avoid procedure mistakes and ensure the satisfactory obtention of fMRI, they will be asked to assist in a mandatory course.

9. ETHICAL CONSIDERATIONS

This clinical trial protocol applies *Ethics Principles for Medical Research Involving Human Subjects* outlined in the World Medical Association Declaration of Helsinki to ensure the preservation of human rights and ethical values. The study will be carried out following the criteria established in the Nuremberg Code, Belmond Report, and Oviedo Convention. The ethical principles of autonomy, beneficence, no maleficence, and justice are strictly followed in our clinical trial.

To ensure autonomy, all participants will be provided with the information sheet containing all the information about de clinical trial including its aiming, exclusion criteria, methodology, description of the different procedures, potential benefits, and risk for the patients (see Annex 7). In the information sheet, the investigator's phone contact will be also provided to the patient for doubts resolution. To participate in the study, all participants will have to voluntarily sign the informed consent (see Annex 8). The informed consent must be signed by the patient (if possible) or by his/her legal tutor in case the patient is declared no competent due to his/her medical condition. Both information sheets and informed consent have been written following "Guía para la correcta elaboración de un modelo de hoja de información al paciente y consentimiento informado".

Personal data collected during the clinical trial is confidential and we will guarantee personal data protection and fundamental rights of physical people involved in the study following EU 2016/679 of European Parliament and Council, 27th April 2016, on the protection of physical persons regarding the processing of personal data and on the free circulation of these data and Organic Law 3/2018, 5th December, on personal data protection and digital right guarantee. Participants will have the right to access, modify, oppose, or remove their data contained in the file as well as to leave the study at any time.

To ensure beneficence, the clinical trial has been designed following the current evidence of the potential therapeutic benefits of repetitive transcranial magnetic stimulation on language improvement on aphasic patients and we believe that the potential benefit of the study is larger superior to the rTMS risks because nowadays, aphasia has no specific treatment and the only available treatment for it is speech-language which, unfortunately, has limited results.

To ensure no maleficence, our clinical trial will follow the safety precautions and practice recommendations for repetitive transcranial magnetic stimulation established in the consensus conference held at the National Institutes of Health in June 1996 and reviewed and updated in a

consensus conference held in Italy in June 2008 (see Safety). rTMS is considered safe and well-tolerated therapy. However, all adverse effects will be registered and notified by an external company. To ensure participants' safety we will hire Liability insurance.

To ensure justice, we guarantee that all professionals that will participate in our clinical trial will be competent and will be highly qualified and prepared to play their role in the clinical trial. Moreover, we will not tolerate any kind of discrimination during the whole process. We consider that the placebo stimulation is justified in our clinical trial because nowadays, there is no specific treatment for aphasia rehabilitation and in anyways, the patient will receive the standard available treatment which is speech therapy even if he/she is assigned to the control group. The placebo stimulation is considered a safe stimulation.

Before the start of the study, during the preparation stage, the main investigator will send this research protocol for consideration, comment, advice, and approval to the Clinical Research Ethics Committee (CEIC) of Hospital Doctor Josep Trueta according to the *Royal Decree 1090/2015, 4th December*. Moreover, the study protocol will be sent to the hospital's director for approval. Finally, the protocol will be also sent to the "European Medicines Agency" (EMA) and to "Asociación Española del Medicamento y Productos Sanitarios" (AEMPS) for approval.

Finally, all investigators will have to declare no conflict of interest to ensure that the clinical trial has no commercial bias or interest. The ultimate goal of this trial is to develop knowledge to improve human health and quality of life.

10. FEASIBILITY

The principal investigator of this clinical trial is an experimented neurologist with wide knowledge and experience in the treatment and rehabilitation of patients who suffered a stroke.

The clinical trial takes place in Hospital Josep Trueta which is a reference health center of the sanitary region of Girona. The neurology department of Hospital Josep Trueta is a reference service for all urgent and highly complex neurological pathology in the sanitary region of Girona and it attends around 800 patients/year with stroke. Thus, the diagnosis of post-stroke aphasia and participant recruitment will be performed by qualified and experimented neurologists. Most aphasic patients diagnosed by a neurologist are sent to the neuropsychology department and the speech therapist of Hospital Josep Trueta which explains their wide knowledge and experience in the assessment, management, and rehabilitation of aphasic patients. Furthermore, the neuropsychologist will be specifically trained to administrate the test needed in this clinical trial and the speech therapist will also be trained to apply personalized and accurate speech treatment to the included patients according to their language deficits.

Hospital Josep Trueta has many years of experience in investigation. The research institute of Hospital Josep Trueta is Institut d'Investigació Biomèdica de Girona (IdIBGi), a research center that belongs to the network of centers CERCA of Generalitat de Catalunya and that aims to promote, develop, manage, transfer and disseminate biomedical research, scientific and technological knowledge, teaching and training in the field of life sciences and health. IdIBGi has many ongoing research projects and together with the research group of the neurology department, they work actively in three main areas: cerebral vascular pathology, demyelinating diseases, and neurodegenerative diseases. Therefore, the neurology department has enough experience to carry out this clinical trial.

Repetitive transcranial magnetic therapy is not applied in clinical practice except in the case of refractory depression in some health centers. Hospital Josep Trueta has an experimented neurophysiology department with specialized and qualified neurophysiologists and with enough available means to carry out the clinical trial. However, the stimulation technique is unknown for most professionals which is the reason why all neurophysiologists will have to receive and pass a rTMS training course imparted by the Guttmann Institute.

11. WORK PLAN AND CHRONOGRAM

11.1 WORK PLAN

RESEARCH TEAM

Our team will include the following personal:

- Principal Investigator (PI)
- 3 neurologists from the neurology service (NRL)
- 2 neuropsychologists (NPH)
- 2 neurophysiologists (NPS)
- 1 speech therapist (ST)
- 1 functional radiologist specialized in fMRI and technicians (FR)
- External companies for the following services:
    - EXT → database creation, randomization, and codification of patients and statistical data analysis.
    - CRO→ data monitoring and quality control

TASKS

The study will take approximately 3 years. The study will have the following stages:

1. **Preparation: protocol elaboration and approval, planning, and formation (≈ 3 months)**

    1.1 Protocol elaboration: PI is responsible for elaborating the protocol.

    1.2 Protocol approval: the protocol must be approved by the CEIC. PI is responsible for this activity. CEIC will evaluate, comment, give advice, and approve the protocol. Investigators will follow CEIC indications.

    1.3 Neuropsychological test translation and validation: The neuropsychological tests (BDAE, BNT, SAQL-39, SADQ-10) that will be used to assess the aphasic patients in our clinical trial are only available in Spanish version for BDAE, BNT, and SADQ-10 and English version for SAQL-39. The patients included in our clinical trial are Catalan-native and Spanish-native and we want to assess them in their native language so, we will traduce the Spanish tests to

Catalan, and they will have to follow a process of validation before the start of the clinical trial. PI will be responsible for this process.

1.4 Database creation: PI will coordinate with an external company specialized in data management to elaborate on a database to facilitate the data collection for the research team.

1.5 Research team meeting: the meeting aims to inform and coordinate the research team. We will review the protocol, discuss the work plan, and task assignment.

1.6 Neuropsychologist training: the neuropsychologist participating in our clinical trial will follow a training course where they will learn how to assess aphasic patients using the Boston Diagnostic Aphasia Diagnose, Boston Naming Test, Stroke and Aphasia Quality of Life Scale, and Stroke Aphasic Depression Questionnaire. The neuropsychologist participating in the fMRI obtention through semantical categorical evocation will also be trained for it. The course will last one day (5h).

1.7 Neurophysiologist training: the neurophysiologists participating in our clinical trial will assist in a formation course on repetitive transcranial magnetic stimulation. This course will have theoretical and practical parts and it will last two days (10h).

