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THE ROLE OF TMS IN BRAIN PLASTICITY IN HEALTH AND DISEASE

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O PAPEL DA ESTIMULAÇÃO MAGNÉTICA TRANSCRANIANA NA PLASTICIDADE CEREBRAL, NA SAÚDE E NA DOENÇA

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Aos meus pais

" *Two roads diverged in a wood, and I*

I took the one less travelled by,

And that has made all the difference. "

- Robert Frost

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ABSTRACT

Stroke is the third major cause of death and a main source of disability around the globe. Several strategies are being applied to deal with the deficits that are sustained after the event. However, they often lack efficacy, which propelled the search for new interventions. Transcranial magnetic stimulation (TMS) appears as a potential solution. This way, we analysed the state-of-the-art by conducting two systematic reviews on the application of TMS to the rehabilitation of post-stroke deficits and verified that the majority of the literature obtained promising results, showing functional improvements attributed to the stimulation. Nevertheless, some studies report negative results and there is also a possibility of bias for non-publication of negative outcomes. Moreover, we observed high variability related to the implementation of protocols and parameters of stimulation. Also, the mechanisms of action of this technique and its impact on the human brain are not yet fully clear and individual differences in the response to the protocols are noteworthy.

This way, we have decided to investigate the neurophysiological impact of a recently proposed TMS inhibitory protocol, the continuous theta burst (cTBS), which has been being studied as a possible treatment for several pathologies, including post-stroke deficits. The hypothesis behind this approach is that inhibition of the unaffected hemisphere would release the lesioned hemisphere from contralateral suppression with a subsequent favourable increase in cortical excitability.

We recruited 20 healthy participants and 10 subacute stroke patients and started by evaluating the impact of an ischemic brain lesion on neurophysiology. In this study, we determined the active motor threshold, with single-pulse transcranial magnetic stimulation, and recorded brain electrical activity at rest and during execution of simple (arm elevation) and complex (thumb opposition) tasks, through electroencephalography (EEG). Additionally, in stroke patients we evaluated motor function of the affected upper limb with the Wolf Motor Function Test (WMFT). We found out that a stroke lesion affects the dynamics of cortical oscillations by significantly decreasing event-related desynchronization (ERD), i.e. increasing *beta* power, in the context of motor preparation and execution of bimanual thumb opposition. Moreover, we observed a significant moderate negative correlation between these levels of *beta* rhythm and the velocity of execution in WMFT tasks, in patients.

Then, we studied the impact of continuous theta burst stimulation, applied over the primary motor cortex, in both healthy and patient groups. We analysed changes in cortical oscillations at rest and with motor execution, by repeating the EEG recordings post-stimulation, and assessed differences that could be induced by the stimulation in the peak-to-peak amplitude of motor-evoked potentials, measured by electromyography.

In healthy subjects, we found a significant increase in contralateral *mu* and *beta* rhythms, for the arm elevation task, after stimulation. These findings are consistent with the notion that that the protocol decreased ERD and that this inhibitory effect has unexpectedly propagated to the contralateral hemisphere, in healthy participants.

Concerning the intervention approach, patients were randomized into two groups: one receiving real and the other sham cTBS, over the unaffected hemisphere. We observed significant changes in contralateral oscillations after stimulation, specifically in the *beta* band, only for the patients allocated to the real intervention group. The results from the affected thumb opposition task indicate an increase in ERD, suggesting the expected excitatory response on the sensorimotor cortical areas of the affected hemisphere, unlike in healthy participants.

Our results suggest that the effects of continuous theta burst stimulation might be different in health and in disease, and also task-dependent.

Changes in the amplitude of motor-evoked potentials showed a bimodal distribution for both healthy and post-stroke participants, revealing opposite responses in terms of polarity of effects. Changes in motor function were also not significant, which is expectable from a single session intervention.

We conclude that continuous theta burst stimulation changes brain's neurophysiology by altering contralateral event-related synchronization/ desynchronization patterns. The impact of the stimulation seems to be different between healthy and pathological populations, and our hypothesis was only confirmed in the latter case. These findings may have significant implications for future neurorehabilitation approaches.

Keywords: Stroke, cerebrovascular accident, neurorehabilitation, brain stimulation, transcranial magnetic stimulation, continuous theta burst stimulation, brain oscillations, motor rhythms.

RESUMO

O acidente vascular cerebral (AVC) é a terceira causa mais frequente de morte e um dos principais responsáveis por incapacidade, a nível mundial. Diversas estratégias têm vindo a ser usadas para lidar com os défices que surgem com o evento. Não obstante, estas são recorrentemente insuficientes, impulsionando a procura por novas e mais eficazes intervenções. A estimulação magnética transcraniana (EMT) apresenta-se como uma potencial solução. Neste sentido, analisámos o estado-da-arte, conduzindo duas revisões sistemáticas com enfoque na aplicação da EMT para reabilitação de défices pós-AVC e verificámos que a maioria dos trabalhos descritos na literatura obtiveram resultados promissores, com melhorias funcionais atribuídas à estimulação. Contudo, alguns estudos reportam resultados negativos, existindo igualmente a possibilidade de um viés associado à não-publicação de descobertas negativas. Observámos ainda uma elevada variabilidade relacionada com a implementação de protocolos e parâmetros de estimulação. Adicionalmente, os mecanismos de ação desta técnica e o seu impacto no cérebro humano não são ainda completamente claros e existem diferenças individuais na resposta aos protocolos que devem ser salientadas.

Deste modo, decidimos investigar o impacto neurofisiológico de um protocolo inibitório de EMT recentemente proposto, o theta burst contínuo (cTBS), que tem vindo a ser estudado como possível tratamento para diversas patologias, incluindo défices pós-AVC. A hipótese subjacente a esta abordagem é a de que a inibição do hemisfério não afectado libertaria o hemisfério lesado da supressão contralateral, com um subsequente aumento favorável da excitabilidade cortical.

Recrutámos 20 indivíduos saudáveis e 10 doentes que sofreram um acidente vascular cerebral e se encontravam numa fase subaguda da doença, e começámos por avaliar o impacto de uma lesão cerebral isquémica na neurofisiologia. Neste estudo, determinámos o limiar motor ativo, através de estimulação magnética transcraniana por pulsos únicos, e registámos a atividade elétrica cerebral em repouso e durante a execução de tarefas simples (elevação dos braços) e complexas (oposição do polegar), com recurso à eletroencefalografia (EEG). Especificamente para os doentes, avaliámos ainda a função motora do membro superior afetado, usando a escala Wolf Motor Function Test (WMFT). Observámos que a lesão afeta a dinâmica das oscilações corticais, diminuindo significativamente a dessincronização (ERD), isto é, aumentando a atividade das ondas beta, no contexto da preparação e execução da oposição bimanual dos polegares. Adicionalmente, detetou-se uma correlação moderada significativa, no sentido negativo, entre estes níveis do ritmo beta e a velocidade de execução das tarefas no WMFT, em doentes.

De seguida, estudámos o impacto do theta burst contínuo, quando aplicado no córtex motor primário, quer em indivíduos saudáveis como no grupo de doentes. Analisámos alterações nas oscilações corticais em repouso e com execução de movimento, repetindo a gravação do EEG,

pós-estimulação, e estimámos diferenças que poderiam ser induzidas pela estimulação na amplitude pico-a-pico dos potenciais evocados motores, medidas por eletromiografia.

Nos voluntários saudáveis, encontrámos um aumento significativo dos ritmos mu e beta contralaterais, para a elevação do braço, pós-estimulação. Estes achados são consistentes com a noção de que o protocolo diminuiu a ERD e que este efeito inibitório se propagou inesperadamente para o hemisfério contralateral, em participantes saudáveis.

Relativamente à abordagem de intervenção, os doentes foram divididos, aleatoriamente, em dois grupos: um que recebeu cTBS real e outro placebo, no hemisfério não afetado. Observámos alterações significativas nas oscilações contralaterais após a estimulação, especificamente na banda beta, apenas para os doentes alocados ao grupo da intervenção real. Os resultados para a oposição do polegar afetado indicaram um aumento na ERD, sugerindo a resposta excitatória esperada nas áreas corticais sensoriomotoras do hemisfério afetado, contrariamente ao observado em participantes saudáveis.

Os nossos resultados sugerem que os efeitos do theta burst contínuo podem ser diferentes na saúde e na doença, e também variar consoante as tarefas motoras.

As alterações na amplitude dos potenciais evocados motores mostraram uma distribuição bimodal quer nos participantes saudáveis como no grupo pós-AVC, revelando respostas opostas em termos de polaridade dos efeitos. As alterações da função motora também não foram significativas, o que é expectável de uma intervenção com uma única sessão.

Concluímos que o theta burst contínuo altera a neurofisiologia cerebral através da modificação dos padrões de sincronização/dessincronização do hemisfério contralateral. O impacto da estimulação parece ser diferente entre populações saudáveis ou com patologias, e a nossa hipótese foi confirmada apenas no último caso. Estes resultados poderão ter implicações significativas para abordagens futuras de neuroreabilitação.

Palavras-chave: AVC, acidente vascular cerebral, neuroreabilitação, estimulação cerebral, estimulação magnética transcraniana, theta burst contínuo, oscilações cerebrais, ritmos motores.

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LIST OF SYMBOLS AND ABBREVIATIONS

A

Ag/AgCl – silver/silver chloride
aMT – active motor threshold

B

B – magnetic field
BDNF – brain-derived neurotrophic factor

C

C – capacitance
Ca^{2+} – calcium ions
CHUC – Coimbra Hospital and University Centre
CMCT – central motor conduction time
CSP – cortical silent period
cTBS – continuous TBS
CVA – cerebrovascular accident

D

D – diode
DC – direct current
D-waves – direct waves

E

E – electric field
EEG – electroencephalography
EMG – electromyography
ERD – event-related desynchronization
ERPs – event-related potentials
ERS – event-related synchronization

F

FA – flip angle
FAS – functional ability scale
fMRI – functional MRI
FOV – field-of-view

G

GABA – gamma-aminobutyric acid
Group C – control group
Group E – experimental group

H

HF – high-frequency

I

I-waves – indirect waves
ICA – independent component analysis
ICF – intracortical facilitation
ICI – intracortical inhibition
ICNAS – Institute of Nuclear Sciences Applied to Health
ISI – inter-stimulus interval
iTBS – intermittent TBS

L

L – inductance
LF – low-frequency
LH – left hemisphere
LICI – long-interval intracortical inhibition
LTD – long-term depression
LTP – long-term potentiation

M

M1 – primary motor cortex
Mg^{2+} – magnesium ions
MCA – middle cerebral artery
MEP's – motor-evoked potentials
MPRAGE – magnetization-prepared rapid acquisition gradient echo
MRI – magnetic resonance imaging
MT – motor threshold

N

NIRS – near-infrared spectroscopy
NMDA – N-methyl-D-aspartate

P

PET – positron emission tomography
PMd – dorsal premotor cortex
pp-TMS – paired-pulse TMS

Q

QPS – quadripulse stimulation

R

R – resistance
RCT – randomized controlled trial
RH – right hemisphere
rTMS – repetitive TMS

S

S – thyristor
SICI – short-interval intracortical inhibition
SPECT – single-photon emission computed tomography
sp-TMS – single-pulse TMS

T

TBS – theta burst stimulation
tDCS – transcranial direct current stimulation
TE – echo time
TI – inversion time
TMS – transcranial magnetic stimulation
TR – repetition time

W

WHO – World Health Organization
WMFT – Wolf Motor Function Test

Chapter

1

PREFACE

1.1. INTRODUCTION

I truly believe that life should be a source of continuous learning, in which people must develop their personal and professional skills. Therefore, I have applied for a doctoral program to expand my knowledge in a subject of great importance. I have a particular interest in health and in biomedical research as a way to improve the prevention, diagnosis and treatment of diseases. In this context, I have found the transcranial magnetic stimulation technique and its application to stroke recovery as a highly motivating topic. I hope that, with this work, I can contribute to a better understanding of this method in post-stroke neurorehabilitation.

1.2. MOTIVATION

Stroke is one of the most frequent causes of death and a leading cause of disability. Alternative more effective techniques for stroke rehabilitation have been sought to overcome limitations of conventional therapies. Transcranial magnetic stimulation (TMS) arises as a promising tool in this context. It has been intensely studied throughout the last years. In fact, nowadays it is being applied to the study of neurological and psychiatric diseases and to investigate and understand brain mechanisms in fundamental neuroscience. It is expected that the use of TMS in clinical neuroscience and therapeutic applications and in basic research will continue to grow, associated with new protocols and technological advances (Rossi *et al.* 2009). However, a consensus has not yet been reached about the optimal parameters of stimulation as a function of the clinical application. There are very similar studies with surprisingly different results, raising the issue of replicability, and, on the other hand, studies with very distinct parameters that produce similar outcomes (Heaton 2012).

Several studies report changes in excitability of the stimulated area and also of the contralateral hemisphere. However, the mechanisms underlying these effects are not well-established and need further investigation (Davila-Pérez *et al.* 2018). In line with the current state of the field, this project aims to investigate the mechanisms of TMS and its impact in neurophysiology, in health and in stroke.

1.3. AIMS

The main objectives of this thesis are to understand the role of TMS, specifically of the continuous theta burst (cTBS) protocol, in brain physiology and plasticity in health and in stroke and their implications for neurorehabilitation. Thereby, it is our goal to:

- Study changes in neurophysiology induced by an ischemic cerebral lesion;
- Assess the effects of stimulation in brain excitability, in health and in stroke;
- Investigate the impact of cTBS on cortical oscillatory patterns in the stimulated and contralateral hemispheres, of healthy individuals and patients;
- Test the theory that ipsilateral inhibition leads to contralateral disinhibition following stimulation with a continuous theta burst protocol;
- Evaluate whether the responses to TMS are similar in health and in stroke;
- Analyse the potential of continuous theta burst stimulation as an intervention applied for stroke neurorehabilitation.

1.4. PROJECT'S OVERVIEW

In this Project, we recruited subacute stroke patients from Coimbra Hospital and University Centre (CHUC) and age-matched healthy volunteers, who fulfilled established eligibility criteria. Experiments were carried out at the facilities of Institute of Nuclear Sciences Applied to Health (ICNAS).

We started by studying the changes induced by a stroke lesion in cortical excitability and brain oscillations at rest and during motor planning and execution.

Then, we applied continuous theta burst TMS to the primary motor cortex of healthy individuals to investigate the mechanisms underlying responses to the stimulation protocol, using single-pulse TMS and electroencephalography at rest and

with motor tasks. Since most part of the research works focus on the effects of non-invasive stimulation in gross movements after stroke, its impact in fine motor function has not been revealed yet (O'Brien *et al.* 2018). This way, in this Project we studied the influence of TMS on neurophysiological responses, with motor preparation and execution of both gross and finer motor tasks. Measurements were all taken in the same visit, before and after one session of stimulation. After considering the cortical responses to the protocol in the healthy brain, we delivered continuous theta burst to the unaffected hemisphere of stroke patients. In this context, the role of the protocol on the restoration of cortical activity was analysed, testing the hypothesis of a favourable effect of the inhibition induced on the unaffected hemisphere, according to the above-mentioned hypothesis. In patients, we added an additional visit of follow-up, to determine if potential changes were maintained three months after stimulation in the subacute stage of stroke.

1.5. THESIS' STRUCTURE

This thesis is organized into chapters. In the next chapter (**Chapter 2**) some background is provided to help understanding all the work that was carried out. It covers some introductory notes about the clinical neuroscience of stroke and the challenges that it encompasses, disclosing the need for new studies in this area. Then, the transcranial magnetic stimulation technique is described as well as its working principles. Taking into account the importance of electroencephalography to investigate brain's physiology in this work, we also included a brief overview on the concepts underlying this procedure. In order to understand which advances have been made on the application of TMS as an intervention tool for stroke motor rehabilitation and what contribution we could give to expand the knowledge in this field, we conducted an analysis of the current state-of-the-art, given in **Chapter 3.** Although this thesis focuses the study of transcranial magnetic stimulation when applied to the rehabilitation of the motor system, one cannot disregard the presence of other relevant post-stroke deficits that are also pointed out as benefiting from TMS intervention. Neglect, which is often present following a stroke event, has particularly been intensely studied since it is an important cause of impaired global functional rehabilitation (Allart *et al.* 2020, Gammeri

et al. 2020, Tsujimoto *et al.* 2020). Actually, this was the first neuropsychological symptom that was targeted by non-invasive brain stimulation as a treatment option (Oliveri 2011, Gammeri *et al.* 2020). The literature proposes a negative direct impact of severe somatosensory deficits on the rehabilitation of the motor function, possibly justified by the role of somatosensory input in fine movements (Zandvliet *et al.* 2020). Moreover, this deficit is identified as a valuable model to understand the intra- and inter-hemispheric cortical effects of a unilateral brain lesion (Oliveri 2011), which is highly relevant to explain the hypothesis that motivates our work. This way, **Chapter 4** targets the use of TMS to the recovery from neglect and, additionally, other deficits that can appear after a cerebrovascular accident, namely aphasia and dysphagia. Afterwards, the experimental methods are described (**Chapter 5**) and the results are presented and discussed (**Chapters 6 to 8**), following the IMRAD (Introduction, Methods, Results, and Discussion) structure. In **Chapter 9**, we unite the findings from each work into an integrated discussion, providing global considerations and implications of our findings. The last chapter of this dissertation (**Chapter 10**) presents the concluding remarks and points out issues that should be addressed by future studies.

BACKGROUND

2.1. STROKE

Definition

Stroke or cerebrovascular accident (CVA) was defined by the World Health Organization (WHO), in 1970, as

> *"rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin"* cited in (Sacco *et al.* 2013).

Even though this definition is still adopted, a group of experts in multidisciplinary fields, led by American Heart Association/American Stroke Association, came together to develop a most updated definition of stroke, based on the new findings that have been discovered since then (Sacco *et al.* 2013), adding silent infarctions and silent haemorrhages to the definition (Coupland *et al.* 2017). The summary of the resulting definition is presented in **Table 2.1.1**.

Table 2.1.1 – Summary of stroke definition, including different sub-types. Adapted from (Sacco *et al.* 2013).

DEFINITION OF STROKE	
	Central Nervous System Infarction
	Brain, spinal cord, or retinal cell death attributable to ischemia, based on: ❖ *Pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or* ❖ *Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other aetiologies excluded.*
	Ischemic Stroke
	An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.
	Silent Central Nervous System Infarction
	Imaging or neuropathological evidence of Central Nervous System infarction, without a history of acute neurological dysfunction attributable to the lesion.
	Intracerebral Haemorrhage
	A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

DEFINITION OF STROKE	**Stroke Caused by Intracerebral Haemorrhage**
	Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.
	Silent Cerebral Haemorrhage
	A focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion.
	Subarachnoid Haemorrhage
	Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord).
	Stroke Caused by Subarachnoid Haemorrhage
	Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.
	Stroke Caused by Cerebral Venous Thrombosis
	Infarction or haemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible oedema without infarction or haemorrhage do not qualify as stroke.
	Stroke, Not Otherwise Specified
	An episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.

Nevertheless, despite the evolution that has been made regarding the definition of stroke, it is still not universally accepted, with the inclusion of silent pathology being a point of disagreement (Coupland *et al.* 2017).

There are two main types of cerebrovascular accident defined according to its causes – ischemic and haemorrhagic (Barros 2012).

Ischemic stroke (**Figure 2.1.1, on the left**) is related to the appearance of blood clots or thrombi on the cerebral arteries, which block the blood flow and the cerebral irrigation. The deficient blood inflow to the cerebral tissues prevents them to receive nutrients, such as glucose and oxygen, which are crucial to their metabolism and survival. Consequently, we may observe cellular death or brain lesions, associated to a loss of function on the affected area. The brain areas which are more often affected are those irrigated by the middle cerebral artery (MCA) (Barros 2012).
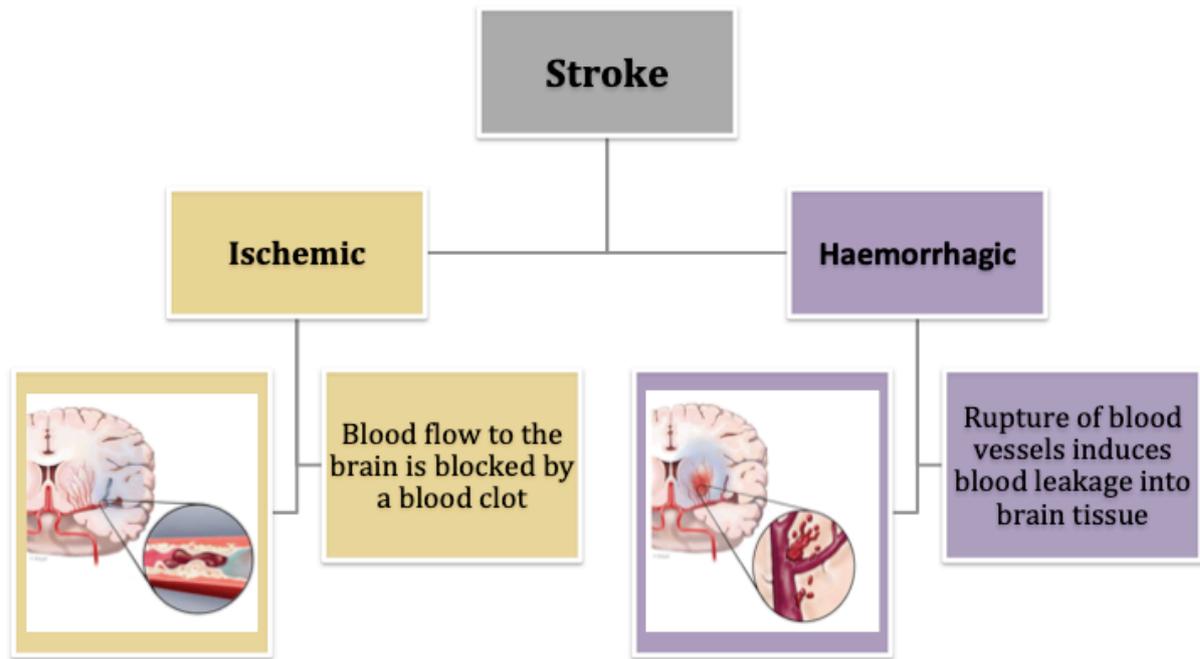
Figure 2.1.1 – Scheme distinguishing ischemic stroke, with the blockage of an artery, from haemorrhagic stroke, where it is possible to observe vascular rupture. Adapted from (Heart and Stroke Foundation of Canada 2015).