1.8 Radiologist training: radiologists participating in our clinical trial will assist in a formation course on fMRI obtention specifically in aphasic patients. This course will have theoretical and practical parts and it will last two days (10h).

2. Study conduct: Data collection, intervention, and follow-up (≈ 2 years)

2.1 Patients recruitment, obtention of informed consent, and collection of the baseline data: the neurologists will be in charge of recruiting patients in our clinical trial according to the inclusion and exclusion criteria. At the same time, a neurologist will have the responsibility to inform the patients and obtain informed consent. Moreover, the collection of baseline data will be done in this phase (see Data Collection). The patient's recruitment will last 1 year.

2.2 Patients randomization and codification: An external company will be responsible to anonymize, codify, and randomize the included patients.

2.3 Performance of pre-stimulation neuropsychological tests: the neuropsychologist will administer the following test: Boston Diagnostic Aphasia Diagnose (including Boston Naming Test), Stroke and Aphasia Quality of Life Scale, and Stroke Aphasic Depression Questionnaire. BDAE, Stroke, and Aphasia Quality of Life Scale will be administered to the patient but and Stroke Aphasic Depression Questionnaire will be administered to patients' caregivers. Therefore, the patients must assist to visit with his/her main caregiver (see Data Collection). The test will be administered between 1-2 weeks before the stimulation.

2.4 Obtention of pre-stimulation fMRI: the radiologists specialized in functional magnetic resonance imaging will be responsible for the acquisition of the fMRI of the patient. The fMRI will be performed with the support of a neuropsychologist who will be responsible for elaborating the fMRI stimuli. The fMRI stimuli will consist of semantical categorical evocation (animal names, phonetic and word starting with *p*, *a,* or *s*). During the basal stimuli, patients will be presented with a visual stimulus consisting of 3 dots inside a square. The fMRI will be obtained between 1-2 weeks before the stimulation.

2.5 rTMS stimulation + speech and language therapy: the specialized neurophysiologists are responsible for applying rTMS to the patients. According to the randomization, the patient will receive real- rTMS or sham- rTMS. Patients receiving real-rTMS will receive the stimulation protocol A or B according to their fMRI results. Patients receiving sham-rTMS will receive the stimulation protocol C or D according to their fMRI results. Patients will receive 1 session/day only on working days for 2 weeks resulting in a sum of 10 stimulation sessions. After every session, possible side effects will be reported and collected. The stimulation session will last between 5-20 minutes depending on the stimulation protocol (See Data Collection). All patients will receive a 45-minute speech therapy focused on their linguistic symptoms.

2.6 Performance of post-stimulation neuropsychological tests (BDAE, SADQ-10, SAQOL-39): following the same procedure described in point 2.4. The test will be administered during the following week after the last stimulation day.

2.7 Long-term data collection: we will administer the neuropsychological test (BDAE, SADQ-10, SAQOL-39) 6 months and 1 year after the stimulation intervention as described in point 2.3.

2.8 Data monitoring and quality control: Contract Research Organization (CRO) will periodically monitor the obtained data and run quality control tests (once every 6 months during the study conduct).

2.9 Research team meetings: research team meetings will periodically meet to evaluate and solve practical emerging problems and ensure quality control of the clinical trial. The meeting will take place approximately every 6 months.

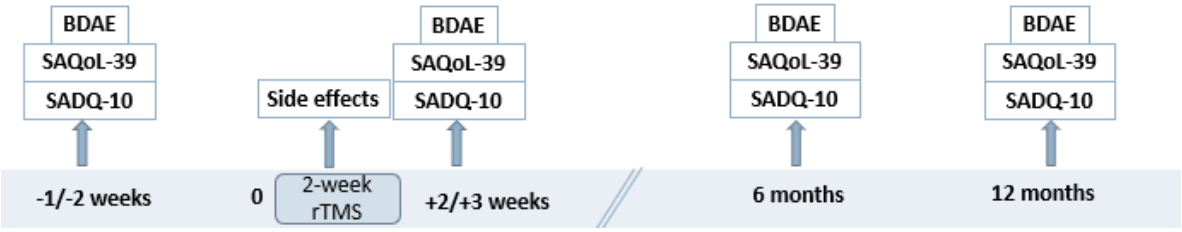


Figure 13 Review of data collection

3. Data analysis (≈ 4 months)

3.1 Statistical analysis: the statistical analysis will be done by an external company by the end of the data collection process. It will last approximately 3 months.

3.2 Interpretation and discussion of the results: the results will be discussed by the whole research team.

3.3 Research team meeting: the results and conclusions obtained from the clinical trial will be exposed and discussed during a final research team meeting.

3.4 Elaborating on the final report: PI is in charge of elaborating on the final paper that will be sent to all members of the research team.

4. Divulgation and publication (≈ 2 months)

4.1 Publication of the clinical trial: our clinical trial will be published by a scientific review. The main investigator will be in charge of contacting the review to publish the clinical trial and will manage its publication.

4.2 Divulgation of the clinical trial: the results of the clinical trial will be exposed to national and international conferences.

11. 2 CHRONOGRAM

Stage	Task name	Assigned to	november-20	december-20	january-21	february-21	march-21	april-21	may-21	june-21	july-21	august-21	september-21	october-21	november-21	december-21	january-22	february-22	march-22	april-22	may-22	june-22	july-22	august-22	september-22	october-22	november-22	december-22	january-23	february-23	march-23	april-23	may-23	june-23	july-23	august-23	september-23
PREPARATION	Protocol elaboration	PI																																			
	Protocol approval	PI																																			
	Test translation and validatic	PI																																			
	Database creation	EXT																																			
	Team meating	ALL																																			
	Neurophysiologist training	NPH																																			
	Neuropsychologist training	NPS																																			
	Functional radiologist training	FR																																			
INTERVENTION	Patients recruitment	NRL																																			
	Randomization & codification	EXT																																			
	fMRI obtention	FR+NPH																																			
	rTMS stimulation	NPH																																			
	Speech therapy	ST																																			
	Data colection	ALL																																			
	Data monitoring	EXT																																			
	Data quality control	EXT																																			
	Team meating	ALL																																			
ANALYSIS	Statistical analysis	EXT																																			
	Interpretation of the results	ALL																																			
	Team meating	ALL																																			
	Elaborating the final report	PI																																			
DIV	Publication	PI																																			
	Divulgation	PI																																			

12. BUDGET

Not included costs:

- Personal costs of staff working in Hospital Josep Trueta: the personnel participating in our clinical trial will not be paid for this reason. We want that their motivation to join the study is not economical. The research team will be rewarded by the scientific prestige and intellectual knowledge.
- Available materials in Hospital Josep Trueta: we dispose of the following material in the hospital: the TMS device and software, the fMRI device and software, and the license and material of BDAE.
- Neuropsychologic test licenses: SAQoL-39 and SADQ-10 are open licensed, and we do not need to pay for them.

Included costs:

Material costs:

- Printing costs: study information sheet (5 pages), informed consent (2 pages), safety screening questionnaire (2 pages), response sheet of BDAE (2 pages), response sheet of SAQoL-39 (3 pages), response sheet of SADQ-10 (2 pages). Therefore, for each patient included in our clinical trial, we will need to print approximately 16 pages.
- Earplugs: every patient will need to wear earplugs during the stimulation for safety reasons. The cost of them is 0.5€/unit.
- rTMS structural costs: according to literature, the structural costs of a single rTMS session is approximately 34€ and each participant receives 10 sessions. (61)
- TMS *Neuronavigation* system: according to a budget provided by a specialized company, the cost of the TMS *Neuronavigation* system is around 15.000€.
- fMRI structural costs: the structural cost of one single scan is 330€ approximately.