On the other hand, when the stroke is haemorrhagic (**Figure 2.1.1, on the right**) one can observe a sudden vascular rupture in a particular location, which gives rise to a blood leakage. This type is less frequent (Barros 2012). In fact, the majority of stroke events are ischemic (87%), while only 10% represent intracerebral haemorrhage and 3% account for subarachnoid haemorrhage (Benjamin *et al.* 2018).

Stroke in numbers

Stroke has a strong economic impact (Barros 2012) and in global public health (Costa *et al.* 2011). It is one of the main causes of mortality (Costa *et al.* 2011, Benjamin *et al.* 2018), originating 11.8% of death worldwide (Benjamin *et al.* 2018). WHO reported that every year there are 15 million people presenting with stroke, of which 5 million die as a consequence of the event (Barros 2012, Rangel *et al.* 2013). It was estimated that in 2015 stroke caused 1 death each 3 minutes and 45 seconds, approximately (Benjamin *et al.* 2018). In Portugal, every hour 6 people experience a stroke, from which 2 to 3 die (Sousa-Uva and Dias 2014). This is the 5th country in the

whole world with higher mortality rates due to cerebrovascular accident, presenting 2 to 3 times more deaths than the other countries of the European Union (Barros 2012).

In 2014, Sousa-Uva & Dias developed a transversal study of prevalence in Portugal, through telephone interviews, and obtained the data summarized in **Figure 2.1.2**. They described a prevalence of 1.9%, with a majority among men (Sousa-Uva and Dias 2014). By analysing different age groups, they found that from 64 to 74 years there was a marked increase in stroke prevalence in both genders, wherein the highest value in this range was observed for males (14.1%) (Sousa-Uva and Dias 2014).
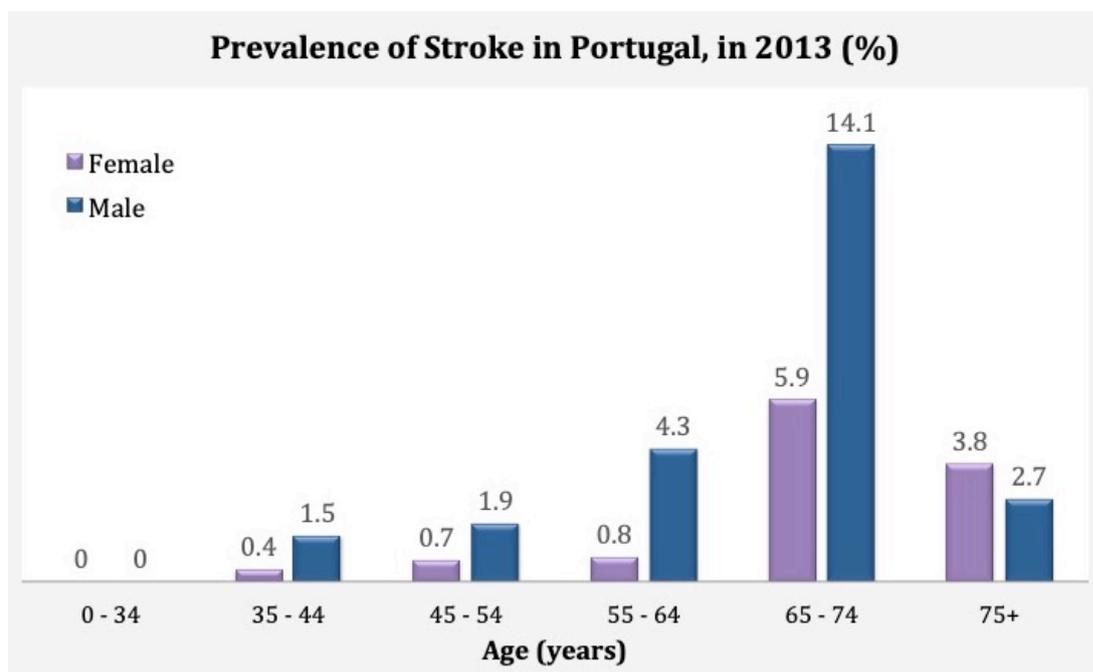
Figure 2.1.2 – Prevalence of stroke in Portugal, for different age groups. Data collected from (Sousa-Uva and Dias 2014).

Even though the mortality rate in Portugal has decreased from 61.9% in 2011 to 49.7% in 2015, as reported by Direção-Geral da Saúde, morbidity increased 1.6% between 2011 and 2016 (Direcção-Geral da Saúde 2017).

American Heart Association, Inc. predicts that by 2030, more 3.4 million adults will have had a stroke, showing a prevalence increase of 20.5% from 2012. The increase in prevalence of stroke survivors is possibly explained by the growth of aging population (Mozaffarian *et al.* 2015, Benjamin *et al.* 2018).

Risk factors

There are several factors (**Table 2.1.2**) that can influence the probability of developing a cerebrovascular accident. Some can be controlled, by changing behaviours and lifestyles, whereas others are intrinsic to the individual and cannot be modified (Barros 2012).

Table 2.1.2 – Summary of risk factors, including intrinsic and clinical factors as well as those related to lifestyle and others. Collected and adapted from (Barros 2012, Benjamin *et al.* 2018).

Intrinsic factors	
Age	the probability of stroke occurrence increases exponentially with age
Gender	males are more frequently affected (however, mortality is higher among women, possibly because they have strokes in older ages compared to men)
Race	black subjects are more susceptible
Genetics	it is thought that there is a familiar tendency

Clinical factors	
Hypertension	in association with advanced age, this is the most important factor
Diabetes mellitus	duplicates the risk of stroke
Hyperlipidaemia	originates changes in the blood vessels that, in turn, cause lesions
Cardiac diseases	some cardiac diseases, such as acute myocardial infarction, form clots that move through the heart and to the extra-cardiac circulation; this way, they can enter on the cerebral circulation and increase the risk for CVA

Lifestyle	
Tobacco	raises the risk of CVA between 200 and 400%
Alcohol	increases particularly the risk of haemorrhagic stroke
Physical activity	a sedentary lifestyle can also increase the likelihood

Other	
Climate	extreme temperatures are prejudicial and constitute a factor risk
Contraceptive pills and hormone replacement therapy	when administered in high doses, the risk increases two to seven times; there is no evidence that low doses have a negative effect, except when associated to other factors

Symptoms

Along with the occurrence of a stroke, a cluster of neurologic symptoms appears. These are observed on the contralateral side of the brain lesion, since most sensory and

motor representations are crossed to the other side of the body, i.e. when the lesion occurs on the right hemisphere, symptoms are observed on the left side of the body, and *vice-versa* (Barros 2012).

> *"The most common symptom of a stroke is sudden weakness or numbness of the face, arm or leg, most often on one side of the body. Other symptoms include: confusion, difficulty speaking or understanding speech; difficulty seeing with one or both eyes; difficulty walking, dizziness, loss of balance or coordination; severe headache with no known cause; fainting or unconsciousness."* (World Health Organization 2015)

Complications

After stroke, there is a large incidence of medical complications, ranging between 40% and 96%, which may compromise recovery (Langhorne *et al.* 2000). Langhorne *et al.* reported that 85% of patients experienced, in their study, one or more pre-specified complications while they were hospitalized. These could include recurrent stroke, epileptic seizure, infection, pressure sore/skin break, fall, thromboembolism, pain, depression, anxiety, confusion, emotionalism, among others (Langhorne *et al.* 2000).

Deficits

Stroke patients often have to deal with impairments that affect their independence and quality-of-life. Just 15% of the patients reveal no deficit, while approximately 37% of the individuals present mild alterations, 16% show moderate incapacity, 32% intense changes or are left bedridden or on a wheelchair (Rangel *et al.* 2013). During the first six months after the onset, 40% to 50% of survivors are totally or partially dependent; until the end of the first year this estimate reduces to 33%. After the first year, motor deficits can be reported in more than half of the patients and cognitive impairments in 30% to 35% of subjects. Although less common, language or swallowing problems, visual sensory disorders, perception issues, hearing difficulties, uncontrolled sphincter and psychological problems as dementia, personality and behaviour alterations, emotional changes and instability can also occur. The deficits presented by a given patient depend on variable factors, such as age, stroke type, lesion location, among others (Barros 2012).

2.2. IMPROVING PATIENTS' QUALITY-OF-LIFE

After stroke, patients often need to integrate rehabilitation programs that aim to restore and maintain function, to educate them and their families and to reintegrate them in the society (Costa *et al.* 2011). For a successful recovery, early interventions are crucial (Rangel *et al.* 2013).

There are centres focused on stroke rehabilitation, with professionals from multidisciplinary fields, which offer specific strategies for recovery of this disease and intensive monitoring with daily therapy. On those centres, patients usually undergo physiotherapy and occupational therapy on a daily basis (Johansson 2000). A review by Cochrane that included 5855 patients reported better prognosis concerning mortality and dependency likelihoods for those participants who were integrated in a stroke unit (Benjamin *et al.* 2018).

Rangel et al. reported that physiotherapy was the most frequent intervention in their study (Rangel *et al.* 2013). Physical therapy represents an essential tool for motor recovery; nevertheless, the outcomes are often limited, in particular when applied to chronic patients (Avenanti *et al.* 2012). Actually, Legg *et al*. conducted a systematic review (Legg *et al.* 2017), wherein they claimed that the use of occupational therapy to improve post-stroke daily living activities is supported by low-quality evidence mostly from studies with methodological weaknesses. Also, a strategy for language rehabilitation can be intensive daily language therapy; still, recovery from aphasia is often incomplete (Weiduschat *et al.* 2011, Kindler *et al.* 2012).

In stroke rehabilitation, pharmacological interventions are frequently applied (Johansson 2000, Carter *et al.* 2010, Keser and Francisco 2015), which can be more or less effective depending on the time elapsed since stroke, the lesion size and type, and on the interaction with other simultaneous interventions (Johansson 2000). The combination of drugs with physical therapy also arises as a rehabilitation strategy, in a way that several authors describe better improvement with amphetamine together with physical therapy (Hallett 2001, Carter *et al.* 2010, Lokk *et al.* 2011, Keser and Francisco 2015). Although amphetamine receives a lot of attention for this purpose, its efficacy for motor rehabilitation in humans is controversial (Carter *et al.* 2010, Lokk *et al.* 2011, Schuster *et al.* 2011, Keser and Francisco 2015).

A need for more effective approaches in stroke rehabilitation is well recognized (Dafotakis *et al.* 2008, Higgins *et al.* 2013). Recovery is not always effective, with only 46% of patients becoming independent after the rehabilitation program and the remaining showing severe (20%), moderate (8%) or mild (26%) impairments (Barros 2012). Commonly, cognitive impairments hinder rehabilitation; therefore, strategies implemented on the acute phase focusing on cognitive recuperation would be relevant (Costa *et al.* 2011).

Rationale for a different approach

After stroke, a loss of function occurs due to cell death in the infarcted area and cell dysfunction on the surrounding regions. Remote areas, including those on the contralateral hemisphere, that are connected to the lesioned region, have their function compromised by diaschisis (Pekna *et al.* 2012, Hara 2015, Kubis 2016) caused by hypometabolism, neurovascular uncoupling and aberrant neurotransmission (Pekna *et al.* 2012). The belief that a brain lesion in an adult human induces damage that cannot be repaired by neuroplastic phenomena has been challenged by several observations, e.g., by spontaneous recovery reported within the first days after a cerebrovascular accident (Hallett 2001, Pekna *et al.* 2012, Kubis 2016). According to Pekna *et al.* it is thought that this recovery is associated to three phases:

> *"(1) reversal of diaschisis, activation of cell genesis, and repair; (2) changing the properties of existing neuronal pathways; and (3) neuroanatomical plasticity leading to the formation of new neuronal connections"* (Pekna *et al.* 2012).

The presence of a brain lesion can act as a trigger for brain adaptation and plasticity (Johansson 2000, Johnston 2009, Sampaio-Baptista *et al.* 2018). In fact, when a lesion occurs in the motor cortex, motor areas that previously were not contributing significantly to the function that was lost are recruited, changing motor maps. In the early phase after stroke onset, during the recovery process, an activation increase is observed in the motor areas of both hemispheres, although markedly more prominent on the contralesional hemisphere. This activation of the unaffected hemisphere, which is quite relevant concerning the experimental approach followed in this thesis, frequently decreases in the following stage of recovery (Pekna *et al.* 2012, Hara 2015, Boddington

and Reynolds 2017). Furthermore, cortical inhibition has been reported shortly after stroke in some patients; this excessive inhibition was hypothesized to be associated to a dysregulation of intrinsic GABAergic interneurons combined with interhemispheric inhibition transmitted through crossed callosal fibers (Johnston 2009, Amantea and Bagetta 2017, Boddington and Reynolds 2017).

Neuronal plasticity has commonly positive consequences; however, sometimes excessive plasticity plays a negative role and can be implicated in the pathogenesis of neurological disorders (Johnston 2009, Kokinovic and Medini 2018). The understanding of the physiology of brain plasticity can be used to design interventions for stroke rehabilitation (Hallett 2001, Pekna *et al.* 2012, Hara 2015). New approaches have been studied and applied to modulate neural plasticity, in order to up-regulate or down-regulate it, depending on whether it is playing an adaptive or maladaptive role, respectively (Hummel and Cohen 2005, Kubis 2016, Sampaio-Baptista *et al.* 2018). One of the possible tools is transcranial magnetic stimulation (TMS). In fact, TMS presents the promising ability to induce, measure and even modify local and network plasticity (Freitas *et al.* 2013). Accordingly, transcranial magnetic stimulation arises as one encouraging therapy for stroke rehabilitation by potentially modulating neuroplasticity (Pekna *et al.* 2012, Kubis 2016).

2.3. TRANSCRANIAL MAGNETIC STIMULATION (TMS)

It was in the ancient Greece that Scribonious Largus proposed the use of electrical currents for the treatment of medical conditions, as gout and headaches. At that time, he treated such disorders through the application of electric torpedo fish to the affected area. Thenceforward several techniques and equipment have been studied and developed to interact with neural activity, of which one of the most promising is transcranial magnetic stimulation (Wagner 2006).

Description

Transcranial magnetic stimulation (**Figure 2.3.1** illustrates a typical TMS equipment) is a technique introduced by Anthony Barker *et al*. in 1985 (Groppa *et al.*

2012, Paiva 2012). This equipment is used for artificial stimulation of the nervous tissue, including the cerebral cortex, spinal roots and cranial and peripheral nerves (Kobayashi and Pascual-Leone 2003, Heaton 2012). Transcranial magnetic stimulation leads to excitation of axons, mostly those that are found inside the cerebral cortex instead of those positioned in deep locations of the corticospinal tract (Ilmoniemi *et al.* 1999, Paiva 2012), which makes this technique suitable for the study of response to stimulation or excitability on the cortex (Paiva 2012). This is very promising as a therapeutic tool and in the diagnosis, evaluation of prognosis and study of the progression of different neurologic and psychiatric disorders (Kobayashi and Pascual-Leone 2003, Chipchase *et al.* 2012, Heaton 2012). TMS allows the measurement of distinct physiological parameters that are relevant to the study of several pathological conditions.

Figure 2.3.1 – MagPro stimulator, from MagVenture company (MagVenture 2016).

Basic principles of functioning

Transcranial magnetic stimulation is based on the electromagnetic induction principle (Kobayashi and Pascual-Leone 2003, Groppa *et al.* 2012, Lioumis 2012).

In TMS, an electric coil connected to a high-voltage (400V-3000V) and high-current (4000A-20000A) system (Groppa *et al.* 2012) induces a magnetic pulse that is perpendicular to the current flow in the coil, according to the Faraday's law of magnetic induction (George *et al.* 1999, O'Shea and Walsh 2007, Heaton 2012). The discharge of capacitors, sites wherein electric charges are stored, through the TMS coil produces a current pulse on the circuit, which generates in approximately 100-200 microseconds a time-varying magnetic pulse in the coil neighbourhood (George *et al.* 1999, Rossi *et al.* 2009, Groppa *et al.* 2012). The strength of the magnetic field induced by this stimulation technique can reach typical peak values of about 1 to 2.5 T (George *et al.* 1999, Groppa *et al.* 2012). When the brain is adjacent to the generated magnetic field, a current is

induced there, with opposite direction to the coil's current if the current is increasing, otherwise if the current is decreasing, according to the Lenz's law (George *et al.* 1999, Vidal-Dourado *et al.* 2014, Janssen 2016). Therefore, the magnetic field induces an electric field in the brain with magnitude proportional to the rate of change of current in the TMS coil (Rossi *et al.* 2009), in the order of 100 mV/mm (Ilmoniemi *et al.* 1999).

Equation 2.3.1 presents the Biot-Savart law, which describes the magnetic field **B** in a point r over time, produced by the electric current in the coil (Ilmoniemi *et al.* 1999, Lioumis 2012):

$$\boldsymbol{B}(\boldsymbol{r}, t) = \frac{\mu_0}{4\pi} I(t) \oint_c \frac{d\boldsymbol{l} \times (\boldsymbol{r} - \boldsymbol{r}')}{|\boldsymbol{r} - \boldsymbol{r}'|^3}$$

Equation 2.3.1 – The magnetic field that is produced by the transcranial magnetic stimulator coil, described by the Biot-Savart law (Ilmoniemi *et al.* 1999, Lioumis 2012).

where C symbolizes the coil windings (the current path), μ_0 represents the magnetic permeability of free space ($\mu_0 = 4\pi \times 10^{-7}$ H/m) (Ilmoniemi *et al.* 1999, Lioumis 2012), *I(t)* the time-dependent current in the coil wire (Lioumis 2012), and $d\boldsymbol{l}$ is a vector applied in a point r' of the coil wire, with the direction of the current along the wire (Ilmoniemi *et al.* 1999, Lioumis 2012).

The electric field **E** (V/m) is induced in the brain as described by Maxwell's equation (Faraday's law of induction) (Ilmoniemi *et al.* 1999, Janssen 2016) (**Equation 2.3.2**):

$$\nabla \times \boldsymbol{E} = -\frac{\partial \boldsymbol{B}}{\partial t}$$

Equation 2.3.2 – Maxwell's equation, describing the induction of the electric field in the brain (Ilmoniemi *et al.* 1999, Lioumis 2012).

where **B** represents the magnetic field generated by the coil and ∇ symbolizes the three-dimensional gradient operator ($\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}$) (Janssen 2016).

The electric field that is induced in the brain tissue is indeed a combination of the primary electric field originated directly from the magnetic field produced by the coil (E_1) and a secondary field (E_2). Actually, since the conductivity in the tissue is not uniform, the E_1 generated current runs through the tissue producing an uneven distribution of the electric charges that generates E_2, as described by **Equation 2.3.3**:

$$\nabla \cdot \boldsymbol{E_2} \ = \ \frac{\rho}{\varepsilon_0}$$

Equation 2.3.3 – Secondary field created by the primary electric field (Ilmoniemi *et al.* 1999, Lioumis 2012).

where ρ represents the charge density ($\rho = \rho(\mathbf{r})$) (Lioumis 2012) and ε_0 is the permittivity of free space (ε_0 = 8.854187817×10^{-12} F·m^{-1}) (Janssen 2016). Thus, the electric field in the brain is $\boldsymbol{E} = \boldsymbol{E_1} + \boldsymbol{E_2}$ (Ilmoniemi *et al.* 1999, Lioumis 2012).

This way, although we call it magnetic stimulation, the magnetic field acts like a mean to induce the electric current in the neural tissue, being this induced electric current what activates neurons (Ilmoniemi *et al.* 1999, Groppa *et al.* 2012, Janssen 2016). The current flow in the brain affects the transmembrane potential, altering the electric charges on both sides of the cell membranes, often being enough to produce a local membrane depolarization and firing of neuronal populations (George *et al.* 1999, Ilmoniemi *et al.* 1999, Rossi *et al.* 2009). In **Figure 2.3.2** it is possible to observe the chain events related to TMS application.
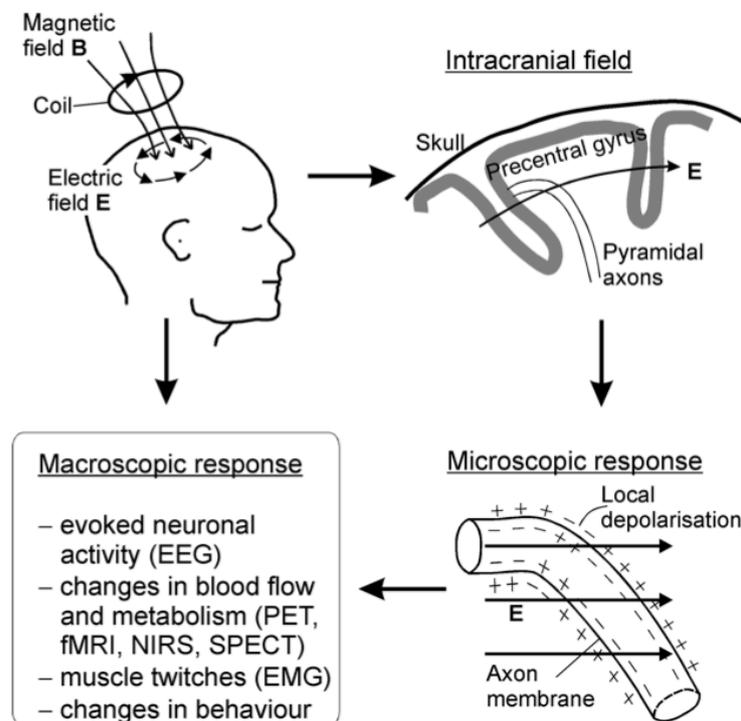
Figure 2.3.2 – Schematic representation of the production of the magnetic field by the transcranial magnetic stimulator coil and the induction of the electric current on the brain. Chain events produced by this mechanism, including both microscopic and macroscopic responses. Included with permission from Professor Risto Ilmoniemi (Ilmoniemi *et al.* 1999).