Personal costs:

- rTMS trainer: the professional impairing the rTMS training course will be paid 35€/hour and he/she will perform a 10-hour course.
- Neuropsychologist trainer: the professional impairing the neuropsychologist training course will be paid 35€/hour and he/she will perform a 5-hour course.

- Functional radiologist trainer: the professional impairing the fMRI training course will be paid 35€/hour and he/she will perform a 10-hour course.

Travel costs:

- rTMS training course: the neurophysiologists attending the rTMS training course will be paid 100€ to cover the travel and meal expenses per attendant, per course. Two neurophysiologists will be attending the course.
- Neuropsychologist training course: the neuropsychologist attending the neuropsychology training course will be paid 50€ to cover the travel and meal expenses per attendant, per course. Two neuropsychologists will be attending the course.
- Functional radiologist training course: the functional radiologist attending the fMRI training course will be paid 100€ to cover the travel and meal expenses per person, per course. One neuropsychologist will be attending the course.
- National and international congress: the two attendants will be paid 400€/attendant for the national congress and they will be paid 600€/attendant for the international congress to cover the travel and meal expenses.

Subcontracted services

- Database creation and statistical analysis: the creation of the database and the statistical analysis service is budgeted 30€/hour, with an estimated total of 150 hours of work.
- Data monitorization and quality control: an external and independent company will be hired to monitor and assess the quality of data collection and statistical analysis. This service will be paid 30€/hour, with an estimated total of 50 hours of work.
- Liability insurance. The established budget for this service is 19,200€ (300€/patient). The insurance will cover all the possible damages derived from the study.

Divulgation costs

- Publication fees. It is expected to publish the clinical trial into a journal article exposing the main results. It is assumed 2,000€ for publication fees.
- National and international congress. To disseminate the results, PI will present the study results on congresses. It is expected that two attendants will attend the national (600€ per inscription) and the international congress (1000€ per inscription).

ITEM	Cost per unit	Nº of units	Subtotal
Material costs			
Printing cost (Information sheet, informed consent, neuropsychological tests evaluation sheets)	0.05€/page	16 pages x 64 patients	51.2€
Earplugs	0.5€/unit	64 units	32€
rTMS equipment	34€/session	10 sessions/patient x 64 patients	21. 760€
TMS Neuronavigator	15.000/unit	1 unit	15.000€
fMRI	330€/ scan	1 scan x 64 patient	21.120€
Total			**57.963,2€**
Personal costs			
rTMS trainer	35€/hour	10 hours	350€
Neuropsychologist trainer	35€/hour	5 hours	175€
fMRI trainer	35€/hour	10 hours	350€
Total			**875€**
Travel costs			
rTMS training	100€/attendant	2 attendants	200€
Neuropsychologist training	50€/attendant	2 attendants	100€
fMRI training	100€/attendant	1 attendant	200€
National congress	400€/attendant	2 attendants	800€
International congress	600€/attendant	2 attendants	1200€
Total			**2.500€**
Subcontracted services			
Database creation and statistical analysis	30€/hour	150 hours	4500€
Data monitoring and quality control	30€/hour	50 hours	1500€
Liability insurance	19.200€/insurance	1 insurance	19.200€
Total			**25.200€**
Divulgation costs			
Publication costs	2000€/publication	1 publication	2000€
Inscription to national congress	600€/inscription	2 inscriptions	1200€
Inscription to international congress	1000€/inscription	2 inscriptions	2000€
Total			**5.200€**
Total of the project			**91.738,2€**

13. CONFLICT OF INTEREST

The authors declare no conflict of interest

14. HEALTH IMPACT

As mentioned before, aphasia is one of the most disabling sequelae of stroke, and unfortunately, it affects the quality of life of these patients as it has a huge impact on personal, social, familiar, and work-life. Moreover, patients with post-stroke aphasia have greater mortality and morbidity than stroke patients without aphasia. Nowadays, there is no specific treatment for aphasia rehabilitation except for speech therapy.

If the outcome obtained in this clinical trial is positive and the hypothesis is demonstrated, it would represent huge progress for aphasia rehabilitation. This clinical trial would provide hope to all affected patients and families because it will be demonstrated that rTMS could help aphasic patients to finally recover their ability to communicate.

Moreover, this clinical trial could be the methodological model for future research in post-stroke rehabilitation regarding other stroke sequelae such as motor impairment, dysphagia, and hemineglígence between others. The clinical trial could also be helpful to develop treatment strategies for neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

Future research would be required to assess rTMS efficacy to improve aphasia and other stroke sequelae as well as to treat or reduce other neurological symptoms due to different neurological diseases.

In conclusion, we believe that rTMS is an available, low-cost, and easy to deliver technique with huge potential in the neurological rehabilitation field.

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16. ANNEXES

16. 1 RANKIN SCALE[1]

Score	
0	No symptoms at all.
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6	Dead

[1] Available from Kassim et al. (62)

16.2. NIH STROKE SCALE[2]

1a—Level of consciousness	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation 2 = Not alert; requires repeated stimulation 3 = Unresponsive or responds only with reflex
1b—Level of consciousness questions: What is your age? What is the month?	0 = Answers two questions correctly 1 = Answers one question correctly 2 = Answers neither questions correctly
1c—Level of consciousness commands: Open and close your eyes Grip and release your hand	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2—Best gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3—Visual	0 = No visual lost 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4—Facial palsy	0 = Normal symmetric movements 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis of one or both sides
5—Motor arm Left arm Right arm	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
6—Motor leg Left leg Right leg	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
7—Limb ataxia	0 = Absent 1 = Present in one limb 2 = Present in two limbs
8—Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe-to-total sensory loss
9—Best language	0 = No aphasia; normal 1 = Mild-to-moderate aphasia 2 = Severe aphasia 3 = Mute; global aphasia
10—Dysarthria	0 = Normal 1 = Mild-to-moderate dysarthria 2 = Severe dysarthria
11—Extinction and inattention	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention or extinction
Score = 0–42	

[2] Available from Denier et al. (63)

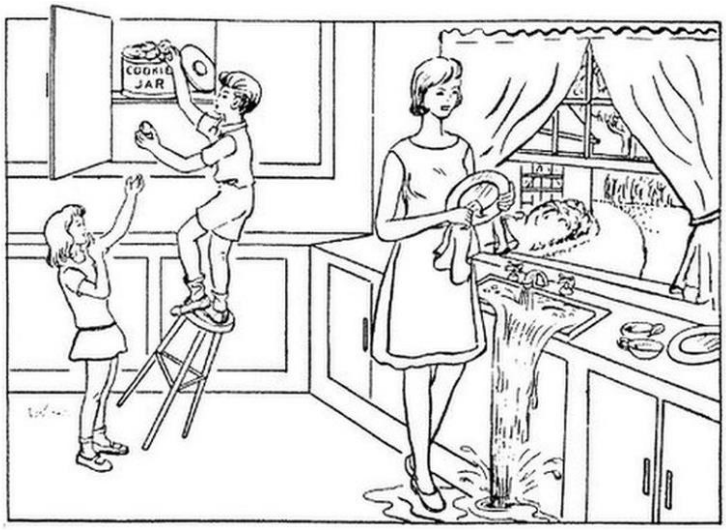
16.3. BOSTON DIAGNOSTIC APHASIA EXAMINATION

16.3.1 APHASIA SEVERITY RATING SCALE[3]

0. **Ausencia de habla o de comprensión auditiva.**
1. **La comunicación se efectúa en su totalidad a partir de expresiones incompletas; gran necesidad de inferencia, preguntas y adivinación por parte del oyente. El caudal de información que puede ser intercambiado es limitado y el peso de la conversación recae sobre el oyente.**
2. **El paciente puede, con la ayuda del examinador, mantener una conversación sobre temas familiares. Hay fracasos frecuentes al intentar expresar una idea, pero el paciente comparte el peso de la conversación con el examinador.**
3. **El paciente puede referirse a prácticamente todos los problemas de la vida diaria con muy pequeña ayuda o sin ella. Sin embargo, la reducción del habla, de la comprensión o de ambas hace sumamente difícil o imposible la conversación sobre cierto tipo de temas.**
4. **Hay alguna pérdida obvia de fluidez en el habla o de facilidad de comprensión, sin limitación significativa de las ideas expresadas o de su forma de expresión.**
5. **Mínimos deterioros observables en el habla; el paciente puede presentar dificultades subjetivas no evidentes para el oyente.**