It is reported that, in a homogeneous medium, the activation of a straight axon occurs at locations with maximum $\frac{\partial E_x}{\partial x}$, where E_x represents the component of the electric field along the axon (Ilmoniemi *et al.* 1999, Lioumis 2012). Since there are no straight axons in the cortex, the field amplitude becomes a key variable for cortical excitation, rather than the electric field gradient (Ilmoniemi *et al.* 1999). Thereafter, excitation is more likely to occur at bends of axons, at constrictions in the extracellular space or at terminations of axons or dendrites (Ilmoniemi *et al.* 1999, Lioumis 2012).

At the macroscopic level, we can observe evoked neuronal activity, as event-related potentials (ERPs), detected by electroencephalography (EEG) (Ilmoniemi *et al.* 1999, Bliss and Cooke 2011) and changes in blood flow and metabolism detected with positron emission tomography (PET), functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS) or single-photon emission computed tomography (SPECT) (Ilmoniemi *et al.* 1999). Depending on the stimulation area, different responses can be observed. Following stimulation of the primary visual cortex, for instance, subjects can observe flashes of light (phosphenes), with their eyes closed (Huerta and Volpe 2009, Chervyakov *et al.* 2015). Also, when we position the coil over the motor cortex and apply a suprathreshold intensity, descending volleys are induced in the pyramidal tract, projecting on corticospinal tract, and producing action potentials that evoke muscle contraction (twitches) of the corresponding peripheral muscle measured by electromyography (**Figure 2.3.3**) (Ilmoniemi *et al.* 1999, Huerta and Volpe 2009, Lioumis 2012, Klomjai *et al.* 2015). The descending volleys can have different origins. When the axons of corticospinal neurons are directly activated in the subcortical white matter or axon initial segment, direct waves (D-waves) are produced (Hanajima *et al.* 2003, Volz *et al.* 2015, Niemann *et al.* 2018). On the other hand, it is believed that the indirect activation of neurons in the pyramidal tract, through mono- and polysynaptic inputs, defines the appearance of indirect waves (I-waves), in turn (Hanajima *et al.* 2003, Volz *et al.* 2015). These can be divided into early or late I-waves, whether the neural circuits involved and descending connections are less or more complex, respectively (Niemann *et al.* 2018). Therefore, the application of single monophasic pulses of TMS over the primary motor cortex can induce diverse combinations of direct and indirect waves that depend on the induced current directions, originating motor-evoked potentials with distinct latencies (Volz *et al.* 2015).
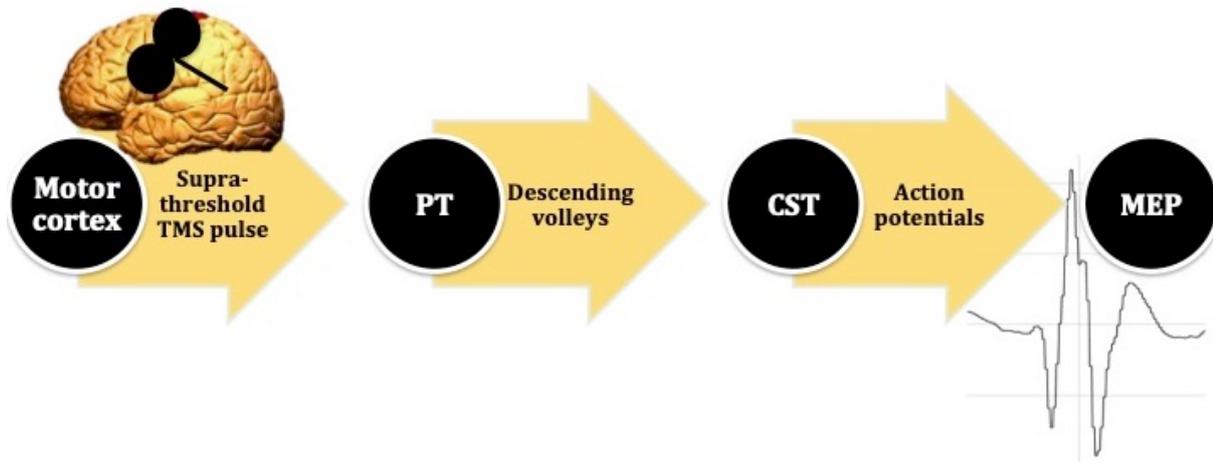
Figure 2.3.3 – Motoneuron activation evoking a motor-evoked potential (MEP) after stimulation over the motor cortex, with a suprathreshold intensity. PT stands for pyramidal tract and CST indicates corticospinal tract. Adapted from (Klomjai *et al.* 2015).

Long-term potentiation and long-term depression

N-methyl-D-aspartate (NMDA) receptors on postsynaptic neural membranes gate a cationic channel. During normal resting potential, this channel is blocked by magnesium ions (Mg^{2+}). Following depolarization of the membrane (activity dependence of the receptor), Mg^{2+} ions disconnect and NMDA receptors become activated. By enabling the entrance of calcium ions (Ca^{2+}) on the postsynaptic neuron, a calcium-sensitive signalling pathway is triggered that will induce an increase in synaptic strength and, thereafter, long-term potentiation (LTP) (Chervyakov *et al.* 2015, Klomjai *et al.* 2015). LTP is a type of plasticity that increases the efficacy of synaptic transmission (Bliss and Cooke 2011). Surprisingly, but possibly related to the activity dependence rule, long-term depression (LTD), which decreases synaptic transmission (Bliss and Cooke 2011), seems to rely also on the activation of NMDA receptors. However, in LTD the increase in Ca^{2+} concentration (from ~ 10^{-9} M at rest to ~ 10^{-6} M) is slower and less pronounced, compared with LTP, where it increases up to ~ 10^{-3} M (Huerta and Volpe 2009, Chervyakov *et al.* 2015, Klomjai *et al.* 2015).

Although the mechanisms underlying the effects of repetitive TMS are still not clear, it is widely believed that they can be associated to LTP and LTD (Chervyakov *et al.* 2015, Klomjai *et al.* 2015, Kubis 2016), through glutamatergic or GABAergic neurotransmission, respectively (Boonzaier *et al.* 2018). By manipulating the strength of synapses, repetitive TMS can act as a therapeutic intervention for plasticity-related

disorders, when synaptic drive is either pathologically augmented or diminished (Bliss and Cooke 2011).

Instrumentation

The pulses of electric current in the TMS coil are produced by the *RCL* oscillator circuit illustrated on **Figure 2.3.4**, composed of a large capacitor (with capacitance *C*), a thyristor switch and the coil (with inductance *L*), connected in series. *R* represents the resistance that is present in the cables, capacitor, thyristor and coil. The gating of the thyristor *S* into the conducting form allows the discharging of the capacitor, first charged to 2000 to 3000 V, through the coil. The waveform of the generated electric current is usually a damped sinusoidal, with the pulse lasting approximately 300 microseconds and with a peak value between 5000 and 10000 A (Ilmoniemi *et al.* 1999).
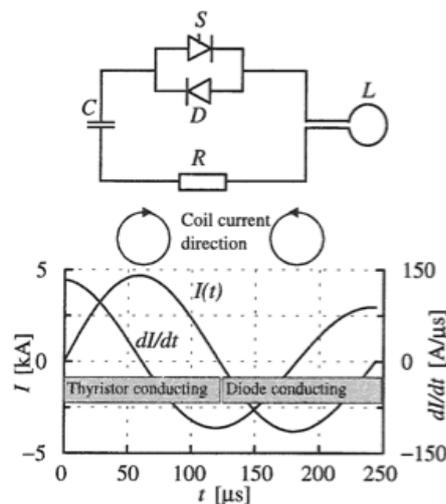
Figure 2.3.4 – Stimulator circuit and temporal derivative and current waveforms. *C* represents capacitance of the capacitor, *L* is used for inductance of the coil, *R* for resistance, *S* for thyristor and *D* indicates the diode. Included with permission from Professor Risto Ilmoniemi (Ilmoniemi *et al.* 1999).

Pulses can typically admit either monophasic or biphasic waveforms (**Figure 2.3.5**) (Ilmoniemi *et al.* 1999, Kammer *et al.* 2001). When, for example, the diode *D* is connected forward directly in parallel with the capacitor, one can observe a monophasic pulse. This way, the magnetic field increases quickly from zero until the peak value and then returns to zero more slowly (Ilmoniemi *et al.* 1999). It is noteworthy that even though the magnetic field can be monophasic, the resultant electric current is never monophasic in the brain since the time derivative of the magnetic field acquires the opposite sign when the field starts returning to zero (Ilmoniemi *et al.* 1999). A biphasic pulse is characterized by one damped cycle of a sinusoid (Ilmoniemi *et al.* 1999). When

the capacitor is discharged, there is a current flow from the anode to the cathode until it reaches its peak value; after that, the current flows in the reverse direction, through the diode (Ilmoniemi *et al.* 1999). If termination of the thyristor gating occurs during the second half-cycle, the oscillation ends after cycle completion (Ilmoniemi *et al.* 1999). Usually, monophasic waveforms are applied in single-pulse TMS and biphasic in repetitive TMS, since it requires less energy (Klomjai *et al.* 2015). Indeed, when generating biphasic pulses, a great part of the energy is restored in the capacitor throughout the oscillation period (Kammer *et al.* 2001).
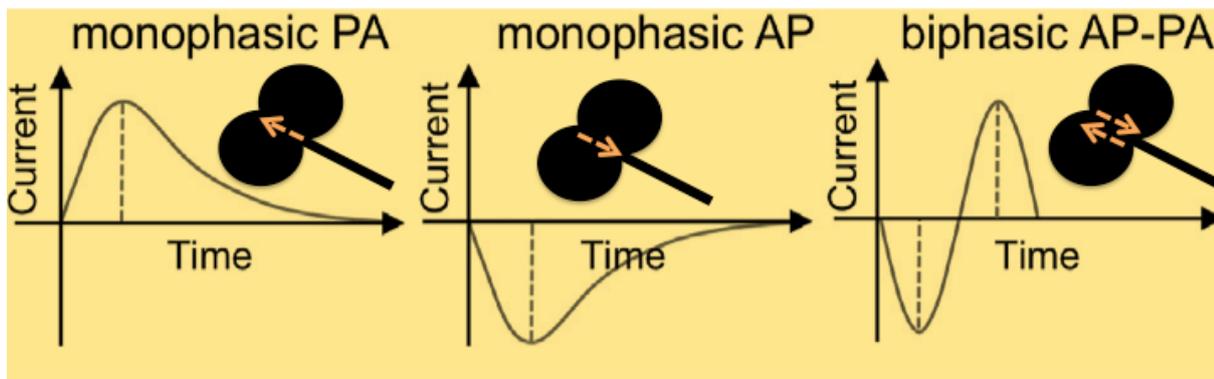
Figure 2.3.5 – Monophasic and biphasic pulse waveforms in the posterior-to-anterior (PA) and anterior-to-posterior (AP) induced current directions. Adapted from (Davila-Pérez *et al.* 2018).

The importance of coil's selection

Coils or electromagnets are the apparatus responsible for generating electromagnetic fields (Vidal-Dourado *et al.* 2014). The design of the coil is decisive since it affects the distribution of the current and the location of stimulation (Wagner 2006).

Strong forces are generated, proportional to the square of the current, up to the order of tens of kilonewtons, which is required to have into account when designing the coil. They are often composed of 10 to 30 concentric turns of rectangular copper wire, which gives a minimum induction of approximately 15 microhenries (Ilmoniemi *et al.* 1999). According to Wagner *et al.* (2006), typical coil inductances can reach up to 150 microhenries. The wire insulation, often composed by varnish, film or mylar paper, needs to have the required dielectric strength and to resist chemical solvents of the potting material, usually made of epoxy resin or polyurethane foam (Ilmoniemi *et al.*

1999). Moreover, in repetitive TMS (see 'paradigms' section) tens of W/Hz of power are dissipated in the coil and the temperature increases. For safety reasons, the surface temperature is restricted to 41ºC. To prevent excessive heating, there are built-in temperature sensors and cooling systems that can be used. Additionally, it is also possible to reduce the resistance of the coil to relieve power consumption and temperature increase (Ilmoniemi *et al.* 1999).

Two standard coils are frequently used in transcranial magnetic stimulation – the circular and the figure-of-eight (also named double, butterfly or 8-shaped), with the diameter varying between 50 and 150 mm (Ilmoniemi *et al.* 1999).

Many researchers use circular coils with different diameters, where a larger diameter allows a deepest but less focused stimulation (Rossi *et al.* 2009, Groppa *et al.* 2012). The circular coil can induce an electric field widely distributed enabling the simultaneous stimulation of the two hemispheres (Kobayashi and Pascual-Leone 2003, Paiva 2012). The strongest current is localized under the ring of the coil (as it can be observed in **Figure 2.3.6**); thus, the ring should be positioned over the target cortical region to ensure an effective stimulation (Groppa *et al.* 2012). On the other hand, the figure-of-eight coil possesses two circles placed side by side and originates a more focused magnetic pulse, enabling more control of neuronal excitation (Ilmoniemi *et al.* 1999, Kobayashi and Pascual-Leone 2003, Rossi *et al.* 2009, Groppa *et al.* 2012). The electrical current flows in opposite directions in each circumference, converging on a central point wherein the current is superior (**Figure 2.3.6**) (Amassian and Maccabee 2006, O'Shea and Walsh 2007). Therefore, the centre of the coil should be placed over the target region, tangential to the scalp (Groppa *et al.* 2012, Paiva 2012).
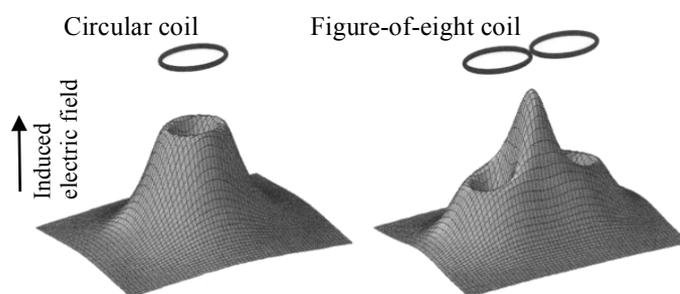
Figure 2.3.6 – The difference on the distribution of the electric field induced under two different coils, the circular and the figure-of-eight. Included with permission from Professor Risto Ilmoniemi (Ilmoniemi *et al.* 1999).

White matter presents lower impedance compared with grey matter, which translates into stronger electrical currents on superficial brain areas (Klomjai *et al.* 2015). Also, field strength is reduced with distance (Janssen 2016). Actually, TMS pulses can only reach structures that are as far as approximately 2 cm from the surface (Huerta and Volpe 2009). Therefore, TMS is indicated for the stimulation of superficial structures (Klomjai *et al.* 2015), namely cortex, cerebellum and spinal cord, but not of deep areas like hippocampus, amygdala, striatum, thalamus or brainstem (Huerta and Volpe 2009). Theoretically it can be used to stimulate deeper brain areas; nevertheless, all regions between the coil and the target are stimulated with higher strengths. To overcome this issue, different coils are being studied, as the H-coil which allows a more gradual decay with distance (Janssen 2016).

Paradigms

There are three main groups of transcranial magnetic stimulation paradigms: single-pulse TMS (where one stimulus is applied at each time), paired-pulse TMS (pairs of stimuli are separated by variable time intervals) and repetitive TMS (trains of repetitive stimuli) (Kobayashi and Pascual-Leone 2003, O'Shea and Walsh 2007, Rossi *et al.* 2009).

Single-pulse TMS (sp-TMS) is the most used (Müller *et al.* 2013). It can activate a great number of cortical neurons at the same time (Nakamura *et al.* 1997) and allows the measurement of relevant neurophysiological parameters (Heaton 2012), such as motor threshold (MT), motor-evoked potentials (MEPs), central motor conduction time (CMCT) and cortical silent period (CSP). These parameters can be used on the diagnosis and evaluation of diseases.

In the paired-pulse TMS (pp-TMS) two magnetic pulses are generated, separated by milliseconds (Conforto *et al.* 2003, Heaton 2012). Usually, the first pulse has a subthreshold intensity while the second pulse is suprathreshold (Conforto *et al.* 2003). The time elapsed between the two pulses (ISI – inter-stimulus interval) is associated to cortical excitation or inhibition (Heaton 2012). Although it can vary according to the muscle and intensity of the stimulus, for intervals between the two pulses from 1 to 6 ms, one frequently observe a suppression of the response test stimulus associated with a short-interval intracortical inhibition (SICI), whereas for intervals between 8 and 30 ms it is often detected an enhancement of test stimulus related with intracortical facilitation

(ICF). In addition, from 50 to 200 ms the response to the test stimulus is also suppressed due to a long-interval intracortical inhibition (LICI) (Kimiskidis *et al.* 2014). In pp-TMS a single stimulus can be applied to two different cerebral regions (Kobayashi and Pascual-Leone 2003). Paired-pulse, like single-pulse TMS, has been used in the study of neural plasticity and to evaluate the evolution and prognosis of diseases (Conforto *et al.* 2003).

On the other hand, repetitive TMS (rTMS) consists on trains of stimuli with the same intensity, applied to a specific cerebral location (Kobayashi and Pascual-Leone 2003). While single-pulse TMS is able to interact with motor, sensory and cognitive systems, affecting them for a short period, rTMS has the ability to modify cortical functioning for a more extended period (Hanakawa *et al.* 2009, Heaton 2012). In fact, rTMS modulates excitability, inducing plastic changes lasting more than the stimulation period, generally at the synaptic level (Heaton 2012). In contrast to single-pulse and paired-pulse, which are applied for diagnostic purposes (Müller *et al.* 2013) and research, rTMS is frequently used as a therapeutic intervention (Freitas *et al.* 2013, Müller *et al.* 2013), since it may be potentially used to normalize abnormal levels of activity in the cortex (Herrmann and Ebmeier 2009). This technique can increase or decrease cerebral cortex excitability in the stimulated location and in remote areas, along anatomical functional connections, depending on the selected parameters (Kobayashi and Pascual-Leone 2003, Rossi *et al.* 2009). Actually, TMS parameters, particularly stimulation frequency, determine if the effects are excitatory or inhibitory (O'Shea and Walsh 2007). Repetitive TMS can be divided into its conventional (**Figure 2.3.7**) and patterned forms (**Figure 2.3.8**). While in conventional protocols single pulses are repeated in a regular way, in patterned rTMS rapid pulses are applied repetitively at an high frequency, intercalated with short pauses in stimulation (Rossi *et al.* 2009). In conventional rTMS, high frequencies usually induce a cortical excitation whereas the inhibition of cortical excitability occurs for low frequencies (≤ 1 Hz) (Herrmann and Ebmeier 2009, Rossi *et al.* 2009, Heaton 2012). In general, while high-frequencies may be able to induce LTP, low-frequency protocols may lead to LTD (Huerta and Volpe 2009, Bliss and Cooke 2011, Chervyakov *et al.* 2015, Klomjai *et al.* 2015).
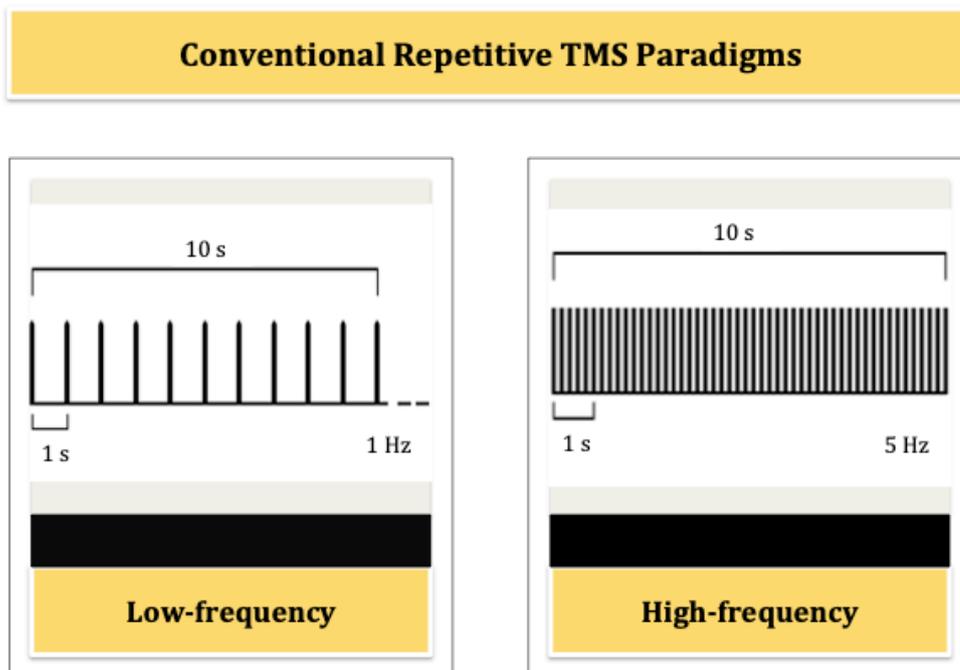
Figure 2.3.7 – Conventional repetitive transcranial magnetic stimulation, including both low-frequency (1 Hz) and high-frequency (5 Hz) protocols. Adapted from (Rossi *et al.* 2009).

The most common patterned rTMS forms are continuous and intermittent theta burst stimulation (TBS) (Rossini *et al.* 2010, Sandrini *et al.* 2011), which are based on the *theta* rhythm (Huerta and Volpe 2009, Klomjai *et al.* 2015), having the same periodicity (Huerta and Volpe 2009). Continuous TBS (cTBS) consists of 3 pulses at 50 Hz that are applied with a frequency of 5 Hz, i.e. every 200 milliseconds, with low intensity (usually 80% of active motor threshold) (Rossini *et al.* 2010, Sandrini *et al.* 2011). This protocol can be applied either for 20 seconds (300 stimuli) or for 40 seconds (600 stimuli) (Rossini *et al.* 2010). It has been demonstrated to reduce motor cortex excitability temporarily, with the effect lasting up to 20 min if the protocol duration is 20 seconds or until 1 hour if the protocol is administered for 40 seconds (Sandrini *et al.* 2011). On the other hand, in intermittent TBS (iTBS) each burst is applied for 2 seconds, with a pause of 8 seconds without stimulation (Rossini *et al.* 2010, Sandrini *et al.* 2011) and is repeated for 190 seconds, which induces a facilitatory effect (Sandrini *et al.* 2011) that lasts a minimum of 15 minutes (Klomjai *et al.* 2015). The application of theta burst stimulation protocols is growing and receiving particular attention given their short duration and low intensities (Wu *et al.* 2012, Vernet *et al.* 2013, Goldsworthy *et al.* 2014). Some authors have also been applying modified theta

burst stimulation protocols (Sandrini *et al.* 2011). Quadripulse stimulation (QPS) is an example of a recent patterned rTMS protocol in which repeated trains of four monophasic pulses are applied. The ISI can vary from 1.5 to 1250 milliseconds, with shorter intervals causing facilitation and longer intervals inducing inhibition (Rossini *et al.* 2010).
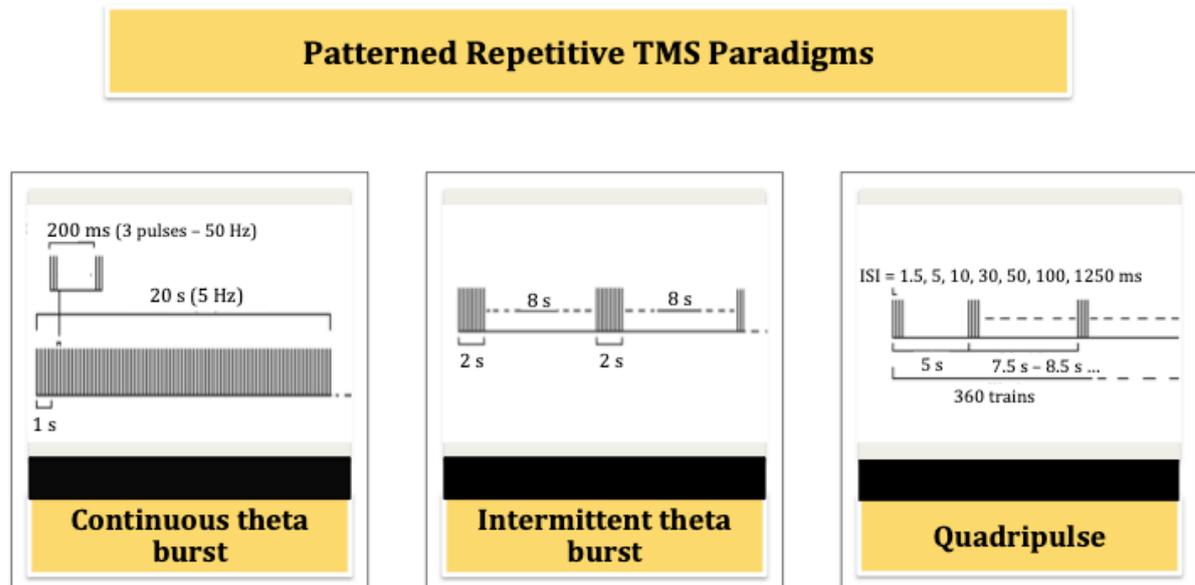
Figure 2.3.8 – Patterned rTMS, represented by continuous (cTBS) and intermittent (iTBS) theta burst stimulation, and by quadripulse stimulation (QPS). Adapted from (Rossi *et al.* 2009).

Few attempts have been made to compare protocols and confirm their efficacy (Heaton 2012). Variable effects were observed according to the frequency, intensity, duration and local of stimulation, yielding uncertainties about the optimal parameters of stimulation to induce changes at the cortical level (Herrmann and Ebmeier 2009, Heaton 2012, Paiva 2012). In fact, some subjects respond well to the defined protocols, whilst others present absence of response or even contrary effects to the expected. This variability is worrying since many therapeutic trials used similar parameters assuming that they were obtaining a consistent and desired effect on the cortex (Heaton 2012). Some authors suggested that factors such as age, gender, genotype, caffeine intake and hour of the day could influence the response to TMS (Chipchase *et al.* 2012). The effect of TMS can also be affected by factors such as geometry and orientation of the generated electric field and by the waveform (Paiva 2012).

Safety

There is no evidence that the stimulation with TMS produces significant risk or undesired effects if adequate safety precautions are taken (Heaton 2012). Thus, TMS is safe, non-invasive and is not painful (Kobayashi and Pascual-Leone 2003, Herrmann and Ebmeier 2009, Chipchase *et al.* 2012, Groppa *et al.* 2012). There is no need for analgesics or anaesthesia (George *et al.* 1999, Herrmann and Ebmeier 2009). Frequent side effects reported by patients are a transient headache, neck pain and discomfort on the stimulated area (George *et al.* 1999, Rossi 2013). These mild effects occur in up to 40% of individuals receiving traditional high-frequency repetitive TMS and in only a few subjects following the more recent theta burst paradigms (<3%) (Rossi 2013).

There is a risk of seizure induction, being this the most severe side effect, occurring particularly in subjects taking medication that could lower seizure threshold (Rossi *et al.* 2009), or at a higher risk for epilepsy (Rossini *et al.* 2010), or when using high-frequencies that could induce neuronal spikes (Ruohonen 1998, Assenza *et al.* 2017). However, this is an extremely rare event, which is said to be associated to a crude per-subject risk of 1.4% in epileptic patients. In general, the risk of a seizure following theta burst stimulation was reported to be as low as 0.02% (Rossi 2013).

Applications

Transcranial magnetic stimulation assumes potential in several clinical applications (George *et al.* 1999) as, for example, in the evaluation of motor and sensory functions, in language, memory, learning and visual processing, among others (George *et al.* 1999, Paiva 2012). Some neurologic diseases present disturbances in cortical excitability, which can be detected by TMS (Kobayashi and Pascual-Leone 2003). Associated to particular pathologies, we can observe, for instance, an alteration on the conduction times or even specific shapes of the motor-evoked potentials (Wagner 2006). Therefore, this can be a valuable tool in assisting the diagnosis and classification of different pathologies. In **Table 2.3.1** are presented some diagnostic applications of TMS.

This technique has also been employed in research for brain mapping, to study the link between cortical location and function (Wagner 2006).

Also, repetitive TMS represents a promising treatment for a great number of neuropsychiatric conditions (Rossi *et al.* 2009), having the potential to normalize pathologically enhanced or diminished levels of cortical activity (Kobayashi and Pascual-Leone 2003). Single-pulse stimulation for the migraine headaches and repetitive TMS for the treatment of depression are already approved by Food and Drug Administration (Janssen 2016). Nonetheless, repetitive stimulation paradigms have been being studied with promising results for several therapeutic applications, such as in obsessive-compulsive disorders, pain syndromes, Parkinson, and other conditions.

Table 2.3.1 – Transcranial magnetic stimulation measures that can help on the diagnosis of different pathologies. Adapted from (Kobayashi and Pascual-Leone 2003).

Abnormal Findings	Diseases and Symptoms
Motor Cortex Excitability	
High motor threshold (MT)	*Multiple sclerosis, stroke, agenesis of corpus callosum, brain injury, spinal cord injury or cervical spondylosis*
Low motor threshold (MT)	*Amyotrophic lateral sclerosis, hydrocephalus, epilepsy*
Increased intracortical inhibition (ICI)	*Early-stage amyotrophic lateral sclerosis*
Decreased intracortical inhibition (ICI)	*Parkinson's disease, spinal cord injury or cervical spondylosis, epilepsy*
Motor-Evoked Potentials (MEPs)	
Dispersed	*Multiple sclerosis, stroke*
Small or absent	*Multiple sclerosis, amyotrophic lateral sclerosis, stroke, brain injury, spinal cord injury or cervical spondylosis, hydrocephalus, Bell's palsy*
Large	*Parkinson's disease, dystonia*
Cortical Silent Period (CSP)	
Long	*Multiple sclerosis, stroke, brain injury, spinal cord injury or cervical spondylosis, polyradiculitis, demyelinating polyneuropathy, epilepsy*
Short	*Amyotrophic lateral sclerosis, Parkinson's disease, dystonia, agenesis of corpus callosum*
Absent	*Spinal cord injury or cervical spondylosis*

Central Motor Conduction Time (CMCT)		
Long		*Multiple sclerosis, amyotrophic lateral sclerosis, stroke, secondary parkinsonism, secondary dystonia, brain injury, spinal cord injury or cervical spondylosis*

The neurorehabilitation of stroke with this technique is also an emergent field with exciting results (Chervyakov *et al.* 2015). Thus, we conducted two systematic reviews to understand what advances have been made in the use of rTMS for recovery of motor function (**Chapter 3**) and other deficits (**Chapter 4**) following a stroke event and what are the current gaps and limitations that need to be addressed by future studies.

2.4. ELECTROENCEPHALOGRAPHY (EEG)

Description

Electroencephalography (EEG) is a technique introduced on human studies in 1929, by Hans Berger (Davidson *et al.* 2007, Duncan *et al.* 2014). It became more broadly disseminated in 1935, after a live demonstration (Davidson *et al.* 2007). It allows the non-invasive, painless and relatively inexpensive study of brain electrical activity (Light *et al.* 2010, Duncan *et al.* 2014), frequently with typical minimum lengths of 35 to 45 minutes (Duncan *et al.* 2014). EEG is still pointed out as the gold standard in the evaluation of brain electrical activity, being able to detect and quantify fluctuations in a wide spectrum of frequencies (Kalitzin *et al.* 2019). This system provides a great temporal resolution, in the order of milliseconds, which is of great value for the study of brain electrical activity linking with dynamic behaviours that vary over short periods of time (Davidson *et al.* 2007, Lioumis 2012). Conversely, as a trade-off, it has a poor spatial resolution even when using high-density electrodes arrays (up to 256 channels) that allow larger coverage of the scalp and lesser inter-electrode distance (Davidson *et al.* 2007). To overcome this issue, EEG is frequently used in combination with magnetic resonance imaging (Teplan 2002).

On **Figure 2.4.1** an EEG amplifier equipment and a quick-cap electrode system is illustrated.

Figure 2.4.1 – EEG 64-channel amplifier and quick cap electrode system, by Compumedis NeuroScan (Compumedics NeuroScan 2015).

When analysing results, one must have into consideration that normal ranges change according to factors that have a strong impact on EEG, such as age and different stages of awareness (Binnie and Prior 1994, Niedermeyer 1999).

Procedure and principles of functioning

The brain's electrical activity arises from biochemical processes in cells that produce ionic currents (Schaul 1998). Brain electrical activity comprises action potentials, which are fast and generate confined electric fields, and postsynaptic potentials, that are slower and more widespread (Binnie and Prior 1994). The postsynaptic potentials from cortical pyramidal cells are those that are mainly measured by EEG (Schaul 1998, Teplan 2002).

To record the brain electrical activity, electrodes constituted by chloride silver, gold or tin, are placed on the scalp and fixed with an adhesive material or incorporated into a cap or net system (Davidson *et al.* 2007). Electrodes are filled with a conductive gel that helps signal acquisition (Davidson *et al.* 2007). For the recording of long periods, it is possible to insert needle electrodes under the scalp but then the procedure becomes invasive (Teplan 2002).

The electrodes are usually positioned according to the International 10/20 System, being arranged at fixed distances in steps of 10 or 20% from anatomical landmarks like the nasion, inion and preauricular points. The electrodes placed on the left hemisphere assume odd numbers while for the right hemisphere even numbers are attributed and for the midline it is adopted letter "z". Moreover, "Fp" stands for frontal pole, "F" for frontal, "C" for central, "P" for parietal, "O" for occipital and "T" for temporal electrodes (Davidson *et al.* 2007, Duncan *et al.* 2014). With the introduction of more

electrodes, in high-density EEG systems, it is required to use different notation schemes; however, "translation maps" allow a fast analysis of the data in terms of the original 10-20 system (Davidson *et al.* 2007). Usually, additional letter codes are included to identify extra electrodes (an example can be observed in **Figure 2.4.2**) such that "AF" represents intermediate electrodes between "Fp" and "F", "FC" are located between "F" and "C", "FT" represents the electrodes between "F" and "T", "CP" is for the area from "C" to "P", "TP" is the intermediate between "T" and "P" and "PO" designates the locals from "P" to "O". The usage of the standard 10-20 sites facilitates the comparison of results between studies. Therefore, it is of great importance that the positioning of the electrodes is always the same and consistent both across subjects and studies (Davidson *et al.* 2007).

Then, the activity is measured in microvolts and is recorded as a potential difference among pairs of electrodes that is amplified and, subsequently, displayed on a monitor after the signal is converted from analog to digital (Teplan 2002, Duncan *et al.* 2014). The reference selection differs extensively between researchers, though the most used are linked-ears and average reference (Davidson *et al.* 2007).

The signal is susceptible to artefacts that can be technical, due to impedance fluctuation or cable movements, for example, or associated to the subject, including those caused by body or eye movements (Teplan 2002).
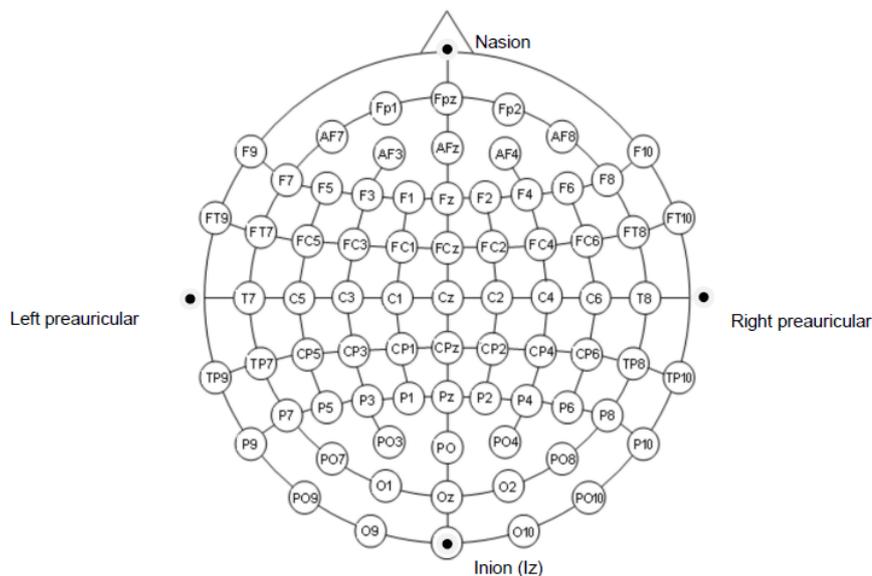
Figure 2.4.2 – Example of a montage for a high-density cap (g.tec medical engineering 2015).

Quantification

According to Davidson *et al.*, the raw signal of the EEG can be regarded as being mostly dominated by a few bands of rhythmic patterns of activity. Afterwards, it is possible to select epochs for calculating the power spectrum, which can give information about the contribution of each frequency to the whole spectrum. The electroencephalogram signal is decomposed into its underlying sine wave components by a fast Fourier transformation. Then, the resultant elements can be used to calculate the amount of power, commonly expressed in μV^2, for different frequencies (Davidson *et al.* 2007).

EEG data can be displayed in a topographic map, in scalp space, with a stylised head outline (Lopes da Silva 1990, Binnie and Prior 1994), pictured with colour maps to help in identifying areas with different brain activity (Teplan 2002). However, there is an increasing tendency to analyse brain activity patterns in source space, improving the spatial localization obtained by scalp recording (Caschera *et al.* 2017, Shenoy Handiru *et al.* 2017, van Lutterveld *et al.* 2017).

Oscillatory patterns and motor execution

The electroencephalogram is usually decomposed into bands established with different frequency ranges. Different waves can be observed in the EEG (see **Figure 2.4.3**), arising from synchronization of populations of neurons that produce typical oscillatory patterns (Pfurtscheller *et al.* 2006, Lopes da Silva 2013, Assenza *et al.* 2017). In fact, brain electrical rhythms emerge from the activity of specific neural assemblies (Lopes da Silva 2013, Assenza *et al.* 2017) and are commonly described by their specific frequencies and amplitudes (Davidson *et al.* 2007, Assenza *et al.* 2017).

Delta rhythm, below 4 Hz, is normal up to 1 year of age and is mostly frontal and temporal; in healthy adults these waves are normal in moderate to deep sleep (Steriade *et al.* 1990, Duncan *et al.* 2014). This way, the augmentation of *delta* rhythms during lengthy tasks might be justified by fatigue (Schapkin *et al.* 2020). Furthermore, it is believed that these oscillations play a role in spatial memory and navigation (Duarte *et al.* 2016), as well as in decision, detection of stimuli and sensory processes (Bohle *et al.* 2019, Moezzi *et al.* 2019). They can, nonetheless, indicate a possibility of brain

dysfunction in an alert state (Steriade *et al.* 1990, Duncan *et al.* 2014), associated with subcortical brain lesions that do not reach cortex or with cortical plasticity mechanisms (Assenza *et al.* 2017). *Theta* rhythm, from 4 to 7 Hz (Lopes da Silva 2013, Duncan *et al.* 2014), is normally seen predominantly in frontal and temporal areas in children until 13 years old; in adults it is commonly observed in drowsiness and, more clearly, in light sleep (Niedermeyer 1999, Duncan *et al.* 2014). These waves are also present in activated behavioural conditions, specifically in the hippocampus (Steriade *et al.* 1990, Moezzi *et al.* 2019). *Theta* rhythm has been reported in cognition (Simões *et al.* 2018, Moezzi *et al.* 2019) and during mental tasks, such as problem solving (Niedermeyer 1999) and memory (Lopes da Silva 2013, Moezzi *et al.* 2019, Schapkin *et al.* 2020). Also, rodent experiments claimed an important link between *theta* activity and spatial navigation (Duarte *et al.* 2016). It can, however, indicate possible brain dysfunction when greatly present in an alert adult (Niedermeyer 1999, Duncan *et al.* 2014). *Alpha* waves are characterized by frequencies between 8 and 13 Hz, appear symmetrical and posteriorly, typically predominating in the occipital region, when the individual has the eyes closed, are reduced in drowsiness and disappear when the eyes are opened (Steriade *et al.* 1990, Niedermeyer 1999, Duncan *et al.* 2014) or when subject becomes alert for some reason (Teplan 2002). Moreover, central or centroparietal *alpha* was also reported, with similar frequency but distinct topography and reactivity, which acquired the designation of *mu* rhythm (Arroyo *et al.* 1993, Niedermeyer 1999). This rhythm is highly associated to motor functions (Niedermeyer 1999) and is weakened (desynchronized) by motor readiness or execution, specially in the contralateral space (Arroyo *et al.* 1993, Niedermeyer 1999, Pfurtscheller *et al.* 2006). Above 13 Hz (Niedermeyer 1999, Duncan *et al.* 2014) and up to 30 Hz, we can observe *beta* activity (Kilavik *et al.* 2013, Athanasiou *et al.* 2018) symmetrical and in parietal and frontal regions; although eye opening does not affect *beta* waves, a reduction or even absence in the presence of cortical damage, on the lesioned areas (Duncan *et al.* 2014) and an increase in sleepiness or light sleep can exist (Cooper *et al.* 2005). The involvement of *beta* rhythm in the sensorimotor system has been reported (Kilavik *et al.* 2013, Zheng and Colgin 2015, Athanasiou *et al.* 2018), with its activity being more pronounced in sensorimotor mechanisms rather than resting periods (Kilavik *et al.* 2013). It is believed that it can be implicated in the attentional anticipation of visual cues prior to a motor response (Zheng and Colgin 2015). These oscillations play an important role in movement execution and postural

maintenance (Kilavik *et al.* 2013, Athanasiou *et al.* 2018) and as biomarkers in motor skill acquisition (Athanasiou *et al.* 2018). Lastly, *gamma* activity is observed for frequencies superior to 30 Hz (Niedermeyer 1999, Lopes da Silva 2013) and up to 90 Hz (Lopes da Silva 2013). When suitable stimuli are visualized, *gamma* oscillations may be detected in the occipital region (Murty *et al.* 2020) This rhythm is involved in holistic processing (Castelhano *et al.* 2015), sensory mechanisms (Moezzi *et al.* 2019) and perception (Lopes da Silva 2013, Castelhano *et al.* 2017) and in high-level cognition (Castelhano *et al.* 2017, Moezzi *et al.* 2019). An association between abnormal *gamma* activity patterns, such as in autism spectrum disorders, and an imbalance between excitation and inhibition has been proposed (Castelhano *et al.* 2018). Also, pathological alterations in *gamma* oscillations may be observed in some neuropsychiatric disorders (Bernardino *et al.* 2013).
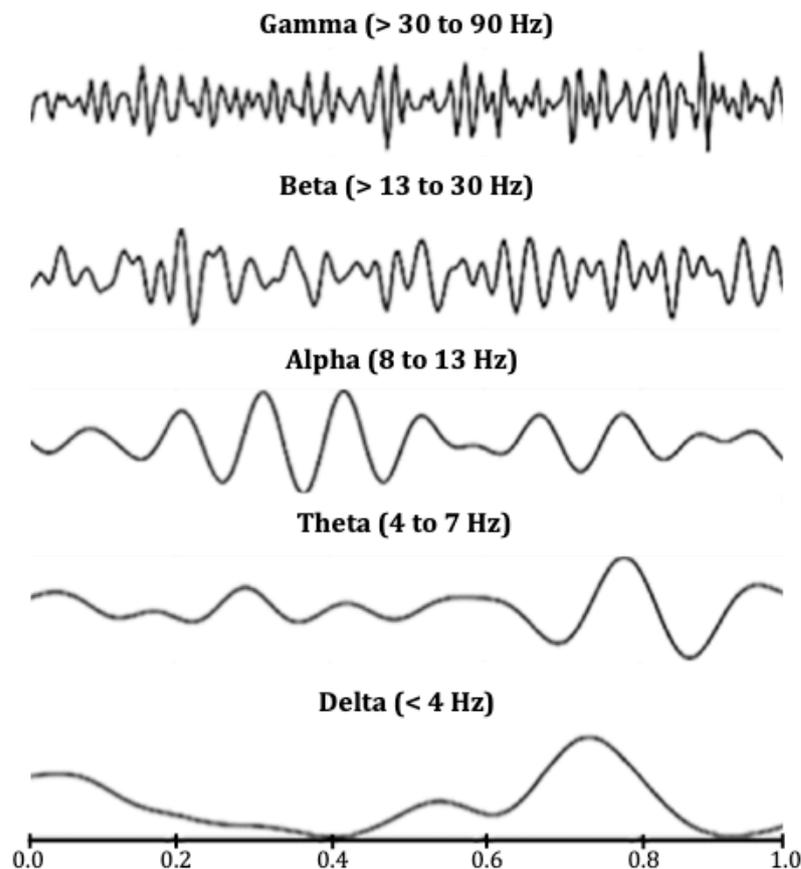
Figure 2.4.3 – Electroencephalographic waveforms that are usually studied. Adapted from (Medithe and Nelakuditi 2016).