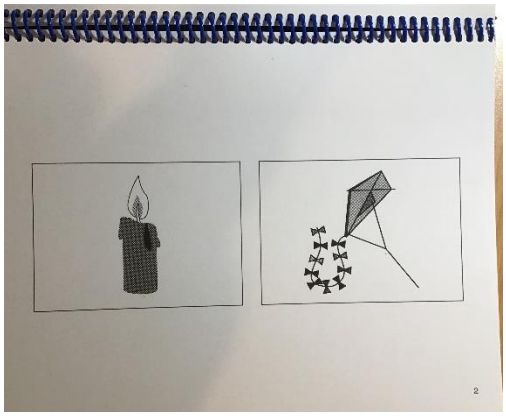
16.3.2 COOKIE THEFT PICTURE[4]

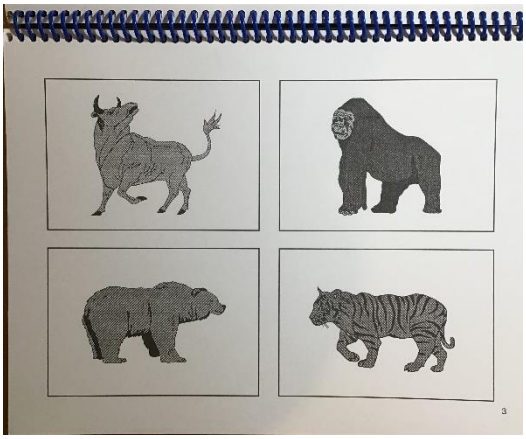
Descripción de una lámina:
Muestre el dibujo de "El Robo de las Galletas" de la lámina 1 e indíquele al paciente: "DÍGAME TODO LO QUE VEA QUE ESTÁ PASANDO EN ESTA LÁMINA". Señale todos los rasgos ignorados por el paciente y solicite más elaboración si la respuesta del paciente es más pobre de lo que aparenta su capacidad potencial. Escriba al pie de la letra todo lo que pueda. Para la administración Estándar y Ampliada, se recomienda grabar la descripción y tener su transcripción para facilitar la puntuación.

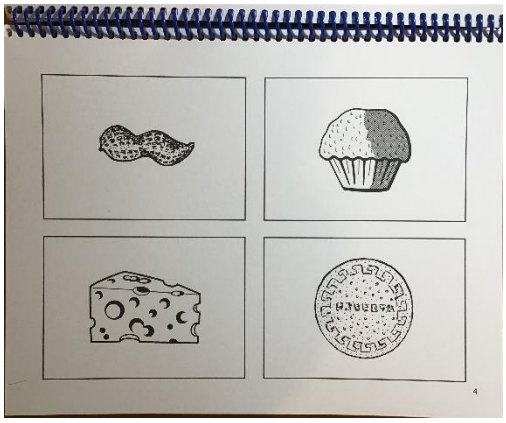


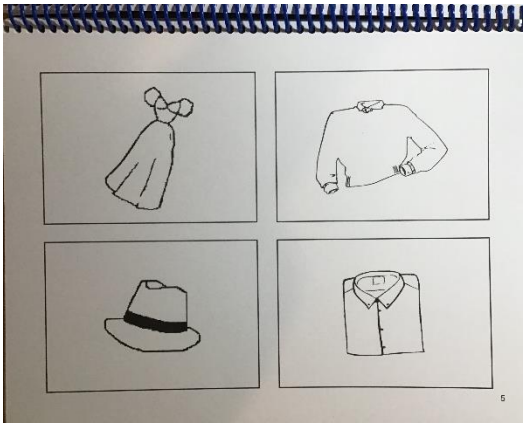
[3] Available from Goodglass et al. (64)
[4] Available from Goodglass et al. (64)

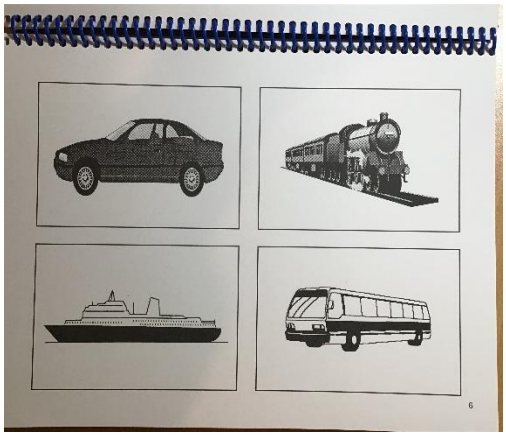
16.3.3 WORD DISCRIMINATION CARDS[5]

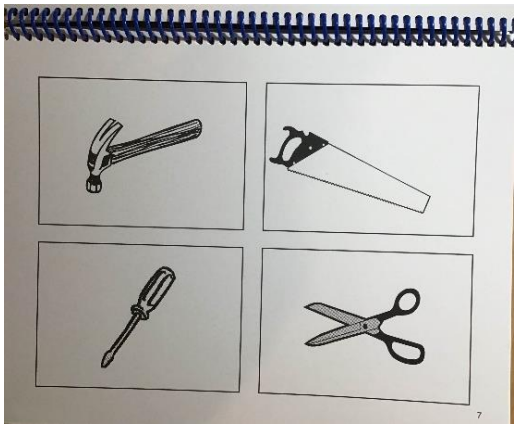




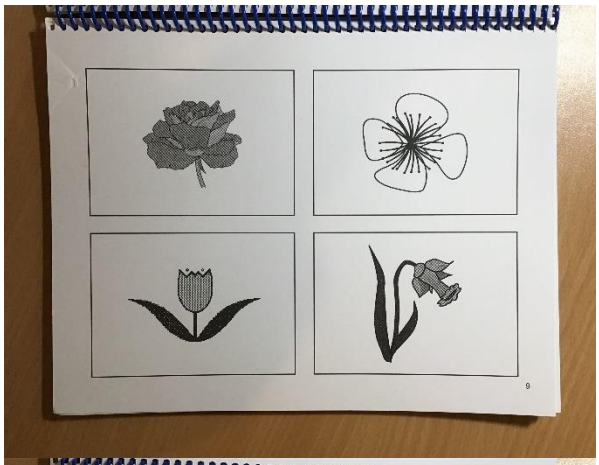


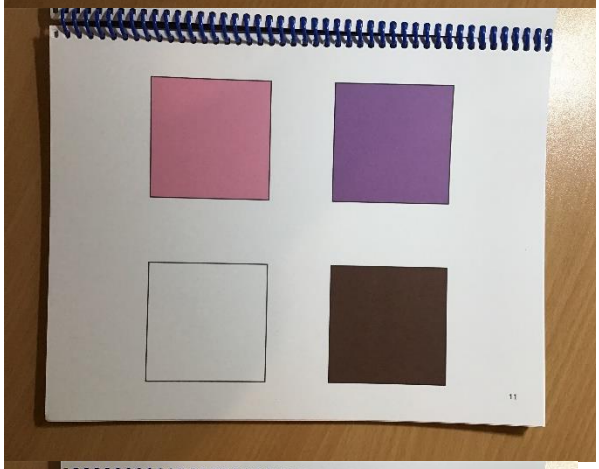




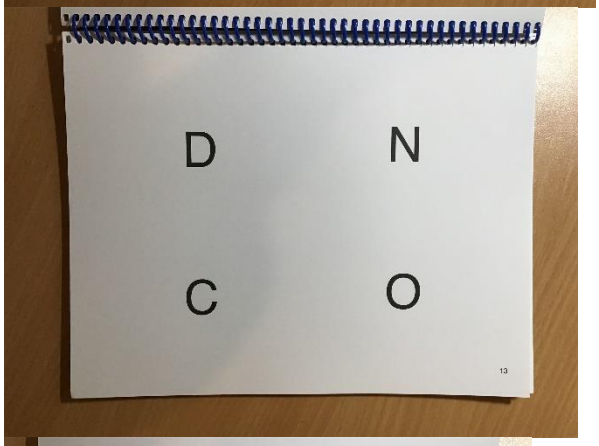


[5] Available from Goodglass et al.(64)