Neural activity can appear in response to a stimulus, which can be either internal or external, producing event-related potentials (ERPs), which correspond to stimulus-locked EEG measures (Teplan 2002). Frequency bands that change their amplitude or

power in response to a stimulus have often been associated to *alpha* and *beta* rhythms (Assenza *et al.* 2017). During motor preparation and execution, *mu* and *beta* rhythms are diminished on the sensorimotor areas, indicating a decrease in synchrony described as an event-related desynchronization (ERD), which arises approximately 2 seconds before the beginning of the movement (Pfurtscheller and Lopes Da Silva 1999, Fu *et al.* 2006, Takemi *et al.* 2013, Rossiter *et al.* 2014). This way, ERD of *mu* and *beta* bands is related to an activation of cortical network (Pfurtscheller and Lopes Da Silva 1999, Platz *et al.* 2000). With cessation of the movement, there is a rebound of the *beta* activity, associated to a deactivation and an inhibition of the motor neurons, reflected by event-related synchronization (ERS) (Pfurtscheller and Lopes Da Silva 1999, Neuper *et al.* 2006, Rossiter *et al.* 2014).

Applications

EEG constitutes a direct measure of brain function often used in bio-behavioural sciences, investigating basic cognitive processes, development, emotional function and dysfunction (Teplan 2002, Davidson *et al.* 2007).

In diagnosis, when the EEG reveals abnormal patterns, it might indicate general pathological processes, which are frequently not specific to a certain disease, such that the findings should be analysed as inserted in a particular context and used as a means to assisting the diagnosis (Binnie and Prior 1994, Duncan *et al.* 2014). The diminution of activity is the most reliable anomalous EEG finding, suggesting a past cerebral infarct or a subdural haematoma when the amplitude is reduced and indicating brain death with electrocerebral silence (Binnie and Prior 1994). The most known application of the electroencephalogram is the study of epilepsy; it is usually observed a spike-wave activity in the presence of typical absence epilepsy and, sometimes, in generalised epilepsy and focal inter-ictal epileptiform discharges in partial seizure disorders (Duncan *et al.* 2014). Additionally, among the main clinical applications Binnie & Prior listed states of altered consciousness, parasomnias, dementias, toxic confusional states, cerebral infections and other encephalopathies. Patients with dysfunction of diencephalic or brainstem structures may present bilateral rhythmic slow activities over the frontal or posterior temporal areas (Binnie and Prior 1994).

Moreover, EEG can be used to quantify the intensity of sedation and to manage and predict the outcome of patients in a coma (Duncan *et al.* 2014).

Brain stimulation methods, such as transcranial magnetic stimulation, can interfere with ongoing oscillatory activity. The application of TMS pulses can evoke oscillations in the occipital (*alpha* frequencies), parietal (*beta* range) and frontal (*beta* or *gamma* rhythms) cortices (Assenza *et al.* 2017). Some authors are, this way, combining electroencephalography with TMS, by recording the electroencephalographic activity immediately before, during or after stimulation (O'Shea and Walsh 2007, Rossi *et al.* 2009), which can also provide spatial information (Lioumis 2012). The combination of both methods can potentially improve the diagnosis and treatment of pathologies wherein there is an alteration of brain oscillations and even function as a predictor of prognosis (Assenza *et al.* 2017).

EEG in stroke patients

Following a stroke event, brain rhythms are often altered and are identified as promising biomarkers in injury and its rehabilitation (Cassidy *et al.* 2020, Popa *et al.* 2020). In the acute phase of the cerebral infarction, in the first hours and days, EEG changes are already seen preceding those observed on Computed Tomography. Usually, there is a localised decrease on normal cortical rhythms, accompanied by a main surrounding slow wave abnormality, in which individual waves have frequencies below 1 Hz (Binnie and Prior 1994).

Large infarction of the middle cerebral artery can originate a malignant oedematous course associated to a mortality rate that can reach 80%. Electroencephalography may not only enable the analysis of functional changes after an ischemic stroke, but also provide data to predict the patients that will develop malignant oedema (Burghaus *et al.* 2007). In this context, Burghaus *et al.* reported that when there is no *delta* activity and *theta* and fast *beta* frequencies are observed there is a prediction of a benign course. On the contrary, diffuse widespread slowing and slow *delta* activity on the lesioned hemisphere may be associated to a prediction of a malignant course (Burghaus *et al.* 2007). These hypotheses are, nonetheless, arguable as the permanence of *theta* or *delta* oscillations in neurologic pathological conditions, such as stroke, might be interpreted as a result of network impairments or, on the other hand, as an indication of brain reorganization and beneficial plasticity processes (Assenza *et al.* 2017, Cassidy *et al.* 2020).

Regarding *alpha* rhythm, a decrease in relative power can be observed in both hemispheres, influencing rehabilitation after stroke (Popa *et al.* 2020). Actually, patients who show reduced levels of *alpha* power on the ipsilesional hemisphere are predicted to have poorer improvement of deficits, with this decrease being more marked in those areas involved on the deficits that remain 3 months after a unilateral middle/anterior cerebral artery ischemic event (Assenza *et al.* 2017). Moreover, after an ischemic stroke leading to motor impairments, there is a decrease in bi-hemispheric *beta* levels and ERS following a somatosensory stimulus. Similarly, smaller reductions can indicate better prognosis, since *beta* is a pivotal rhythm for the normal performance of the motor system (Assenza *et al.* 2017, Cassidy *et al.* 2020).

In summary, EEG is a relevant technique providing very useful pathophysiological information in the clinical neuroscience context.

Chapter

3

STATE-OF-THE-ART

THE USE OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR STROKE REHABILITATION: A SYSTEMATIC REVIEW

Objectives: Stroke is a leading cause of disability. Alternative and more effective techniques for stroke rehabilitation have been sought to overcome limitations of conventional therapies. Repetitive transcranial magnetic stimulation (rTMS) arises as a promising tool in this context. This systematic review aims to provide a state of the art on the application of rTMS in stroke patients and to assess its effectiveness in clinical rehabilitation of motor function. *Methods:* Studies included in this review were identified by searching PubMed and ISI Web of Science. The search terms were (rTMS OR "repetitive transcranial magnetic stimulation") AND (stroke OR "cerebrovascular accident" OR CVA) AND (rehab OR rehabilitation OR recover*). The retrieved records were assessed for eligibility and the most relevant features extracted to a summary table. *Results:* Seventy out of 691 records were deemed eligible, according to the selection criteria. The majority of the articles report rTMS showing potential in improving motor function, although some negative reports, all from randomized controlled trials, contradict this claim. Future studies are needed because there is a possibility that a bias for non-publication of negative results may be present. *Conclusions:* rTMS has been shown to be a promising tool for stroke rehabilitation, in spite of the lack of standard operational procedures and harmonization. Efforts should be devoted to provide a greater understanding of the underlying mechanisms and protocol standardization.

3.1. INTRODUCTION

Stroke is a global leading cause of disability (Nowak *et al.* 2008, Khedr, Abdel-Fadeil, *et al.* 2009, Khedr *et al.* 2010, Cazzoli *et al.* 2012, Sung *et al.* 2013, Abo *et al.* 2014, Chieffo, De Prezzo, *et al.* 2014, Galvão *et al.* 2014, Du, Tian, *et al.* 2016, Rastgoo *et al.* 2016) and the third most frequent cause of death (Yang *et al.* 2015). Between 55% and 75% of patients that had a stroke episode have functional motor limitations that are present even at 3-6 months after its onset, (Sasaki *et al.* 2013, Abo *et al.* 2014, Rose *et al.* 2014, Wang, Tsai, *et al.* 2014) thereby affecting their quality of life and professional or daily living activities (Galvão *et al.* 2014). Physical therapy represents an essential tool for motor recovery; nevertheless, effect sizes of outcomes are frequently limited, in particular when applied to chronic patients (Avenanti *et al.* 2012). This way, there is a need for more effective approaches for stroke rehabilitation (Higgins *et al.* 2013, Fu *et al.* 2015, Lüdemann-Podubecká *et al.* 2015, Du, Yang, *et al.* 2016).

Under normal conditions, it is believed that a balance of function exists between the hemispheres, regulated by interhemispheric inhibition (Khedr, Abdel-Fadeil, *et al.* 2009, Khedr *et al.* 2010, Seniów *et al.* 2013). According to the interhemispheric competition model, this balance is affected after stroke; the excitability of the contralesional hemisphere is enhanced whereas the affected hemisphere undergoes an abnormally increased interhemispheric inhibition (Ameli *et al.* 2009, Takeuchi *et al.* 2009, Kindler *et al.* 2012, Lin *et al.* 2015, Du, Tian, *et al.* 2016). These excitability changes can be a significant cause for impaired functional recovery (Fregni *et al.* 2006, Liepert *et al.* 2007, Lüdemann-Podubecká *et al.* 2015, Du, Tian, *et al.* 2016, Ludemann-Podubecka *et al.* 2016). As a result, a possible strategy for stroke rehabilitation is the modulation of plasticity by repetitive Transcranial Magnetic Stimulation (rTMS), seeking to restore the normal activity pattern (Ameli *et al.* 2009, Lüdemann-Podubecká *et al.* 2015, Du, Tian, *et al.* 2016).

rTMS is a painless non-invasive brain stimulation tool applied to modulate cortical excitability at the stimulation site and, transsynaptically, at distant sites (Kim *et al.* 2006, Malcolm *et al.* 2007, Ameli *et al.* 2009, Khedr, Abdel-Fadeil, *et al.* 2009, Emara *et al.* 2010, Kakuda, Abo, Nakayama, *et al.* 2013, Galvão *et al.* 2014, Naghdi *et al.* 2015, Du, Yang, *et al.* 2016, Rastgoo *et al.* 2016). Stimulation parameters, mainly frequency, (Kim *et al.* 2006, Malcolm *et al.* 2007, Emara *et al.* 2010) influence its modulatory effect

in terms of resulting excitation or inhibition (Kim *et al.* 2006, Barwood, Murdoch, Whelan, Lloyd, Riek, O'Sullivan, *et al.* 2011, Kindler *et al.* 2012, Waldowski *et al.* 2012, Galvão *et al.* 2014, Yang *et al.* 2015). Low-frequency rTMS (≤ 1 Hz) is commonly used to decrease cortical excitability, whereas high-frequency rTMS (often defined as being ≥ 5Hz) is applied to facilitate it (Chang *et al.* 2010, Emara *et al.* 2010, Conforto *et al.* 2012, Seniów *et al.* 2013, Kim *et al.* 2013, Cha *et al.* 2014, Kim, Choi, *et al.* 2014, Chieffo, Ferrari, *et al.* 2014, Galvão *et al.* 2014, Lin *et al.* 2015, Naghdi *et al.* 2015, Yang *et al.* 2015, Rastgoo *et al.* 2016, Du, Tian, *et al.* 2016, Du, Yang, *et al.* 2016, Hosomi *et al.* 2016). Theta burst stimulation (TBS) is a patterned form of rTMS (Ackerley *et al.* 2010, Kindler *et al.* 2012, Higgins *et al.* 2013, Yang *et al.* 2015) that can also rebalance excitability either by facilitating it (intermittent TBS) or by decreasing it (continuous TBS) (Ackerley *et al.* 2010, Yang *et al.* 2015).

This systematic review was conducted to provide a state of the art on the application of different protocols of rTMS in stroke patients and to assess its clinical effectiveness in the rehabilitation of limb motor function following a stroke event.

3.2.   METHODS

Studies included in this review were identified by searching PubMed and ISI Web of Science. The last search was run on August 9, 2016. The search terms were (rTMS OR "repetitive transcranial magnetic stimulation") AND (stroke OR "cerebrovascular accident" OR CVA) AND (rehab OR rehabilitation OR recover*). Articles were firstly assessed on the basis of their abstracts and titles. The goal was to include studies that reported applying rTMS to rehabilitate motor impairments on the upper and lower limbs in stroke patients. Simultaneously, exclusion criteria were adopted to reject studies (1) not written in English; (2) performing reviews; (3) in children or adolescents; (4) in animals; (5) recruiting only healthy subjects; (6) with sample size inferior to 5 participants; (7) using paired-pulse or single-pulse TMS instead of rTMS; (8) employing other stimulation techniques instead of TMS; (9) focusing on disease or conditions other than stroke; (10) in which the primary objective was not to evaluate the effect of repetitive TMS on the rehabilitation behavioral outcomes; and (11) not explicitly describing the TMS protocol (including coil, stimulation area, number of sessions, frequency, intensity, and pattern).

A data extraction sheet was developed seeking to retrieve relevant information from each study, notably study design, sample size, participants' clinical characteristics, whether additional therapy was performed, details of the TMS protocol, outcome measures, and behavioral results.

3.3.   RESULTS

We identified 691 records through database searching, 275 of which were duplicates (elaborated according to the PRISMA statement requirements (Moher *et al.* 2009); see **Figure 3.3.1**).
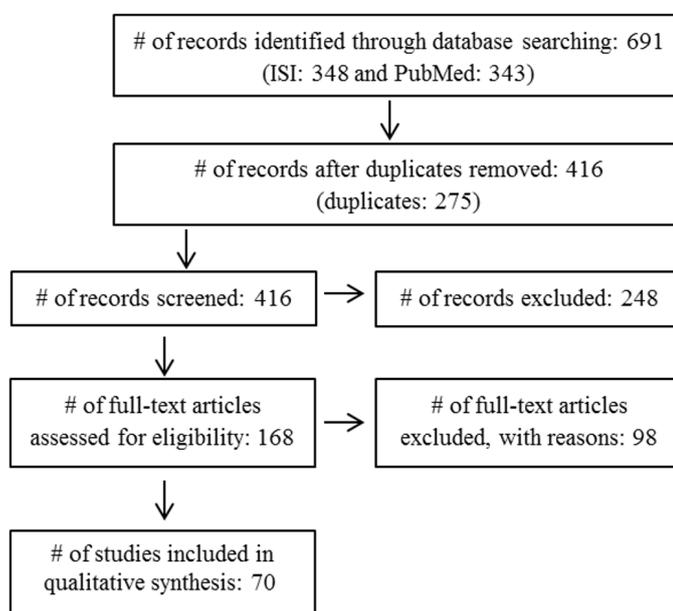
Figure 3.3.1 – Search flow (as described in the PRISMA statement). Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

The remaining 416 articles underwent preliminary screening (of titles and abstracts), with 248 records being excluded because they did not meet the eligibility criteria. After the full-text analysis of each of the 168 individual articles, 70 studies focusing on motor function rehabilitation remained for qualitative synthesis. The studies included for qualitative synthesis were published between 2005 and 2016 and involved a total of 3744 adult patients.

The parameters of rTMS applied to motor recovery in stroke patients and its outcomes are presented in **Table A1.1**, in *Appendix A1*. Also, we provide clinical sample

characterization of patients included in the revised studies (**Table A1.2**). In what follows, the findings reported by the authors are described.

Interventions to improve motor function

The majority of the 70 publications reporting interventions to improve motor function applied TMS to the primary motor cortex (M1). Wang *et al.* (2014) compared the efficacy of inhibiting the contralesional M1 against suppressing the contralesional premotor cortex to rehabilitate motor function and observed that the inhibition of M1 conducted to better improvements. An influence of motor impairment's severity on the effect that the contralesional dorsal premotor cortex (PMd) exerts over the affected hemisphere is described (Ludemann-Podubecka *et al.* 2016). Contralesional PMd is said to have a potentially positive effect on patients with severe hand motor impairment, contrasting to a potentially negative effect on the recovery of mild-to-moderate hand impairment (Ludemann-Podubecka *et al.* 2016). Thereafter, it is suggested that inhibition of contralesional PMd by rTMS should be performed for the rehabilitation of mild to moderate hand motor deficits (Ludemann-Podubecka *et al.* 2016).

In the present review, 39 studies applied inhibitory rTMS to the nonlesioned hemisphere, while 12 studies excited the affected hemisphere and 19 studies addressed both hemispheres either by bilateral stimulation or by studying each of them separately.

Studies of excitability changes after rTMS showed the expected increase on the affected hemisphere (Fregni *et al.* 2006, Kim *et al.* 2006, Talelli *et al.* 2007, Sung *et al.* 2013, Wang, Tsai, *et al.* 2014, Blesneag *et al.* 2015) or a decrease on the unaffected hemisphere (Talelli *et al.* 2007, Nowak *et al.* 2008, Sung *et al.* 2013, Wang, Tsai, *et al.* 2014, Lüdemann-Podubecká *et al.* 2015, Tretriluxana *et al.* 2015). Du *et al.* (2016) observed a significantly enhanced excitability on the lesioned hemisphere and significantly reduced excitability on the nonlesioned hemisphere after the application of 1 Hz rTMS to the unaffected hemisphere. Still, when they stimulated the affected hemisphere with 3 Hz, they only reported a significant change for the lesioned hemisphere (Du, Tian, *et al.* 2016). Lüdemann-Podubecká *et al.* (2016), in turn, did not identify significant changes in motor evoked potentials amplitude, cortical silent period, nor ipsilateral silent period after 1 Hz stimulation over the unaffected PMd. This was possibly because the neurophysiological tests were not sensitive to the activation of connections that are specific to PMd. It is important to verify whether the observed

changes in excitability relate to motor improvement. However, no significant correlation was found by Malcolm *et al.* (2007), Talelli *et al.* (2007), Nowak *et al.* (2008) or Lüdemann-Podubecká *et al.* (2016), raising questions about the relation between physiological changes and motor improvements. Naghdi *et al.* (2015) assessed the ratio between maximum peak-to-peak amplitude of H-reflex and maximum peak-to-peak amplitude of M-wave, as a neurophysiological measure of motor neuron excitability, and they found no significant improvement on this variable, even though they observed improved spasticity. Nevertheless, significant correlations were described by several authors (Takeuchi *et al.* 2005, Fregni *et al.* 2006, Kim *et al.* 2006, Khedr *et al.* 2010, Sung *et al.* 2013, Vongvaivanichakul *et al.* 2014, Wang, Tsai, *et al.* 2014, Lüdemann-Podubecká *et al.* 2015). Du *et al.* (2016) found significant correlations between motor improvement and changes in excitability on the affected hemisphere but not on the unaffected hemisphere. Volz *et al.* (2016) reported a significant improvement on functional connectivity between ipsilesional M1 and bilateral motor areas after stimulation of ipsilesional M1 with intermittent TBS protocol, which correlated with the motor improvement.

Clinical Determinants of Outcome

It is thought that rTMS can have potential beneficial effects even in elderly patients and in patients with a longer time since stroke (Kakuda, Abo, Shimizu, *et al.* 2012). In any, Khedr *et al.* (2010) reported superior improvement in the younger patients, and Chang *et al.* (2010) suggested that the subacute stage is the best period to apply rTMS. Despite of this, 64% of the studies included in this review recruited patients that had suffered from stroke 6 or more months before (mean time poststroke). Moreover, it has been claimed that rTMS effects are not affected by lesion location (Sung *et al.* 2013), whereas others believe that the response to rTMS may even be reversed depending on the location of the primary lesion (Talelli *et al.* 2012). In the study of Ameli *et al.* (2009), high-frequency rTMS over affected M1 reduced significantly the overactivity of the contralesional hemisphere and improved function significantly in subcortical stroke but not in cortical stroke patients. Kakuda *et al.* (2016) found no significant influence of subtype of stroke (intracerebral haemorrhage or cerebral infarction) or lesion location (cortical or subcortical) on the motor improvement.

The Role of Concomitant Interventions

rTMS might not be sufficient to provide the brain the physiological changes required for skill acquisition (Malcolm *et al.* 2007, Kakuda *et al.* 2016). Instead, it is believed that stimulation induces a temporary state wherein learning is optimized (Avenanti *et al.* 2012, Etoh *et al.* 2013) and, therefore, this technique should be combined with rehabilitative training (Malcolm *et al.* 2007, Kakuda *et al.* 2016). An interesting empirical question is which of the interventions, rTMS or motor training, has the main role in motor recovery. According to Galvão *et al*. (2014), inhibitory rTMS, and not motor training, was the main intervention to reduce spasticity.

The Role of TMS Parameters and Experimental Design

It is important to note that TMS parameters vary widely between studies (Higgins *et al.* 2013). Higgins *et al*. (2013) noted that the optimal parameters that should be used are unknown and that effects can differ according to inter-individual or intra-individual variability. It is believed that the duration (Malcolm *et al.* 2007) and the number of sessions have an influence on the magnitude and duration of the clinical effects (Fregni *et al.* 2006, Chang *et al.* 2010, Talelli *et al.* 2012). Lin *et al*. (2015) reported that there are more studies evaluating upper extremity after stroke and just a few applying rTMS to recovery of lower extremity deficits, which was also observed in this systematic review. This is mostly because it is difficult to deliver rTMS with a figure-of-eight coil to the lower limb representations because the leg motor areas are located deep within the interhemispheric fissure (Kakuda, Abo, Nakayama, *et al.* 2013, Kakuda, Abo, Watanabe, *et al.* 2013).