S E
T R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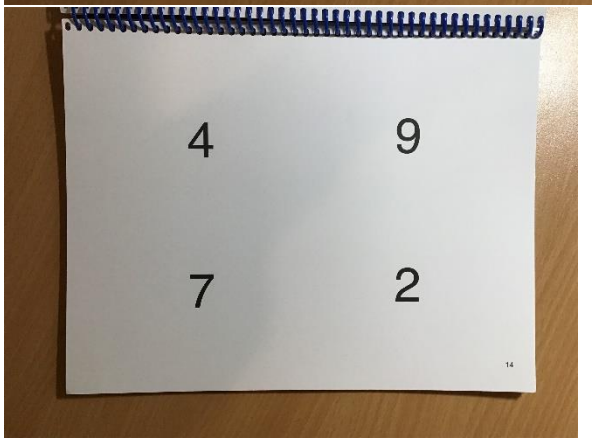
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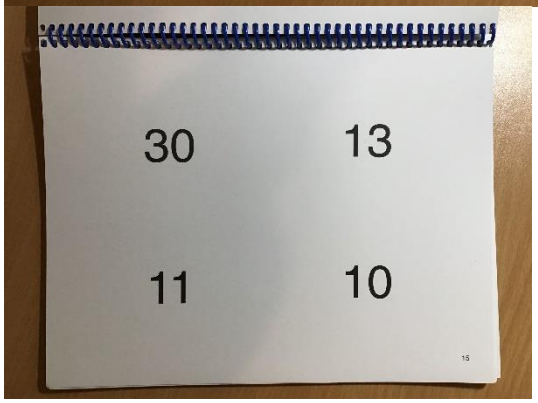
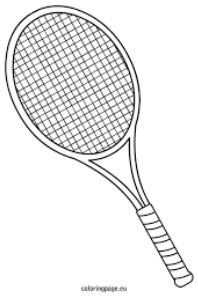
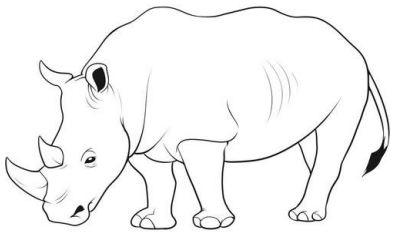

30 13
11 10

16.3.4 BOSTON NAMING TEST CARDS[6]

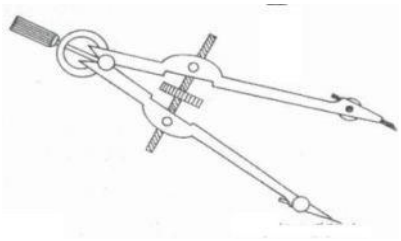
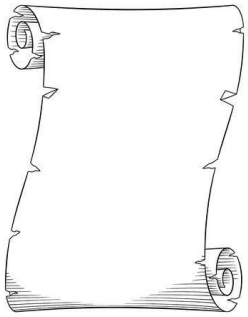
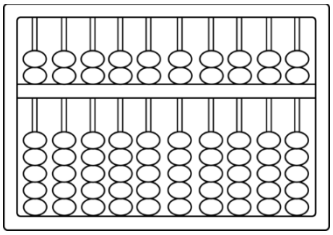








[6] Adapted from Goodglass et al. (64)

16.3.5 RESPONSE SHEET OF BDAE

Nº de codi del pacient →

ASRS

0	1	2	3	4	5

COOKIE THEFT PICTURE (fluència)

Escriu la frase més llarga pronunciada pel paciente (o transcriu-la de la gravació).

…… **→ Nº de paraules:** ☐

DISCRIMINACIÓ DE PARAULES (comprensió)[7]

Anote las respuestas erróneas	< 5" (1 punto)	> 5" (½ punto)	Fracaso (0)
Para las partes del cuerpo, diga: "Señáleme su..."			
1. Hombro			
2. Mejilla			
Para el resto, diga: "Señáleme el/la..."			
3. Vela			
4. Oso			
5. Cacahuete			
6. Camisa			
7. Autocar			
8. Serrucho			
9. Hormiga			
10. Tulipán			
(Colores)			
11. Azul			
12. Marrón			
(Letras)			
13. T			
14. N			
(Números)			
15. 4			
16. 13			
Puntuación:			/16

[7] Adapted from Goodglass et al. (64)

BNT (nominació)

Item	Resposta correcta (1 punt)	Resposta correcta després pista semàntica (0.5 punts)	Latència (en segons)
Arbre (creix en el camp)			
Rellotge (serveix per mirar l'hora)			
Escombra (serveix per netejar)			
Penjador (es troba a l'armari)			
Mascara (part d'una disfressa)			
Raqueta (s'utilitza en un esport)			
Corona (la fan servir els reis)			
Rinoceront (un animal)			
Xanques (s'usen per caminar més alt)			
escala mecànica (serveix per pujar)			
Morrió (s'utilitza pels gossos)			
Acordió (un instrument musical)			
Compàs (serveix per dibuixar)			
Papir (un document)			
Àbac (serveix per contar)			
PUNTUACIÓ TOTAL			/15

REPETICIÓ DE PARAULES (repetició)

Item	Repetició correcta (1 punt)
Marró	
Cadira	
Qué	
Insistir	
Catòlic apostòlic	
PUNTUACIÓ TOTAL	/5

16. 4. STROKE AND APHASIA QUALITY OF LIFE SCALE [8]

16. 4.1 QUESTIONS

Nº de codi del pacient →

Durant la setmana passada, quina dificultat va tenir en…

Cap problema	**5**
Una mica de problemes	**4**
Alguns problemes	**3**
Molts problemes	**2**
No ho podia fer	**1**

1. Preparar-se el menjar? (5/4/3/2/1)
2. Vestir-se? (5/4/3/2/1)
3. Dutxar-se o banyar-se? (5/4/3/2/1)
4. Caminar? (5/4/3/2/1)
5. Mantenir l'equilibri quan s'inclinava? (5/4/3/2/1)
6. Pujar escales? (5/4/3/2/1)
7. Caminar sense aturar-se per descansar o usar la cadira de rodes sense aturar-se per descansar? (5/4/3/2/1)
8. Estar-se dret? (5/4/3/2/1)
9. Aixecar-se de la cadira? (5/4/3/2/1)
10. Fer feina de la casa? (5/4/3/2/1)
11. Acabar feines que tenia començades? (5/4/3/2/1)
12. Escriure o teclejar? (5/4/3/2/1)
13. Posar-se els mitjons? (5/4/3/2/1)
14. Cordar-se els botons? (5/4/3/2/1)
15. Cordar-se la cremallera? (5/4/3/2/1)
16. Obrir una llauna? (5/4/3/2/1)
17. Parlar? (5/4/3/2/1)
18. Fer-se entendre per telèfon? (5/4/3/2/1)
19. Fer que l'altra gent l'entengui? (5/4/3/2/1)

[8] Adapted from Ahmandi et al. (54)

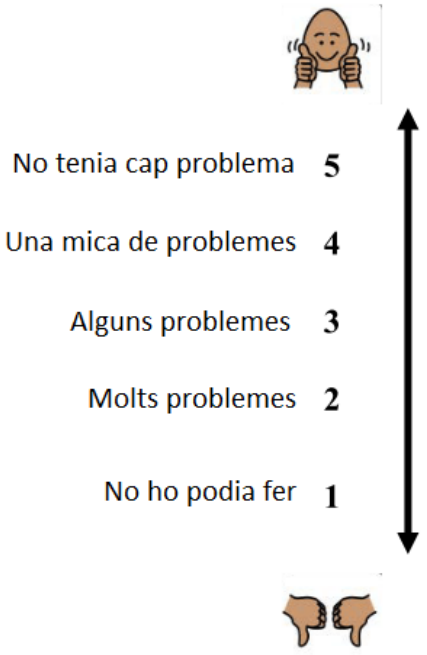
20. Trobar la paraula que volia dir? (5/4/3/2/1)
21. Fer que la resta de gent l'entengui encara que hagi repetit el que ha dit?