Rehabilitation Functional Outcomes

In spite of the variations in experimental design, almost all the included studies report improvements in motor function after stimulation (see **Table A1.1**). Chieffo *et al*. (2014) applied 20-Hz stimulation over bilateral lower limb motor cortical areas and reported that the patients not only maintained the benefits of rTMS but also continued to improve after the intervention. This could be justified by the long-lasting modulatory effects potentiated by the use of the paretic limb on the daily activities (Chieffo, De

Prezzo, *et al.* 2014). Kakuda *et al.* (2011) showed a significant influence of the motor impairment's severity before the intervention on subsequent measures of improvement and Koyama *et al.* (2014) reported a lack of evidence of rTMS effectiveness in improving motor function of severely impaired patients. The findings reported by some authors suggested that inhibition of the contralesional hemisphere would be more effective than excitation of the affected hemisphere, (Khedr, Abdel-Fadeil, *et al.* 2009, Emara *et al.* 2010, Du, Tian, *et al.* 2016) concerning motor function rehabilitation, whereas others described the opposite effect (Talelli *et al.* 2007, Sasaki *et al.* 2013, Cha *et al.* 2014) or no difference (Kim, Choi, *et al.* 2014). Takeuchi *et al.* (2009) found higher improvement when both hemispheres were stimulated (bilateral stimulation) than when stimulating the unaffected hemisphere. Lüdemann-Podubecká *et al.* (2015) found that motor recovery was dependent on hemispheric dominance and reported significant improvements on patients who suffered from stroke on the dominant hemisphere but not on those who had the stroke on the non-dominant hemisphere. On the other hand, stroke on the dominant hemisphere appeared to be related with poorer recovery during motor training, suggesting that those patients would benefit from the adjuvant effect of inhibitory rTMS, in opposition to patients in whom stroke occurred on the non-dominant hemisphere (Lüdemann-Podubecká *et al.* 2015). Tretriluxana *et al.* (2015) studied the influence of object size on reach-to-grasp after 1Hz rTMS over the representational area of the unaffected extensor digitorum communis muscle. It was recognized that patients' movements before intervention were more coordinated when reaching and grasping larger objects. After stimulation, a more pronounced improvement in reach-to-grasp kinematics and coordination for the smaller objects was observed, which indicates an impact of task difficulty on the response to treatment. This could be explained by a greater involvement of M1 contralateral to the hand performing complex tasks, with higher recruitment of cortico-subcortical networks (Tretriluxana *et al.* 2015).

Concerning studies with results not favouring the efficacy of rTMS on rehabilitation, Higgins *et al.* (2013) observed a transient effect of rTMS on excitability that was not translated into a significant effect on behaviour as an adjunct to task-oriented therapy. Blesneag *et al.* (2015) applied 10 sessions of 1-Hz or sham-rTMS to the nonlesioned M1 of patients who had had the stroke 10 days before inclusion and reported that, in spite of observing a greater improvement after real stimulation at 45

days poststroke, at 90 days poststroke, the sham stimulation group scored higher. The differences between groups were not significant at any time point. This way, the low-frequency rTMS group did not show long-term effects on motor function additional to those observed on the sham stimulation group which, according to the authors, could be due to a lack of stratification of patients based on lesion location and deficit's severity (Blesneag *et al.* 2015). Others also failed to demonstrate a significant effect of rTMS on motor function (Malcolm *et al.* 2007, Seniów *et al.* 2012, Talelli *et al.* 2012, Rose *et al.* 2014). Malcolm *et al.* (2007) put forward possible explanations for this absence of effect, including factors related to the stimulation protocol. In addition, it is thought that the effect of the adjuvant therapy is multiplicative of the effect of the behavioural therapy; therefore, if the behavioural therapy had low impact, the effect of the adjuvant therapy might go unnoticed (Malcolm *et al.* 2007).

Considering these results, we decided to evaluate separately the results of randomized controlled trials (RCTs). Although results from RCT and non-RCT studies suggest that TMS is a potentially useful therapeutic intervention for stroke rehabilitation, some cautionary notes emerge from this analysis: the few studies that failed to demonstrate positive results for the efficacy of this technique were all RCTs.

3.4. DISCUSSION

rTMS has been reported to be a safe procedure for clinical rehabilitation of stroke patients. Kakuda *et al.* (2016) included 1725 patients and reported only transient and not severe side effects, namely, minor dizziness, discomfort at stimulation site, and mild headache, by a total of 22 individuals.

After stimulation, an increase of the lesioned hemisphere's excitability and/or a decrease of the unaffected hemisphere's overactivity is often observed. These changes provide evidence for the role of TMS on restoring the balance between hemispheres' activity. However, changes in excitability do not always correlate to functional improvement, as reported in the literature. Nevertheless, the majority of the studies included here support the potential of this technique in improving motor function in stroke patients. It is important to be conservative when evaluating the efficacy of this therapy for motor function rehabilitation because the few studies reporting an absence

of significant effects of TMS are all RCTs. This points out a possibility of bias for nonpublication of negative results, which should be addressed in future studies.

Due to easiness of implementation, the rehabilitation of the upper limb has been more intensively studied than the recovery of lower limb impairments. However, a considerable number of patients deal with loss of function of the lower limbs. Thereafter, more efforts should be devoted to develop an effective protocol for that purpose.

In this systematic review we found a wide variability in the factors that need to be considered when comparing outcomes of rTMS studies. Most studies have dealt with a small sample size (e.g., 54% of all articles reported having up to 20 patients). A common recommendation is that more patients should be recruited in future studies, (Kim *et al.* 2006, 2015, Nowak *et al.* 2008, Emara *et al.* 2010, Barwood, Murdoch, Whelan, Lloyd, Riek, O'Sullivan, *et al.* 2011, Barwood *et al.* 2012, Medina *et al.* 2012, Conforto *et al.* 2012, Sasaki *et al.* 2013, Abo *et al.* 2014, Galvão *et al.* 2014, Tretriluxana *et al.* 2015, Lin *et al.* 2015, Ludemann-Podubecka *et al.* 2016, Volz *et al.* 2016, Du, Yang, *et al.* 2016) overcoming the difficulties in obtaining large and homogeneous samples that fulfil all the adequate eligibility criteria.

As acknowledged by several authors, TMS should be combined with conventional rehabilitation because stimulation optimizes the effects of other interventions instead of providing the brain all the changes needed for skill acquisition. Frequently, rTMS is employed simultaneously with techniques such as occupational therapy and physiotherapy. Nonetheless, this hinders the possibility of distinguishing the effects of rTMS from those of conventional therapy alone, unless a control group following the same treatment excluding rTMS is included (Abo *et al.* 2012, Kakuda, Abo, Shimizu, *et al.* 2012, Talelli *et al.* 2012).

Several authors chose to add sham stimulation as a control method to rule out the placebo effect. However, it is possible that sham stimulation is perceived differently from real stimulation by patients. Nevertheless, it is widely believed that as long as the selected patients are naïve to rTMS, they will probably not discover whether the received stimulation was real or not (Fregni *et al.* 2006, Avenanti *et al.* 2012, Seniów *et al.* 2012, 2013, Khedr *et al.* 2014, Du, Tian, *et al.* 2016, Rastgoo *et al.* 2016, Volz *et al.* 2016).

Concerning additional confounds, Khedr *et al.* (2005, 2014) have suggested that the indirect effects of rTMS in decreasing depression-related symptoms may also influence the outcomes, by changing compliance with treatment, which is worth addressing in future studies.

Important aspects for future research include the usage of structural and functional imaging, which would be useful as read out to understand the role of the type of pathology or lesion location in neuroplasticity (Wang, Tsai, *et al.* 2014) as well as the mechanism of functional recovery after rTMS (Abo *et al.* 2014, Du, Yang, *et al.* 2016). It would also be of great value to evaluate and confirm the plastic changes occurring in the brain following rTMS interventions for stroke rehabilitation (Kakuda, Abo, Watanabe, *et al.* 2013). In addition, the mechanism underlying the variation in excitability within and between hemispheres and the role of the contralesional hemisphere in stroke recovery needs to be clarified (Fregni *et al.* 2006, Ameli *et al.* 2009, Ackerley *et al.* 2010, Galvão *et al.* 2014, Tsai *et al.* 2014, Lüdemann-Podubecká *et al.* 2015).

The intervention protocols are often poorly defined (Talelli *et al.* 2012). The optimal, most effective rTMS parameters and timing for stroke rehabilitation, the optimal duration of each session and the whole treatment, as well as long-term effects of the treatment remain to be elucidated (Kim *et al.* 2006, 2015, Liepert *et al.* 2007, Nowak *et al.* 2008, Khedr, Abo-Elfetoh, *et al.* 2009, Chang *et al.* 2010, Emara *et al.* 2010, Khedr *et al.* 2010, Weiduschat *et al.* 2011, Kakuda, Abo, Kobayashi, Takagishi, *et al.* 2011, Barwood *et al.* 2012, Kindler *et al.* 2012, Waldowski *et al.* 2012, Conforto *et al.* 2012, Kakuda, Abo, Shimizu, *et al.* 2012, Sung *et al.* 2013, Kakuda, Abo, Nakayama, *et al.* 2013, Chieffo, De Prezzo, *et al.* 2014, Galvão *et al.* 2014). There are more studies inhibiting the unaffected hemisphere than exciting the affected hemisphere. However, we cannot assume through this observation that the inhibitory protocols are more effective. Sometimes authors opt to apply low frequencies due to safety reasons, for example. Actually, some authors reported inhibitory protocols applied to the unaffected hemisphere to be more effective than excitatory protocols delivered to the affected hemisphere, whereas others described an opposite result or no difference between them. Concerning the choice of the optimal procedure, it is yet an unresolved issue whether it is more effective for stroke rehabilitation to inhibit the unaffected hemisphere or to excite the affected hemisphere (Khedr, Abdel-Fadeil, *et al.* 2009). This remains as an outstanding question that also affects the implementation of TMS

protocols. It is also important to investigate how many treatment sessions are needed to achieve an optimal effect size (Liepert *et al.* 2007).

There are a variety of factors that can hypothetically affect the effectiveness of the intervention. The influence of factors related to inter-individual variability (such as age, time after stroke, lesion location, and pathologic type) on treatment response remains a major issue (Higgins *et al.* 2013, Sung *et al.* 2013). As emphasized by Barwood *et al.* (2011) the heterogeneity of the individuals in a study, especially for small sample sizes, represents a key confounding factor when interpreting results. Stratifying stroke subtypes, location, and extension of the lesion when recruiting patients has been suggested as a strategy to obtain more accurate findings (Wang, Tsai, *et al.* 2014, Blesneag *et al.* 2015, Fu *et al.* 2015, Hosomi *et al.* 2016). In fact, the efficacy in eligible patients with various levels of impairment should be addressed and adjustments on the protocol be performed according to different stages and severity (Avenanti *et al.* 2012, Conforto *et al.* 2012). It is known that the neural network for dominant hand motor function is somewhat different from that of the non-dominant hand (Seniów *et al.* 2012). Vidal *et al.* (2014) found evidence for an influence of the dominance of the hemisphere that controls action on cortical communication during motor control and Lüdemann-Podubecká *et al.* (2015) reported an impact of hemispheric dominance on motor improvement. Therefore, it would be interesting to address this issue in future research and control for handedness in stroke patients (Seniów *et al.* 2012).

Here we reported a difference on the selected parameters between studies and that the response to a protocol might vary according to patients' individual characteristics. The pursuit of the optimal protocol is very complex because one patient may respond differently from another to TMS parameters and biochemical mechanisms (Yang *et al.* 2015). The study of electrophysiological and neuroimaging data would be of great importance in identifying biomarkers that could help predict the response of each patient to the intervention (Volz *et al.* 2016). This way, researchers should focus on understanding these differences on the responses. It would be valuable to identify the candidates that would benefit the most from the intervention (Liepert *et al.* 2007, Khedr, Abo-Elfetoh, *et al.* 2009, Khedr *et al.* 2010, Kakuda, Abo, Kobayashi, Takagishi, *et al.* 2011, Conforto *et al.* 2012, Talelli *et al.* 2012, Seniów *et al.* 2013) to design a personalized protocol specific to each patient (Emara *et al.* 2010, Higgins *et al.* 2013, Du, Yang, *et al.* 2016).

Also, the diversity of measures that are used to evaluate the outcomes requires caution when interpreting data. It is not easy to quantitatively compare studies and evaluate results due to the variability and putative adequacy of the outcome measures used and respective follow-up periods (Talelli *et al.* 2012).

3.5. CONCLUSIONS

rTMS has been applied in many studies of distinct clinical conditions requiring rehabilitation. The available literature pointed out the value of this technique in improving function in stroke patients without severe adverse events. In fact, it has frequently been reported that patients showed significant improvements in the domains of motor function following rTMS intervention, which brings hope to stroke rehabilitation.

The reviewed studies employed variable protocols and assessed treatment efficacy with different outcome measures, which makes it difficult to compare interventions and evaluate results as well as understand which parameters lead to the best rehabilitation outcomes. Protocol standardization would be an important contribution because a consensual optimal protocol for stroke rehabilitation is not available. In addition, the selection rationale and criteria for the implemented parameters should be made explicit.

We suggest that the first step for a comprehensive understanding of the effects of TMS should be the combination of basic research studies on brain plasticity and the mechanisms underlying its actions as well as the harmonization of standard operating procedures. Moreover, researchers should focus on studying different subgroups of patients and the influence of their physiological state in the TMS effects. Importantly, the protocols of repetitive TMS should be adapted to each clinical subgroup in a personalized manner to optimize the outcomes.

The impact on rehabilitation outcomes has been so far very promising, which enhances the interest of multicentric studies applied to homogeneous cohorts of patients large enough to get stronger statistical and clinical evidence. When these issues are solved, it may be possible to extend the applicability of TMS into a broader clinical context in the scope of stroke recovery.

STATE-OF-THE-ART

TRANSCRANIAL MAGNETIC STIMULATION AS AN INTERVENTION TOOL TO RECOVER FROM LANGUAGE, SWALLOWING AND ATTENTIONAL DEFICITS AFTER STROKE: A SYSTEMATIC REVIEW

Background: Following a stroke event, patients often are severely affected by disabilities that hinder their quality-of-life. There are currently several rehabilitative options and strategies, and it is crucial to find the most effective interventions. The applicability of transcranial magnetic stimulation (TMS) to the recovery of nonmotor functions such as communication skills, swallowing ability and spatial attention after stroke remains important clinical questions. *Summary*: We searched PubMed and ISI Web of Science for articles that used repetitive TMS protocols to rehabilitate post-stroke deficits. We analysed qualitatively 38 articles that met the eligibility criteria; of these, 21 dealt with aphasia, 8 with dysphagia, 8 with neglect and 1 with visual extinction. The efficacy of TMS as an intervention for post-stroke rehabilitation of these nonmotor deficits was studied as well as the current limitations were assessed. *Key Messages*: Most part of the included studies reported statistically significant functional improvements, supporting the use of TMS for the rehabilitation of aphasia, dysphagia and neglect. Future research, with larger sample sizes, is mandatory to confirm its efficacy, determine the optimal stimulation parameters and investigate inter-subject variability.

4.1. INTRODUCTION

Stroke, or cerebrovascular accident, represents the third leading cause of death and one of the most common sources of disability worldwide (Cazzoli *et al.* 2012, Yang *et al.* 2015). Motor deficits after stroke have been given particular attention; however, other types of deficit are also relevant such as communication skills (Szaflarski *et al.* 2011, Kindler *et al.* 2012, Seniów *et al.* 2013), swallowing abilities (Khedr, Abo-Elfetoh, *et al.* 2009, Lee *et al.* 2015) and attention (Lim *et al.* 2010, Kim *et al.* 2013).

Communication

Aphasia, described as a total or partial loss of language functions, (Kindler *et al.* 2012) is a very frequent disability among stroke patients and severely restricts communication and the ability to engage in social interactions (Szaflarski *et al.* 2011, Weiduschat *et al.* 2011, Chieffo, Ferrari, *et al.* 2014, Rubi-Fessen *et al.* 2015). This syndrome arises from damage to the language dominant hemisphere – generally the left hemisphere in right-handed people (Naeser *et al.* 2011, Szaflarski *et al.* 2011, Heiss *et al.* 2013). In fact, aphasia is only associated to a lesion on the right hemisphere in 4% of the aphasia cases with poststroke patients (Heiss *et al.* 2013). Nonfluent aphasia originates problems in speech output such as interrupted speech, word omission or statements with limited syntactic complexity (Medina *et al.* 2012). As a consequence of stroke, it affects about 38% of the patients (Szaflarski *et al.* 2011, Kindler *et al.* 2012, Seniów *et al.* 2013) and becomes chronic in 10% to 18% of survivors (Kindler *et al.* 2012, Seniów *et al.* 2013).

Swallowing

Dysphagia, characterized by a difficulty in swallowing, is also a common poststroke outcome, affecting up to 78% of patients (Khedr, Abo-Elfetoh, *et al.* 2009, Lee *et al.* 2015, Cheng *et al.* 2017). Although the recovery is frequent within a few weeks, its extent varies considerably between subjects (Khedr, Abo-Elfetoh, *et al.* 2009, Du, Yang, *et al.* 2016). A patient is more likely to develop dysphagia if the stroke affects the dominant hemisphere instead of the non-dominant one (Khedr, Abo-Elfetoh, *et al.* 2009). This condition raises the probability of death mostly owing to an increased risk

of pulmonary complications (Park *et al.* 2013) like pneumonia which, in turn, is associated with a third of stroke deaths (Khedr and Abo-Elfetoh 2010).

Attention

Spatial neglect, that is, the inability to attend, reply, react or orient to stimuli located in the contralesional portion of space, (Song *et al.* 2009, Lim *et al.* 2010, Cazzoli *et al.* 2012, Kim *et al.* 2013, 2015, Fu *et al.* 2015, Yang *et al.* 2015) affects from 30% to 81% of patients in the acute phase (Lim *et al.* 2010, Kim *et al.* 2013) and it is sustained in approximately a third of them (Lim *et al.* 2010). It appears most often due to right hemispheric lesions of the middle cerebral artery, damaging the neural substrates of space representation and awareness (Kim *et al.* 2013, Yang *et al.* 2015, Cha and Kim 2016). Additionally, it can emerge associated to damage of other areas such as the parietal or frontal lobe, thalamus or basal ganglia (Yang *et al.* 2015). This disability slows down the functional rehabilitation and increases the length of hospital stay (Song *et al.* 2009, Cazzoli *et al.* 2012). When poststroke patients become chronic, there is a decrease of the incidence of overt neglect and often only signs of visual extinction are observed (Agosta *et al.* 2014), characterized by *"an inability to detect a contralesional stimulus when an ipsilesional stimulus is simultaneously presented"* (Agosta *et al.* 2014).

The search for new methods able to increase the efficacy of recovery programs is crucial (Fu *et al.* 2015, Du, Yang, *et al.* 2016). It is well recognized that, following stroke, the balance of function between the hemispheres is disturbed and the affected hemisphere becomes more inhibited, while the hemisphere contralateral to the lesion shows an increased activity (Ameli *et al.* 2009, Kindler *et al.* 2012, Du, Tian, *et al.* 2016). It is strongly believed that this imbalance of inter-hemispheric excitability limits considerably the recovery of function after stroke (Lüdemann-Podubecká *et al.* 2015, Du, Tian, *et al.* 2016). Transcranial magnetic stimulation (TMS), a technique for the non-invasive brain stimulation, arises as a novel approach to rehabilitate motor and non-motor deficits in stroke patients, due to its ability to modulate brain plasticity (Ameli *et al.* 2009, Du, Tian, *et al.* 2016), either by increasing excitability (with high-frequency protocols or intermittent theta burst stimulation paradigms) or by decreasing it (low-frequency or continuous theta burst stimulation paradigms) (Ackerley *et al.* 2010, Kim

et al. 2013, Seniów *et al.* 2013, Chieffo, Ferrari, *et al.* 2014, Yang *et al.* 2015, Du, Tian, *et al.* 2016, Du, Yang, *et al.* 2016).

In a previous work (Dionísio *et al.* 2018) we performed a systematic review to study the use of repetitive TMS on the rehabilitation of motor function, following stroke. Here, we assess the applicability of TMS to the rehabilitation of non-motor deficits such as post-stroke aphasia, dysphagia and neglect.

4.2. METHODS

We identified articles on PubMed and ISI Web of Science, using the search terms: (rTMS OR "repetitive transcranial magnetic stimulation") AND (stroke OR "cerebrovascular accident" OR CVA) AND (rehab OR rehabilitation OR recover*). The last search was performed on September 12, 2017. We included studies that aimed to improve aphasia, dysphagia, neglect or visual extinction, in post-stroke patients, with repetitive TMS protocols. As for our preceding systematic review (Dionísio *et al.* 2018), we excluded (1) reviews; and studies (2) written in any language other than English; (3) in paediatrics; (4) performed in animals; (5) recruiting just healthy subjects; (6) including less than 5 participants; (7) not using repetitive TMS; (8) applying other stimulation techniques rather than TMS; (9) studying other disease or condition instead of stroke; (10) where the main goal was not to test the efficacy of repetitive TMS on the rehabilitation behavioural outcomes; and (11) that did not report explicitly the complete TMS protocol (including coil, stimulation area, number of sessions, frequency, intensity and pattern).

Data from each study was extracted and the most relevant information was added to a data extraction sheet. This included experimental design, number of participants, clinical characteristics of the patients, therapies subjects were undergoing besides the TMS, description of the stimulation protocol, outcome measures and main results.