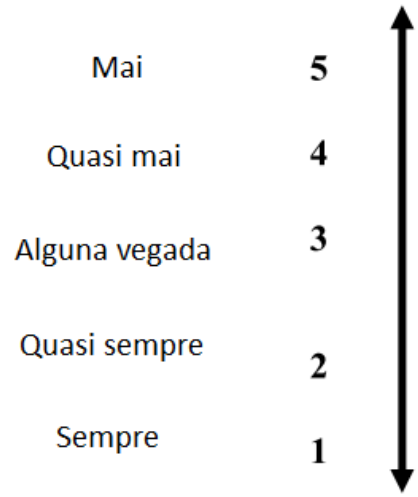
Durant la setmana passada, vostè va…

Mai	**5**
Quasi mai	**4**
Alguna vegada	**3**
Quasi sempre	**2**
Sempre	**1**

1. Escriure's les coses per recordar-les? (5/4/3/2/1)
2. Trobar difícil prendre decisions? (5/4/3/2/1)
3. Sentir-se irritable? (5/4/3/2/1)
4. Sentir que la seva personalitat havia canviat? (5/4/3/2/1)
5. Sentir-se desencoratjat sobre el seu futur? (5/4/3/2/1)
6. Sentir-se desinteressat en altres persones o activitats? (5/4/3/2/1)
7. Sentir-se abandonat per part d'altres persones? (5/4/3/2/1)
8. Tenir poca confiança en vostè mateix? (5/4/3/2/1)
9. Sentir-se cansat la major part del temps? (5/4/3/2/1)
10. Haver-se de aturar i descansar durant el dia? (5/4/3/2/1)
11. Sentir-se massa cansat per fer el que volia fer? (5/4/3/2/1)
12. Sentir que és una molèstia per a la seva família? (5/4/3/2/1)
13. Sentir que els seus problemes de llenguatge influeixen en la seva vida familiar? (5/4/3/2/1)
14. Sortir menys del que li agradaria? (5/4/3/2/1)
15. Realitzar les teves aficions menys del que t'agradaria? (5/4/3/2/1)
16. Veure els teus amics menys del que t'agradaria? (5/4/3/2/1)
17. Sentir que la teva forma física interfereix en la teva vida social? (5/4/3/2/1)
18. Sentir que els teus problemes de llenguatge interferien en la teva vida social? (5/4/3/2/1)

16. 4.2 VISUAL SUPPORT FOR APHASIC PATIENTS TO ANSWER[9]





[9] Adapted from Ryan LM from (55)

16. 5. STROKE APHASIC DEPRESSION QUESTIONAIRE[10]

Nº de codi del pacient →

Por favor indique cuántos días, de los últimos siete, el paciente ha mostrado los comportamientos siguientes:

0= not at all, 1=on 1-4 days, 2=on 4-6 days, 3=every day

1. ¿Tuvo episodios de llanto?
    - Todos los días de esta semana (3)
    - De 4 a 6 días esta semana (2)
    - De 1 a 4 días esta semana (1)
    - Ningún día de esta semana (0)
2. ¿Estuvo inquieto por las noches o pasó malas noches?
    - Todos los días de esta semana (3)
    - De 4 a 6 días esta semana (2)
    - De 1 a 4 días esta semana (1)
    - Ningún día de esta semana (0)
3. ¿Evitó el contacto visual cuando habló con él/ella?
    - Todos los días de esta semana (3)
    - De 4 a 6 días esta semana (2)
    - De 1 a 4 días esta semana (1)
    - Ningún día de esta semana (0)
4. ¿Rompió a llorar?
    - Todos los días de esta semana (3)
    - De 4 a 6 días esta semana (2)
    - De 1 a 4 días esta semana (1)
    - Ningún día de esta semana (0)
5. ¿Se quejó de alguna molestia o dolor?
    - Todos los días de esta semana (3)
    - De 4 a 6 días esta semana (2)
    - De 1 a 4 días esta semana (1)
    - Ningún día de esta semana (0)

[10] Adapted from University of Toronto (65)

6. ¿Se enfadó?
    - Todos los días de esta semana (3)
    - De 4 a 6 días esta semana (2)
    - De 1 a 4 días esta semana (1)
    - Ningún día de esta semana (0)
7. ¿Rechazó la participación en actividades sociales (como visitas, relacionarse o entretenerse)?
    - Todos los días de esta semana (3)
    - De 4 a 6 días esta semana (2)
    - De 1 a 4 días esta semana (1)
    - Ningún día de esta semana (0)
8. ¿Se quedó sentado/a sin hacer nada?
    - Todos los días de esta semana (3)
    - De 4 a 6 días esta semana (2)
    - De 1 a 4 días esta semana (1)
    - Ningún día de esta semana (0)
9. ¿Se mantuvo ocupado/a durante el día?
    - Todos los días de esta semana (3)
    - De 4 a 6 días esta semana (2)
    - De 1 a 4 días esta semana (1)
    - Ningún día de esta semana (0)
10. ¿Estuvo agitado/a e inquieto/a?
    - Todos los días de esta semana (3)
    - De 4 a 6 días esta semana (2)
    - De 1 a 4 días esta semana (1)
    - Ningún día de esta semana (0)

16. 6. SAFETY rTMS SCREENING QUESTIONNAIRE[11]

1. Do you have epilepsy, or have you ever had a convulsion or a seizure?
2. Have you ever had a fainting pell or syncope? If yes, please describe in which occasion(s)
3. Have you ever had severe (i.e., followed by loss of consciousness) head trauma?
4. Do you have any hearing problems or ringing in your ears?
5. Are you pregnant or is there any chance that you might be?
6. Do you have metal in the brain/skull (except titanium)? (e.g., splinters, fragments, clips, etc.)
7. Do you have cochlear implants?
8. Do you have an implanted neurostimulator?
9. Do you have a cardiac pacemaker or intracardiac lines or metal in your body?
10. Do you have a medication infusion device?
11. Are you taking any medications? (Please list)
12. Did you ever have a surgical procedures to your spinal cord?
13. Do you have spinal or ventricular derivations?
14. Did you ever undergo TMS in the past?
15. Did you ever undergo MRI in the past?

Affirmative answers to one or more of questions 1–13 do not represent absolute contraindications to TMS, but the risk/benefit ratio should be carefully balanced by the Principal Investigator of the research project or by the responsible (treating) physician.

[11] Adapted from Rossi et al. (59)

16. 7. INFORMATION SHEET FOR THE PATIENT

FULL D'INFORMACIÓ AL PACIENT

Títol de l'estudi: Estimulació magnètica transcranial en la rehabilitació de pacients amb afàsia després de l'ictus.