4.3. RESULTS

The search we performed in PubMed and ISI Web of Science retrieved a total of 745 records, as can be observed in **Figure 4.3.1** (designed according to the PRISMA statement requirements (Moher *et al.* 2009)). From these records, 299 were duplicates,

remaining 446 for the initial screening based on titles and abstracts. After excluding 272 articles that did not fit the defined criteria, we accessed a total of 174 full-text articles. In the end of this procedure we included in our qualitative synthesis 38 articles, from which 21 focused on aphasia recovery, 8 on dysphagia, 8 on neglect and 1 on visual extinction rehabilitation. These articles were all published between 2009 and 2017 and included a total of 827 adult patients.
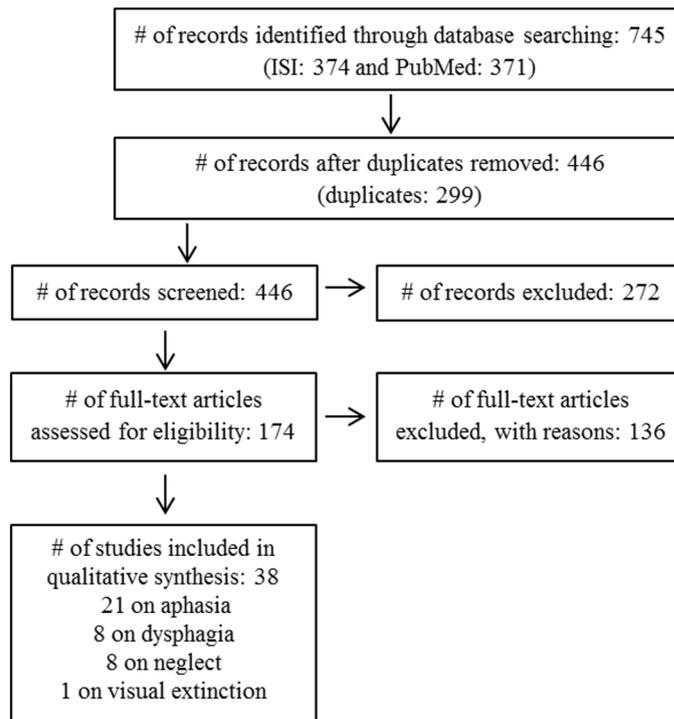
Figure 4.3.1 – Search flow (as described in the PRISMA statement).

We provide relevant information regarding the stimulation protocols and the reported results on supplementary material in *Appendix A2*, namely **Tables A2.1.1**, **A2.1.2** and **A2.1.3**, for aphasia, dysphagia and neglect or visual extinction, respectively. Moreover, on **Tables A2.2.1-A2.2.3**, we present clinical characterization of the patients that were included in the studies we revised.

In this section, we point out the main findings reported by the authors, concerning the stimulation protocols and their efficacy as a rehabilitative intervention.

TMS interventions in aphasia

For aphasia rehabilitation, we considered a total of 21 articles, published between 2011 and 2017. The majority of the studies on aphasia recovery focused on chronic stroke patients; 62% of the included research recruited patients that had had the stroke event more than 1 year before. The stable baseline condition, in the chronic phase, favours a more objective assessment of the TMS effects. However, Kindler *et al*. (2012) observed that the best responders to TBS were those with a shorter interval poststroke. The most part of the analysed studies (20 out of 21) studied the unaffected (right) hemisphere in the inferior frontal gyrus as a stimulation target, the majority in pars triangularis (Brodmann area 45). Medina *et al*. (2012) found the right pars triangularis to be the optimal site of stimulation in 9 of the 10 patients and Naeser *et al.* (2011) claimed that suppression of right pars triangularis, but not of pars opercularis, improved naming in aphasia.

Studies included in this review reported improvements in aphasia recovery with the application of rTMS, mainly in picture naming. Rubi-Fessen *et al*. (2015) also noted that the literature pointed out the most pronounced improvements for picture naming, when rehabilitating the language function. However, the authors obtained significant improvements caused by stimulation on auditory and written comprehension, writing and reading and on functional communication too (Rubi-Fessen *et al.* 2015). Additionally, Barwood *et al*. (2011, 2012) also described improved spontaneous speech and auditory comprehension. In this way, besides the improvements in expressive language, rTMS can improve receptive language performance as well (Barwood, Murdoch, Whelan, Lloyd, Riek, O' Sullivan, *et al.* 2011). Some authors reported an association between changes in brain activity induced by rTMS and language improvement (Szaflarski *et al.* 2011, Thiel *et al.* 2013, Khedr *et al.* 2014), while others did not (Weiduschat *et al.* 2011). Barwood *et al*. (2012), Chieffo *et al*. (2014) and Seniów *et al*. (2013) observed that the patients that obtained larger improvements were those with global aphasia and more severe deficits, suggesting that this tool can modulate language performance even in individuals with quite significant lesions. On the contrary, Naeser *et al*. (2011) observed less improvement in patients with more severe impairment.

Barwood *et al.* (2012) postulated a need to understand the variability of patients' response to rTMS and to explain why there are different responses to treatment. Tsai *et al.* (2014) found no correlation between the effects of the treatment and either subject's age, education, National Institute of Health Stroke Scale score, aphasia type and severity, time since stroke onset or baseline Functional Independent Measurement. Interestingly, they provided evidence that hyper-excitability of the contralesional hemisphere and the absence of diabetes mellitus comorbidity are related to a better response to rTMS treatment for aphasia recovery (Tsai *et al.* 2014).

Chieffo *et al.* (2014) described improvements with 10 Hz-rTMS that were significantly larger than with 1 Hz-rTMS, both applied in the right hemisphere. Heiss *et al.* (2013) recruited both right-handed patients with left-hemispheric stroke and left-handed subjects that experienced a right-hemispheric infarct that led to aphasia. They obtained promising results with low-frequency rTMS (LF-rTMS) and speech and language therapy in the right-handed patients, observing an activation shift to the dominant hemisphere with a concomitant significant recovery in language function. Interestingly, left-handed patients also revealed some improvement in language although a significant shift of activity to the affected hemisphere was not observed (Heiss *et al.* 2013). Findings from functional magnetic resonance imaging described greater activation in the right hemisphere of stroke patients that were recovering from aphasia, when compared to healthy subjects, which suggests that, although it is reported that LF-rTMS applied to the right hemisphere can be effective in improving language, it can be deleterious in those patients (Hara *et al.* 2017). Indeed, it was argued that the characteristics of a left-hemispheric lesion, namely its location and size, can influence the contribution of the right hemisphere to the improvement of language function (Hara *et al.* 2017). Hara *et al.* (2017) used functional near-infrared spectroscopy to localize the hemisphere that was activated for language function, and, this way, group subjects. Patients with a stronger activation for the language functioning on the left hemisphere received a low-frequency protocol applied to the right hemisphere, whereas a high-frequency protocol was applied to the right hemisphere of those subjects with a stronger activation in this hemisphere. Both groups showed improvements in aphasia at comparable levels (Hara *et al.* 2017).

The exploratory study from Medina *et al.* (2012) showed less promising results. Although they observed an improvement on discourse productivity, in the other 3

measures of fluency they tested, namely, sentence productivity, grammatical accuracy and lexical selection, they did not find significant improvement in addition to those observed with sham stimulation. Waldowski *et al.* (2012), in turn, conducted a randomized controlled trial where they made some reservations about the effect of low-frequency rTMS stating that, even though this therapy can be favourable for the rehabilitation of patients with a lesion including the anterior part of language area, it cannot be assumed to be an effective method for all poststroke aphasic patients and that its efficacy should be confirmed. Seniów *et al.* (2013) also observed in their randomized controlled study that this approach was not effective for all aphasics and that the response could depend on individual differences and factors such as lesion site and extent. Interestingly, as previously reported by Waldowsky *et al.* (2012), they also described here a superior, although modest, improvement on those patients with a lesion affecting the frontal part of the language area (Seniów *et al.* 2013). According to Rubi-Fessen *et al.* (2015) 1 possible explanation for the lack of efficacy is the method Seniów *et al.* (2013) used to place the coil over the inferior frontal gyrus (10-20 method) which is said to be not as accurate as the surface distance measurement method adopted by the former.

TMS application to improve dysphagia

We included 8 studies focused on dysphagia recovery, published from 2009 until 2017. Out of the 8 studies, only two of these recruited patients in the chronic phase of the stroke. Cheng *et al.* (2017) pointed out a need for more studies confirming the efficacy of TMS in improving chronic dysphagia. Moreover, applying rTMS in the early phase can be a source of bias when interpreting the intervention results, since patients frequently recover their swallowing abilities in this stage by natural mechanisms (Park *et al.* 2013). rTMS was applied to the oesophageal cortical representation area (Khedr, Abo-Elfetoh, *et al.* 2009, Khedr and Abo-Elfetoh 2010), pharyngeal motor cortex (Park *et al.* 2013), suprahyoid muscle cortical area (Lee *et al.* 2015), mylohyoid cortical area (Verin and Leroi 2009, Du, Yang, *et al.* 2016, Park *et al.* 2017), tongue cortical area (Cheng *et al.* 2017) or abductor pollicis brevis cortical area (Lee *et al.* 2015). A great difference between protocols was observed. Studies applied low-frequency rTMS to suppress the nonlesioned hemisphere (Verin and Leroi 2009, Du, Yang, *et al.* 2016), or high-frequency to facilitate the excitability of either the unaffected (Park *et al.* 2013), the

affected (Khedr, Abo-Elfetoh, *et al.* 2009, Lee *et al.* 2015, Du, Yang, *et al.* 2016, Cheng *et al.* 2017) or even both hemispheres simultaneously (Khedr and Abo-Elfetoh 2010). Park *et al.* (2017) set up a treatment group where patients received high-frequency rTMS (HF-rTMS) over mylohyoid cortical area of the affected hemisphere followed by the same protocol over the unaffected hemisphere and a group receiving HF-rTMS to the affected hemisphere and sham stimulation on the unaffected hemisphere. Stimulation of either hemisphere is hypothetically valid since the swallowing musculature has its representation on both hemispheres and is innervated bilaterally (Du, Yang, *et al.* 2016).

All but one (Cheng *et al.* 2017) of the included studies demonstrated qualitatively good results in improving dysphagia, and were able to describe that patients recovered swallowing ability into different extents. Du *et al.* (2016) applied 1 Hz stimulation to the contralesional hemisphere or 3 Hz to the lesioned hemisphere over the mylohyoid cortical area. The authors reported 1 Hz significantly decreasing the cortical excitability of the unaffected hemisphere and, simultaneously, enhancing significantly the excitability of the affected side. On the other hand, using 3 Hz induced a significant increase of the affected hemisphere's excitability but regarding the unaffected hemisphere it only caused a modest change (Du, Yang, *et al.* 2016). However, according to Khedr *et al.* (2009), the recovery after delivery of 3Hz-rTMS to the affected hemisphere was related with an up-regulation of excitability in the corticobulbar projections from both hemispheres. Therefore, stimulation of the swallowing cortical representations of one hemisphere conducted to an increase in excitability in both hemispheres (Khedr, Abo-Elfetoh, *et al.* 2009). Oropharyngeal dysphagia is thought to be related with a smaller pharyngeal representation on the unaffected hemisphere that grows with return of swallowing (Park *et al.* 2013). Thus, Park *et al.* (2013) stimulated the pharyngeal motor cortex in the unaffected hemisphere with 5Hz-rTMS to increase its excitability and potentially enhance recovery from dysphagia. They reported significant improvement in the function of the pharyngeal phase but not in the oral phase (Park *et al.* 2013).

The neural basis of swallowing has been related to multiple cortical and subcortical areas (Lee *et al.* 2015). Lee *et al.* (2015) divided their patients into 2 groups. In the first group, they used HF-rTMS to stimulate a specific dysphagia-related target, namely the cortical region representing the suprahyoid muscle of the affected side, and described improvements of the swallowing function. In the other group they used the

same parameters to stimulate the cortical area representing the abductor pollicis brevis muscle of the affected side and also observed improvements in swallowing. Possible explanations for these findings are that they are due to the natural recovery or to stimulation of the interconnected site. In fact, once the white matter is interconnected, the stimulation of M1 could have triggered the stimulation of swallowing-related regions. Nevertheless, the authors reported that stimulation of the cortical region representing the suprahyoid muscle was more effective for dysphagia rehabilitation than stimulation of the cortical area representing the abductor pollicis brevis (Lee *et al.* 2015).

Park *et al.* (2017) compared the efficacy of the stimulation of both hemispheres to the stimulation of the affected hemisphere, both at 10 Hz, and observed a considerable superior improvement with bilateral stimulation. Actually, unilateral stimulation was not significantly more effective than sham stimulation in their work, contrarily to what was reported in the literature, which the authors justified with the variability on subjects' characteristics and the small sample size.

Cheng *et al.* (2017) conducted a double-blind, randomized, controlled study where they performed 5 Hz rTMS applied to the tongue cortical area of chronic patients' affected hemisphere and failed to observe significant effects of the treatment of the swallowing function. They identified various possible explanations for their negative results, including the stimulation protocol, which might not be optimized; the outcome measure that was used to assess swallowing function, that could lack sensitivity; the low severity of the deficits, and the absence of an additional therapy such as tongue or swallowing exercises.

Improvement of attentional deficits

We studied 8 publications focusing on neglect rehabilitation and 1 dealing with visual extinction. These were published between 2009 and 2016. The literature applied cTBS (Cazzoli *et al.* 2012, Fu *et al.* 2015) or LF-rTMS (Song *et al.* 2009, Lim *et al.* 2010, Kim *et al.* 2013, 2015) to the unaffected hemisphere over posterior parietal cortex or HF-rTMS to the stroke affected hemisphere, (Kim *et al.* 2013) as an adjuvant to conventional therapy. Moreover, Cha and Kim (2016) applied LF-rTMS over P3, based on the International 10/20 system, and Yang *et al.* (2015) stimulated the contralateral posterior parietal cortex either with cTBS, LF-rTMS or HF-rTMS.

For neglect rehabilitation, 88% of the studies included in this review admitted patients within the first 6 months, considering the mean time post-stroke. Kim et al. (2015) recruited subjects that had the stroke more than 1 year before entering the study.

All studies reported some improvement. However, although Lim *et al.* (2010) observed improvements on their pilot study in the line bisection test, indicating a potential enhancement of recovery in patients with neglect, the Albert test did not show significant differences between the results obtained with or without stimulation. The authors pointed out a need for a prospective randomized, sham-controlled study to evaluate the efficacy of stimulation on hemispatial neglect.

Kim *et al.* (2013) reported that HF significantly improved neglect more than LF-rTMS, which suggests future studies should evaluate the delivery of HF-rTMS to the affected hemisphere. Yang *et al.* (2015) compared different protocols of stimulation, using low-frequencies (1 Hz), high-frequencies (10 Hz) or cTBS and obtained the greater effectiveness with the continuous TBS, demonstrating more clear-cut results. Actually, as confirmed by diffusion tensor imaging, continuous theta burst stimulation enhanced connections of white matter's tract considerably, which suggests recovery at the structural level (Yang *et al.* 2015).

Kim *et al.* (2015) found significantly larger improvements with 10 sessions of LF-rTMS than with a single session. Furthermore, the treatment effects were superior for allocentric compared to egocentric neglect, which was explained by the fact that allocentric neglect patients had wider brain lesions and, thereafter, more severe baseline symptoms (Kim *et al.* 2015). Fu *et al.* (2015) provided initial evidence that increasing number of training runs per day and of stimulation days might enhance and lengthen cTBS efficacy on improvement of visuospatial neglect.

The effects of treatment were evaluated by different outcome measures. Inconsistent changes across outcome measures were noticed, which suggests that different forms of spatial neglect might show distinct test measure responses (Lim *et al.* 2010, Kim *et al.* 2013). Yang *et al.* (2015) observed different responses to the selected tests; patients showed significant greater improvements after intervention in star cancellation test, in comparison to line bisection test. The authors also assumed that this difference could have been originated by the functional heterogeneity of patients (Yang *et al.* 2015). Fu *et al.* (2015) suggested that applying a combination of multiple neglect

tests could be more sensitive than using only a test to detect and define the presence of visuospatial neglect.

Agosta *et al*. (2014) applied 1 Hz-rTMS over the left parietal cortex to reduce visual extinction due to right parietal damage and observed improvements in sustained attention only in the left visual field.

4.4. DISCUSSION

When searching for the application of repetitive TMS protocols to the rehabilitation of aphasia, dysphagia and neglect on stroke patients, it stands out the relatively smaller number of records retrieved, in comparison to the works that deal with motor function rehabilitation (Dionísio *et al.* 2018). This observation stresses the need for more studies evaluating the efficacy of this therapeutic intervention on these disabilities. Moreover, a great number of the studies included in this review recruited a small number of participants.

The influence of the recruitment strategy of the participants must be focus of particular attention, when considering potential sources of bias. We observed that in both dysphagia and neglect rehabilitation, in most of the studies, patients were recruited in the early phase after stroke. This may represent an important source of bias due to the natural recovery mechanisms that frequently occur at this stage (Park *et al.* 2013). On the other hand, most studies on aphasia focused their attention on the recovery of chronic patients, although shorter times after stroke are believed to be optimal to achieve the greatest modulation of plasticity (Kindler *et al.* 2012). The selection of the best moment to intervene, and the time dependence of the intervention should be further studied in larger cohorts of patients, including sham-stimulation groups.

Common to the studies focusing the recovery of aphasia and neglect on this review was the overall preference by applying inhibitory protocols, either low frequencies or continuous theta burst stimulation. Supporting this approach, Yang *et al*. (2015) found cTBS over the contralesional hemisphere to be more effective than low-frequency or high-frequency TMS on the rehabilitation of spatial neglect. Yet, Chieffo *et al*. (2014) and Kim *et al*. (2013) both reported superior improvements with high frequencies applied to the affected hemisphere in opposition to low frequency stimulation of the contralateral hemisphere in the rehabilitation of aphasia and neglect,

respectively. Moreover, Hara *et al*. (2017) stated that applying LF-rTMS to the right hemisphere in aphasia rehabilitation is not suitable for all patients and can even be detrimental on those patients with stronger activation for language on the right hemisphere. In their study, they obtained good results with an HF protocol over the right hemisphere (Hara *et al.* 2017). On the other hand, in the most part of the studies dealing with dysphagia, researchers chose to apply excitatory protocols, either high frequencies or intermittent theta burst stimulation.

The stimulation area was more consensual across studies. For aphasia rehabilitation, most part of the authors chose to stimulate the inferior frontal gyrus, while for neglect the posterior parietal cortex was selected. Dysphagia, in turn, presented a wider inter-study variability both on the stimulation area and on the design of the protocols.

The existing variability limits the conclusions that can be drawn through the observation of the included literature results. In fact, the lack of consistency across studies regarding the selection of the participants, of the protocols and even of the outcome measures that are used to evaluate the efficacy of intervention render definite conclusions about the best protocol not yet possible, because criteria for a meta-analysis are not fulfilled. Future studies are mandatory to define the optimal TMS parameters, number of sessions and suitable outcome measures, since protocol standardization would be crucial to enable the ultimate evaluation of the efficacy of this technique as a rehabilitative intervention.

As we had already observed in our previous work (Dionísio *et al.* 2018), another critical point is the inter-subject variability and patient stratification. We believe that authors should concentrate their efforts on understanding the different responses to protocols, select those patients that could benefit the most from TMS and define biomarkers that could act as predictors of greater efficacy.

Albeit there are several outstanding issues, almost all works included in this systematic review supported the use of TMS on stroke rehabilitation, presenting positive results on the improvement of communication, swallowing and attentional deficits, without the occurrence of serious adverse effects.

4.5. CONCLUSIONS

The application of repetitive TMS protocols to the recovery of a stroke event has been receiving increasing attention in the last years. Considering the novelty of this approach, there are still major issues that need to be investigated, being the most prominent the definition of the parameters of stimulation that bring out the best results. Still, the potential of this method is undeniable. The large majority of the included studies supported the use of TMS for this purpose, reporting statistically significant improvements in aphasia, dysphagia and neglect. Larger clinical trials are needed to validate the efficacy of this technique for stroke rehabilitation.

EXPERIMENTAL PROCEDURE

5.1. INTRODUCTION

This work was approved by the Ethical Committee of the Faculty of Medicine of the University of Coimbra and was conducted in accordance with the Declaration of Helsinki. All participants were informed about the procedures and gave their written informed consent. As mentioned before, in this Project we aimed to study the application of transcranial magnetic stimulation, and specifically of the continuous theta burst protocol, as a neuromodulatory tool. A single-pulse paradigm of TMS was applied to assess its impact in excitability, measured as changes in peak-to-peak amplitude of motor-evoked potentials. Although the measurement of MEPs' peak-to-peak amplitude can be a very useful tool for the assessment of brain excitability and TMS-induced plasticity, it could strongly benefit from the coupling with high-density electroencephalography (Huerta and Volpe 2009). Actually, an interesting field of research is the application of EEG to the study of the effects of brain stimulation on circuit-level events, particularly on network oscillations, since these reflect the processes taking place in intrinsic cortico-cortical loops and cortico-thalamic circuits (Huerta and Volpe 2009). Therefore, we resorted to electroencephalography to evaluate changes in brain electrical activity, namely in *alpha*, *mu* and *beta* rhythms. Electroencephalographic and electromyographic data were collected from both healthy subjects and stroke patients. Besides these procedures, patients also underwent magnetic resonance imaging (MRI) for their lesion characterization and Wolf Motor Function Test (WMFT) to evaluate their response to the protocol in terms of motor function, since this paradigm is being studied as a possible rehabilitative strategy for functional impairments. Moreover, while healthy subjects were evaluated before and after one session of cTBS, stroke patients had an additional visit, at 3 months' follow-up.