Ens dirigim a vostè per informar-lo sobre un estudi d'investigació en el que se'l convida a participar. L'estudi ha estat aprovat pel Comitè d'Ètica de la Investigació amb medicaments i per l'Agència Espanyola de Medicaments i Productes Sanitaris, d'acord amb la legislació vigent, el Reial Decret 1090/2015 de 4 de desembre i Reglament Europeu 536/2014 de 16 abril, por els que es regulen els assaigs clínics amb medicaments.

La nostra intenció és que vostè rebi la informació correcta i suficient per tal de que pugui decidir si accepta o no participar en aquest estudi. Llegeixi aquesta fulla informativa amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir.

Participació voluntària

Vostè ha estat diagnosticat d'afàsia secundària a ictus. L'afàsia secundària a ictus és l'alteració adquirida de la capacitat d'emetre i/o comprendre el llenguatge deguda a la lesió de les estructures cerebrals encarregades del llenguatge com a conseqüència de l'ictus. Així doncs, vostè pateix una seqüela de l'ictus que actualment no disposa d'un tractament específic, sent la teràpia de llenguatge amb logopèdia l'única possibilitat terapèutica de la qual lamentablement, s'obtenen uns resultats limitats.

Ha de saber que la seva participació en aquest estudi és voluntària. Si decideix participar, vostè podrà canviar la seva decisió i retirar el consentiment en qualsevol moment sense que això provoqui una alteració en la relació amb el seu metge/ssa ni es generi cap conseqüència en la seva atenció sanitària.

Objectiu de l'estudi

L'estudi al qual el convidem a participar té l'objectiu principal de determinar si l'ús de l'estimulació transcranial magnètica prèvia a la logopèdia provoca una millora de la seva capacitat de parlar, repetir paraules, anomenar objectes i comprendre el que se li explica respecte el tractament únic amb logopèdia.

Descripció de l'estudi

Aquest estudi va dirigit a pacients que han estat diagnosticats de afàsia no fluent secundària a ictus que a més siguin dretans i que la seva llengua materna sigui el català. Vostè no podrà participar a l'estudi si és menor de 18 anys, té antecedents de ictus, demència o qualsevol malaltia que expliqui la seva alteració del llenguatge o si té contraindicacions per rebre estimulació magnètica.

L'estudi és un assaig clínic que té dos branques de tractament: una rebrà estimulació magnètica real i l'altre rebrà una estimulació simulada que aparentment serà similar a la real però que no esperem que tingui efectes terapèutics. Vostè serà assignat aleatòriament a una d'aquestes dues branques. Volem que sàpiga que ni el metge/ssa o personal mèdic que l'avaluï ni el pacient sabran quin és el tractament que rebrà excepte en el moment de l'estimulació en el qual el personal de neurofisiologia sí que coneixerà el tipus d'estimulació que li aplicarà.

Activitats de l'estudi

La seva participació a l'estudi serà d'aproximadament un any. No obstant això, la fase de tractament en la que rebrà estimulació magnètica (real o placebo depenent del grup al que ha estat assignat) + logopèdia només durarà dues setmanes. La fase de tractament consisteix en sessions diàries de 1.30h (que inclou estimulació magnètica + logopèdia) durant els dies laborals de dues setmanes seguides. Previ a la fase de tractament, vostè serà citat en dues ocasions: la primera ocasió serà citat amb el Servei de Neuropsicologia on se li administraran uns tests per avaluar el grau d'afàsia que té, per veure quin grau d'alteració té en els diferents dominis del llenguatge (parla espontània, nominació, repetició i comprensió) i per veure quin impacte té l'afàsia en la seva qualitat de vida i estat d'ànim. En la segona ocasió, serà citat pel servei de Radiologia per tal de fer-li una Ressonància magnètica funcional. La ressonància magnètica funcional és una prova d'imatge que a més en permet tenir un idea de com funciona el seu cervell mentre vostè parla. Aquesta prova té una durada aproximada de 1h i ens permetrà adaptar els paràmetres de l'estimulació cerebral magnètica que rebrà durant la fase de tractament. Posteriorment a la fase del tractament, se'l citarà de nou amb el servei de Neuropsicologia (durant la setmana següent a l'última sessió de tractament) on se li administraran els mateixos tests que se li havia administrat a la fase prèvia al tractament. Finalment, durant la fase de seguiment se'l citarà de nou amb el servei de Neuropsicologia en dues ocasions: el primer al cap de 6 mesos d'haver rebut l'estimulació i el segon al cap d'un any d'haver-la rebut. En ambdues ocasions, se li administraran els mateixos test que se li havia administrat a la fase prèvia al tractament.

Riscos i molèsties derivats de la seva participació a l'estudi

L'estimulació magnètica transcranial és una tècnica segura i ben tolerada que actualment no està aprovada pel tractament de l'afàsia. L'únic ús aprovat de la tècnica és el tractament de la depressió refractària.

Malgrat ser una tècnica molt segura, alguns pacients han presentat alguns efectes indesitjats que ha de conèixer. Els efectes indesitjats freqüents són mal de cap, mal de coll, sensació de formigueig o dolor a la zona en la que s'aplica l'estimulació. Els efectes indesitjats estanys però greus serien pèrdua auditiva (motiu pel qual ara s'utilitzen taps), convulsions (efecte advers demostrat només amb

persones amb certa predisposició a tenir-ne, amb un risc inferior a 1 cada 1000 pacients tractats), canvis psiquiàtrics (en estudi, s'ha postulat que podrien provocar canvis en estat d'ànims encara que és molt rar) i canvis cognitius.

La rTMS és una tècnica que té una sèrie de contraindicacions que fan que el pacient que les compleix no pugui ser inclòs a l'estudi. Són les següents:

- Implants metàl·lics (implants coclears, clips, stents) o elèctrics (marcapassos, implants cardíacs, desfibril·ladors)
- Antecedent d'epilèpsia o convulsions, TCE o tumor cerebral
- Antecedent de malaltia psiquiàtrica com depressió, mania, esquizofrènia
- Embaràs o lactància
- Abús de substàncies
- Canvi recent en la medicació
- Ús medicació que pugui predisposar a convulsió/atac epilèptic

El seu metge/metgessa responsable revisarà la seva història clínica i li practicarà una exploració física adequada per tal d'assegurar-se que no hi ha cap motiu de seguretat pel qual hagi de ser exclòs de l'estudi.

Possibles beneficis

La seva participació contribuirà a un millor coneixement del procés de rehabilitació de la afàsia i a l'estudi de l'eficàcia d'un possible tractament, que podrà beneficiar als futurs pacients que la pateixin. Al participar en aquest estudi pot ser que la seva afàsia millori però també ha de conèixer que és possible que no obtingui cap benefici per la seva salut al participar en aquest estudi.

Tractaments alternatius

Actualment, el tractament estàndard de l'afàsia secundària a ictus és la rehabilitació mitjançant logopèdia de la qual s'obtenen resultats limitats. Actualment no hi ha cap altre tractament que sigui millor que la logopèdia motiu pel qual estem estudiant altres vies de tractament mitjançant la investigació.

Assegurança

El Promotor de l'estudi disposa d'una pòlissa d'assegurança que s'ajusta a la legislació vigent (Real decret 1090/2015) i que li proporcionarà la compensació i indemnització en cas de dany o lesions que puguin produir-se en relació amb la seva participació a l'estudi, sempre que no siguin conseqüència de la pròpia malaltia que s'estudia o de l'evolució pròpia de la malaltia com a conseqüència de la ineficàcia del tractament.

Si desitja més informació relativa a aquest apartat, consulti amb l'investigador/a principal de l'estudi.

L'informem que és possible que la seva participació en aquest assaig clínic pugui modificar les condicions generals i particulars (cobertura) de les seves pòlisses d'assegurances (vida, salut, accident). Per això, li recomanem que es posi en contacte amb la seva asseguradora per determinar si la participació en aquest estudi afectarà a la seva actual pòlissa d'assegurances.

Protecció de dades personals

El promotor es compromet a l'acompliment de la Llei Orgànica 15/1999, de 13 de desembre de protecció de dades de caràcter personal i als del Reial Decret que la desenvolupa (RD 1720/2007). Les dades recollides per a l'estudi estaran identificats mitjançant un codi, de manera que no inclogui informació que pugui identificar-lo, i només el seu metge/ssa de l'estudi / col·laboradors podrà relacionar aquestes dades amb vostè i amb la seva història clínica. Per tant, la seva identitat no serà revelada a cap persona llevat d'excepcions en cas de urgència mèdica o requeriment legal. El tractament, la comunicació i la cessió dels dades de caràcter personal de tots els participants s'han d'ajustar al que disposa aquesta llei.

L'accés a la seva informació personal identificar quedarà restringit el metge de l' estudi / col·laboradors, autoritats sanitàries (Agència Espanyola de Medicaments i Productes Sanitaris, autoritats sanitàries estrangeres), a el Comitè d'Ètica de la Investigació i personal autoritzat pel promotor (monitors de l'estudi, auditors), quan ho necessitin per comprovar les dades i procediments de l'estudi, però sempre mantenint la confidencialitat dels mateixos d'acord amb la legislació vigent.

Les dades es recolliran en un fitxer de recerca responsabilitat de la institució i es tractaran en el marc de la seva participació en aquest estudi.

El promotor ha d'adoptar les mesures pertinents per a garantir la protecció del seu privacitat i no permetrà que les seves dades es creuin amb altres bases de dades que poguessin la seva identificació. D'acord al que estableix la legislació de protecció de dades, vostè pot exercir els drets d'accés, modificació, oposició i cancel·lació de dades, per a això haurà de dirigir al seu metge de l'estudi.

Les dades codificades poden ser transmesos a tercers i a altres països però en cap cas han de contenir informació que li pugui identificar directament, com a nom i cognoms, inicials, adreça, número de la seguretat social, etc. En el cas que es produeixi aquesta cessió, serà per als mateixos fins de l'estudi descrit o per al seu ús en publicacions científiques però sempre mantenint la confidencialitat dels mateixos d'acord amb la legislació vigent.

Quin tractament rebré quan acabi l 'estudi?

Quan acabi la seva participació rebrà el millor tractament disponible i que el seu metge consideri el més adequat per a la seva malaltia, però és possible que no se li pugui seguir administrant la medicació

de l'estudi. Per tant, ni l'investigador ni el promotor adquireixen cap compromís de mantenir aquest tractament fora d'aquest estudi.

Altra informació rellevant

Qualsevol informació nova referent a la rTMS que sigui descoberta durant la vostra participació a l'estudi i que pugui modificar la seva disposició per participar, us la comunicarà el metge/ssa responsable com més aviat millor.

Ha de saber que pot ser exclòs de l'estudi si el promotor o els investigadors/es de l' estudi ho consideren oportú, ja sigui per motius de seguretat, per qualsevol esdeveniment advers que es produeixi per la medicació en estudi o perquè considerin que no està complint amb els procediments establerts. En qualsevol dels casos, vostè rebrà una explicació adequada del motiu que ha ocasionat la seva retirada de l'estudi.

Al signar el full de consentiment adjunt, es compromet a complir amb els procediments de l'estudi que se li han exposat.

Contacte en cas de dubtes

En cas de necessitar informació o resoldre qualsevol dubte que li sorgeixi durant la seva participació a l'estudi, podrà posar-se en contacte amb el Dr/Dra _____ , a través del telèfon _____ o correu electrònic _____.

Sigui quina sigui la vostre decisió, l'equip investigador vol agrair-li el seu temps i la seva atenció.

Firma del participant Firma de l'investigador/a

Girona, ____ de _____de 20__.

16. 8. INFORMED CONSENT

FULL DE CONSENTIMENT INFORMAT

Títol de l'estudi: Estimulació magnètica transcranial en la rehabilitació de pacients amb afàsia després de l'ictus.

Jo, _____ (nom i cognoms), declaro:

- Haver llegit i entès el full d'informació que se m'ha lliurat
- Haver pogut fer les preguntes que m'hagin sorgit sobre l'assaig i haver-les resolt
- Haver rebut informació suficient sobre l'estudi
- Haver entès el meu paper com a participant en l'estudi
- He parlat amb _____ (investigador principal)
- Comprenc que la meva participació és voluntària
- Entenc que puc retirar-me de l'assaig:
    - Quan vulgui
    - Sense haver de donar explicacions
    - Sense que això repercuteixi en les meves cures mèdiques

De conformitat amb la Llei Orgànica 15/1999, de 13 de desembre de protecció de dades de caràcter personal i el Reial Decret que la desenvolupa (RD 1720/2007), declaro haver estat informat de:

- L'existència d'una base de dades on s'inclouran les meves dades de caràcter personal
- De la finalitat de la seva recollida i dels destinataris de la informació
- Del procés de codificació de les dades
- De la disponibilitat d'exercir els drets d'accés rectificació, cancel·lació i oposició dirigint- me per escrit al titular de la base de dades

Autoritzo a que les dades clíniques referents a la meva malaltia siguin emmagatzemades en un fitxer automatitzat, la informació del qual podrà ésser utilitzada exclusivament per finalitats científiques.

Rebré una còpia firmada i datada d'aquest document de consentiment informat.

Dono lliurement la meva conformitat per participar en l'assaig.

Firma del participant Firma de l'investigador/a

Girona, ____ de _____de 20__.

Quan s'obtingui el consentiment informat en pacients amb capacitat modificada per donar el seu CI.

Firma del representant legal, familiar o persona vinculada de fet

Firma de l'investigador

Girona, ____ de _____de 20___.

16. 9. MULTIDIMENSIONAL HEALTH LOCUS CONTROL[12]

1=STRONGLY DISAGREE **(SD)**
2=MODERATELY DISAGREE **(MD)**
3=SLIGHTLY DISAGREE **(D)**
4=SLIGHTLY AGREE **(A)**
5=MODERATELY AGREE **(MA)**
6=STRONGLY AGREE **(SA)**

Number	Question	SD	MD	D	A	MA	SA
1	If I get sick, it is my own behavior which determines how soon I get well again.	1	2	3	4	5	6
2	No matter what I do, if I am going to get sick, I will get sick.	1	2	3	4	5	6
3	Having regular contact with my physician is the best way for me to avoid illness	1	2	3	4	5	6
4	Most things that affect my health happen to me by accident.	1	2	3	4	5	6
5	Whenever I don't feel well, I should consult a medically trained professional.	1	2	3	4	5	6
6	I am in control of my health.	1	2	3	4	5	6
7	My family has a lot to do with my becoming sick or staying healthy.	1	2	3	4	5	6
8	When I get sick, I am to blame.	1	2	3	4	5	6
9	Luck plays a big part in determining how soon I will recover from an illness.	1	2	3	4	5	6

[12] Adapted from Ross et al (66)

10	Health professionals control my health.	1	2	3	4	5	6
11	My good health is largely a matter of good fortune.	1	2	3	4	5	6
12	The main thing which affects my health is what I myself do.	1	2	3	4	5	6
13	If I take care of myself, I can avoid illness.	1	2	3	4	5	6
14	Whenever I recover from an illness, it's usually because other people (for example, doctors, nurses, family, friends) have been taking good care of me.	1	2	3	4	5	6
15	No matter what I do, I 'm likely to get sick.	1	2	3	4	5	6
16	If it's meant to be, I will stay healthy.	1	2	3	4	5	6
17	If I take the right actions, I can stay healthy.	1	2	3	4	5	6
18	Regarding my health, I can only do what my doctor tells me to do.	1	2	3	4	5	6