A schematic representation of the methodology and order of procedures is presented (**Figure 5.1.1**). Measurements taken in both healthy and post-stroke volunteers at baseline, before the TBS, enabled us to study the impact of an ischemic lesion in neurophysiology (results presented in **Chapter 6**). The comparison between EEG and sp-TMS data collected before and after the repetitive TMS allowed us to assess the effects of continuous TBS in health (results in **Chapter 7**) and in stroke (see **Chapter 8** for results).
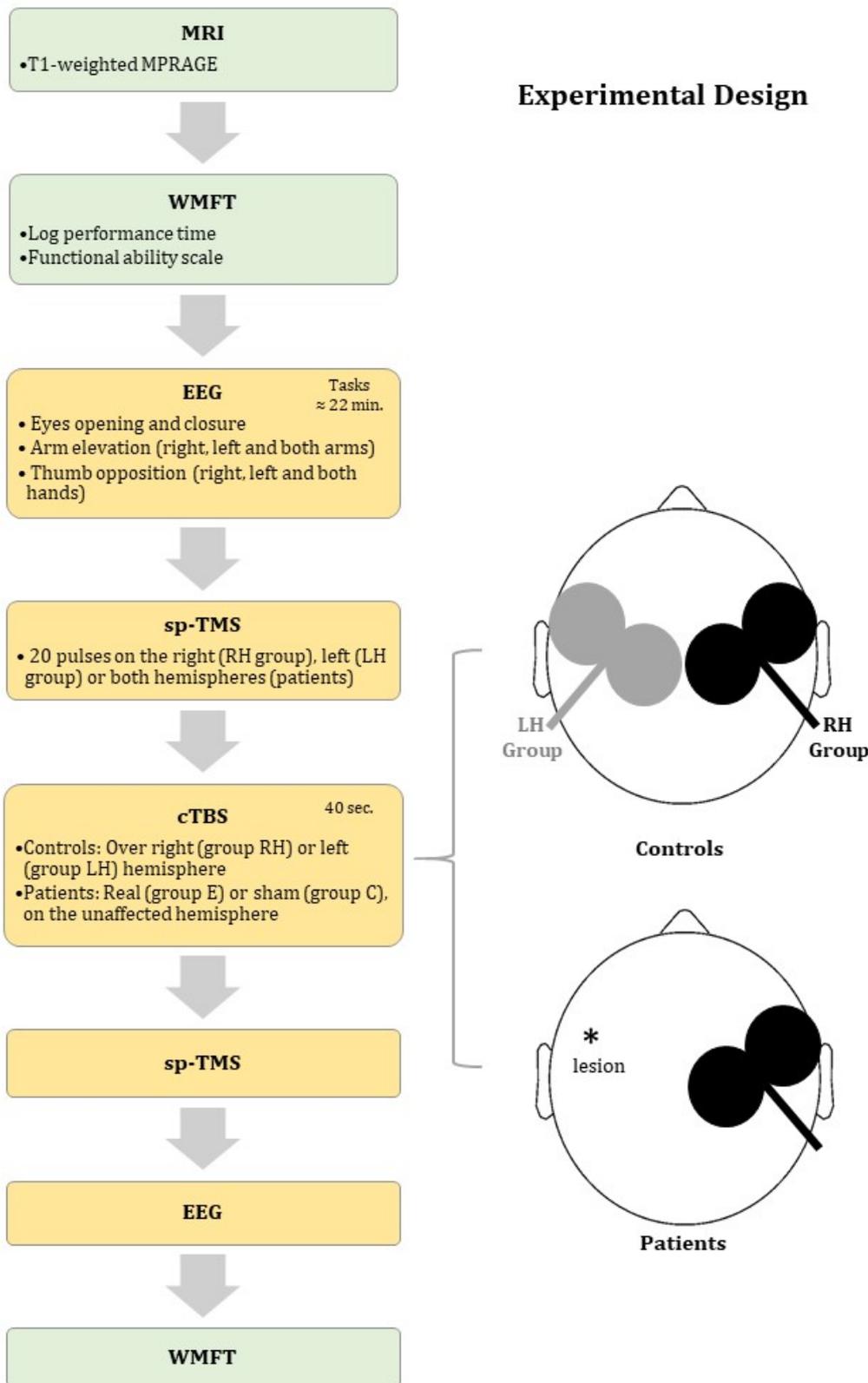
Figure 5.1.1 – Experimental design and procedures. Green boxes represent procedures that were performed only by patients, whereas yellow boxes include procedures that were common to all participants. RH and LH represent the healthy participants who received the cTBS protocol on the right and on the left hemisphere, respectively. Experimental group (group E) includes patients who received real stimulation, while in control group (group C) are those patients who received sham stimulation. Symbol * represents the stroke lesion, which could be either left- or right-sided.

5.2. PARTICIPANTS

Stroke patients were recruited from the Neurology Department and Stroke Unit of CHUC to participate in this experiment if they fulfilled the following inclusion criteria: (1) aged between 18 and 85 years; (2) time since stroke onset of 7 ± 3 days; (3) first-ever MCA ischemic stroke; (4) cortico-subcortical lesion; (5) upper-limb motor deficit; (6) ability to understand the tasks and (7) pre-stroke modified Rankin Scale ≤ 1. In addition, they were excluded if they met any of the exclusion criteria: (1) clinical instability; (2) cognitive impairment; (3) previously diagnosed dementia; (4) history of epilepsy; (5) global or posterior aphasia; (6) neglect; (7) pregnancy; (8) drugs or alcohol abuse; (9) contraindications to TMS. The recruitment phase lasted 21 months, wherein we included 10 post-stroke patients, who were randomized into two groups, one receiving active (experimental group, Group E) and the other receiving placebo stimulation (control group, Group C), in a 1:1 ratio. Clinical and demographic data are presented in **Table 5.2.1** (individual data in *Appendix A3*, **Table A3.1**). Handedness was assessed by an adapted Edinburgh Handedness Inventory questionnaire (Oldfield 1971), where maximum score was 36 points, indicating a strong right-handed dominance.

Table 5.2.1 – Clinical and demographic data of post-stroke volunteers [a].

	Total of participants N = 10	Group E N = 5	Group C N = 5
Age (years; mean ± SD)	67.10 ± 13.470	70.20 ± 8.701	64.00 ± 17.564
Gender (female/male)	4 / 6	1/4	3/2
Handedness (points; mean ± SD)	36.00 ± 0.000	36.00 ± 0.000	36.00 ± 0.000
Time since stroke (days; mean ± SD)	8.50 ± 1.581	8.20 ± 1.643	8.80 ± 1.643
Lesion side (right/left hemisphere)	4 / 6	3/2	1/4
NIHSS (mean ± SD)	6.40 ± 3.718	5.60 ± 2.302	7.20 ± 4.919
Baseline WMFT log time (mean ± SD)	2.14 ± 0.651	2.25 ± 0.729	2.04 ± 0.627
Baseline WMFT FAS (points; mean ± SD)	48.80 ± 31.255	45.80 ± 36.341	51.80 ± 29.235

[a] Abbreviations: FAS – Functional Ability Scale, NIHSS – National Institutes of Health Stroke Scale, SD – Standard deviation, WMFT – Wolf Motor Function Test

Twenty age-matched healthy controls were recruited from our volunteers' database and from ANAI – *Associação Nacional de Apoio ao Idoso*. Ten individuals were stimulated with cTBS on the right hemisphere (Group RH), whereas on the remaining

half the protocol was administered over the left hemisphere (Group LH). Demographic data of healthy individuals is compiled in **Table 5.2.2** (individual data in *Appendix A3*, **Table A3.2**). The age of the participants varied from 41 to 75 years old (mean age Group RH: 61.50 ± 11.965 years, Group LH: 58.90 ± 10.939 years).

Table 5.2.2 – Demographic data of healthy volunteers [a].

	Total of participants
	N = 20
Age (years; mean ± SD)	60.20 ± 11.237
Gender (female/male)	11 / 9
Handedness (points; mean ± SD)	35.75 ± 0.550
Education (years; mean ± SD)	15.00 ± 2.938

[a] Abbreviations: SD – Standard deviation

5.3. REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Stimuli were applied with a MagPro X100 magnetic stimulator, equipped with a 70-mm figure-of-eight coil (MagVenture, Denmark). During stimulation, participants were seating comfortably in an armchair and wearing earplugs. Also, they were asked to relax completely during the experiment, to avoid activation of the hand muscles, that could potentially affect the results (McAllister *et al.* 2011).

We administered TMS to the hotspot of the primary motor cortex, at 45° to the sagittal plane. M1 was selected as the stimulation target since it is believed that it plays the most important role in executive movements, particularly in the recruitment of specific muscles for the upper-limb motor performance (Plow *et al.* 2016). Also, as it was described in **Chapter 3**, it is the main target when concerning motor post-stroke rehabilitation, partially because of its ease of detection. Continuous theta burst stimulation was applied for 40 seconds, as previously described in the literature: with 3 pulses at 50 Hz being applied every 200 milliseconds, for a total of 600 pulses (Sandrini *et al.* 2011). The intensity was defined according to the active motor threshold (aMT), determined as the minimum intensity eliciting at least one visible minimal muscle twitch on the hand, out of three trials, during isometric contraction of the upper limbs.

The effects of the cTBS were evaluated by different measurements, performed before the protocol and 5 minutes after the end of the stimulation, when the greatest effects are thought to take place (Di Lazzaro *et al.* 2005, Chung *et al.* 2016). Also, Vernet *et al.* (2014) reported that the modulation of MEPs peak-to-peak amplitude at 5 minutes post-TBS reveals the greatest within-subject reproducibility. All data were recorded within 1 hour following stimulation, which is believed to be the duration of the neurophysiological effects for the application of cTBS as described (Sandrini *et al.* 2011).

5.4.   SINGLE-PULSE TRANSCRANIAL MAGNETIC STIMULATION

We measured peak-to-peak amplitude of motor-evoked potentials on the stimulated hemisphere of healthy subjects, before and after the repetitive stimulation to assess changes in excitability induced by the protocol. Concerning stroke patients, measurements were performed both in the affected and unaffected hemispheres. This was achieved by giving 20 single-pulses of TMS (a pulse every 6 seconds, approximately), with the same intensity before and after the cTBS protocol, and recording MEPs through surface electromyography (Ag/AgCl electrodes placed in a belly-tendon montage), with a BIOPAC MP-150 system, equipped with an EMG 100C amplifier (Biopac Systems, CA, USA). Electromyographic signal was recorded at 2.500 kHz sampling rate, with a 1000 gain. Signal recording and amplitude measurements were performed with *Acqknowledge* 4.2 software (Biopac Systems, CA, USA).

5.5.   ELECTROENCEPHALOGRAPHY

A high-density electroencephalogram, with 64 channels (QuickCap, NeuroScan, USA) placed according to the International 10-20 system, was recorded for all subjects, before and after continuous theta burst stimulation, by means of a SynAmps2 RT amplifier and Scan 4.5 software (Compumedics, Charlotte, NC). First of all, we cleaned the scalp with Nuprep EEG&ECG abrasive gel and alcohol at 96% to reduce skin impedance. Then, after choosing the adequate size for the subject, we put an EEG cap and filled the 64 electrodes with conductive gel, to conduct the brain electrical signal. The impedances were maintained below 10kΩ to ensure we got the best quality signal

possible. Signal was acquired at a sampling rate of 1000 Hz, low-passed at 200 Hz and high-passed from the DC level.

Before the EEG, we explained all individuals what they would have to do during the acquisition. Subjects were instructed to perform three different tasks following "GO" and "STOP" commands, which were marked during the recordings with *online* triggers. On the first task (**Figure 5.5.1**), participants had to keep the eyes opened for 10 seconds, and then close them for another 10 seconds, each trial. Each instruction was given nine times, totalizing 180 seconds for this task.

Figure 5.5.1 – Representation of the first task, where the participant had to open and close the eyes, according to the instructions.

Concerning motor execution, subjects had to perform six repetitions of the tasks with each upper-limb individually and, afterwards, with both simultaneously. The first motor task was the elevation of the arms at 90° (**Figure 5.5.2**), where the participant had to elevate the arm and then lower it, maintaining each condition (arm up/down) for 15 seconds.
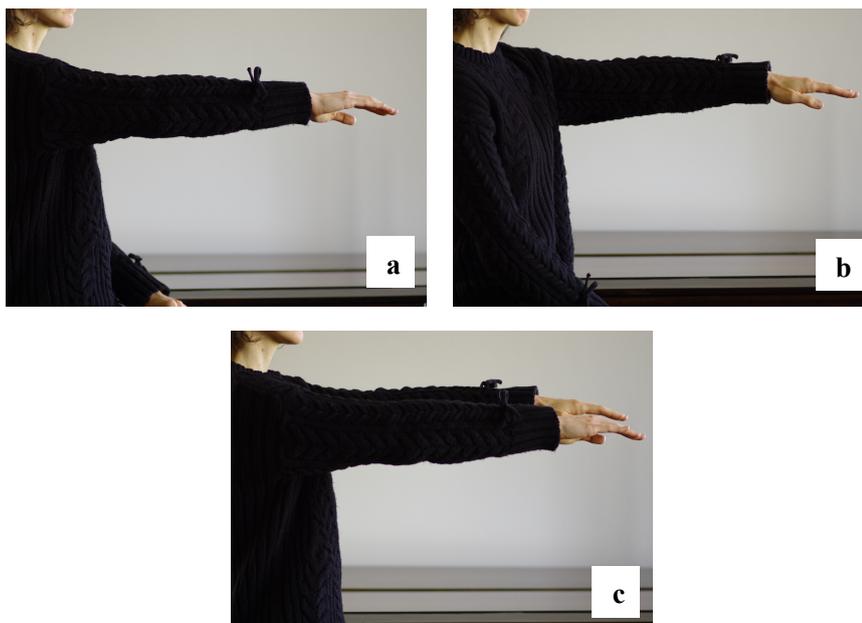
Figure 5.5.2 – Representation of the first motor task, 90° elevation of the right (a) and left (b) upper-limbs individually and in simultaneous (c).

The last movement consisted on thumb opposition (**Figure 5.5.3**), where the subject was instructed to touch with the thumb on the other fingers consecutively for 15 seconds, and then stop the movement, reposition and keep still for another 15 seconds.
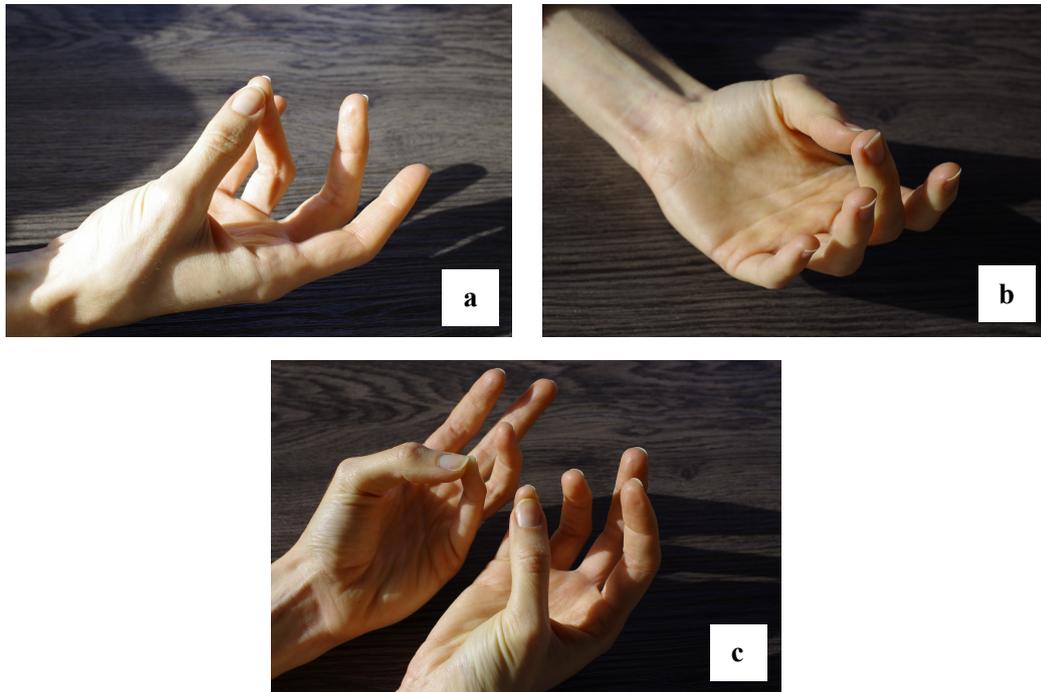
Figure 5.5.3 – Illustration of the second motor task: opposition of the thumb from the right (a) and left (b) hands and bimanual thumb opposition (c).

The complete motor paradigm lasted 1080 seconds (540 seconds per task).

We processed EEG data *offline* with Scan 4.5 (Compumedics, Charlotte, NC) and EEGLAB (Delorme and Makeig 2004), a MATLAB toolbox (v.14.1.1b). First of all, we filtered the signal with Scan Edit 4.5, from 1 to 45 Hz. Then, pre-processing and power quantifications were carried out in MATLAB (version R2017b, The MathWorks, USA), using EEGLAB and custom scripts [adapted from our previous works by Castelhano *et al.* (2013) and by Silva *et al.* (2016)]. All data was down-sampled from 1000 Hz to 250 Hz. We used average re-reference approach. We removed those channels with bad signal and eliminated muscle artefacts through visual inspection. Components such as eye movements and blinks were rejected by computing Independent Component Analysis (ICA).

We computed amplitude and phase throughout all time window for a large band of frequencies, ranging between 5 to 40 Hz, in steps of 1 Hz (resolution of 1 Hz/frequency bin). The time-frequency analysis was performed accordingly to the method described by Uhlhaas *et al.* and others (Lachaux *et al.* 1999, Rodriguez *et al.*

1999, Uhlhaas *et al.* 2006, Melloni *et al.* 2007, Castelhano *et al.* 2013), through the application of the pseudo Wigner-Ville transformation. Power quantification in the frequencies of interest was obtained within the selected electrode clusters (for electrode selection see **Figure 5.5.4**), in the time range of the epochs defined below.
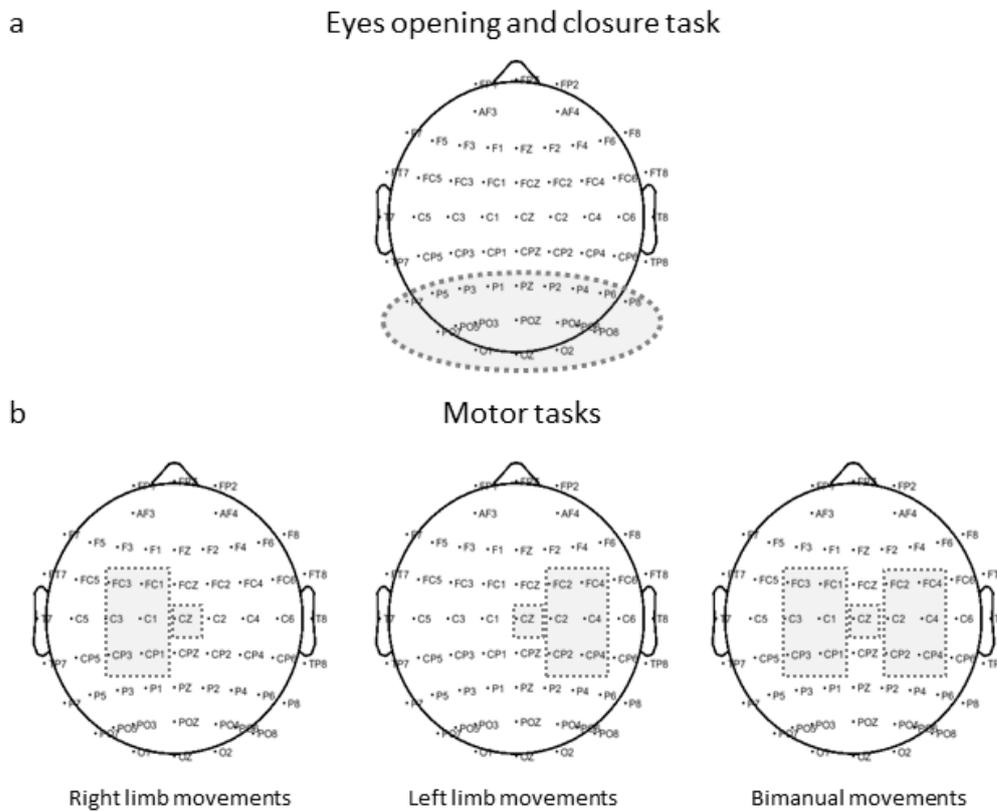
Figure 5.5.4 – Schematic representation of the electrode clusters selected for the quantification of visual *alpha* (a) and *mu* and *beta* rhythms (b).

For the eyes opening and closure, epochs were extracted between -2000 milliseconds and 10000 milliseconds, time-locked to the event, with the baseline being defined from -2000 milliseconds to 0. Quantification of *alpha* power was carried out for the 8–13 Hz frequency band.

For the motor tasks, we carried out quantification of *mu* (10–12 Hz) and *beta* (15–25 Hz) rhythms from -2000 to 0 milliseconds (pre-movement and preparation) and from 0 to 4000 milliseconds (execution, time-locked to the beginning of the movement), wherein epochs comprised between -2000 and -1500 milliseconds were selected as baseline.

Moreover, we plotted scalp ERS/ERD mapping of *mu* and *beta* rhythms with eConnectome (He *et al.* 2011), by using the default parameters.

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5.6. MAGNETIC RESONANCE IMAGING

In addition to the measurements taken for healthy participants, patients also performed a structural 3D T1-weighted MPRAGE (Magnetization-Prepared Rapid Acquisition Gradient Echo) sequence, in order to confirm lesion location and characteristics. Images were collected on a 3-Tesla MRI scanner (Magnetom TIM Trio, Siemens, Erlangen, Germany), with a phased array 12-channel birdcage coil (Siemens). The following parameters were implemented: repetition time (TR) = 2530 ms, echo time (TE) = 3.42 ms, inversion time (TI) = 1100 ms, flip angle (FA) = 7°, 176 single-shot slices, voxel size $1 \times 1 \times 1$ mm^3, field of view (FOV) 256×256 mm^2.

5.7. WOLF MOTOR FUNCTION TEST

We used WMFT to evaluate the functionality of the paretic upper-limb, in stroke patients. We asked participants to execute 15 timed tasks, listed in *Appendix A4* (**Table A4.1**), and registered the performance time for each task, in seconds. The maximum period allowed for completing a single task was 120 seconds. If the patient failed to complete a given task, we attributed the maximum duration. Besides the duration of the movement, we also analysed its quality, as specified in the functional ability scale (FAS). We attributed a number between 0 and 5 for the quality of the exercise, wherein 5 indicates a movement that appears to be normal, with a total maximum score of 75 points. The full description of this 6-point ordinal scale is presented in **Figure A4.1**, *Appendix A4*.

Chapter

6

RESULTS

THE NEUROPHYSIOLOGICAL IMPACT OF SUBACUTE STROKE: CHANGES IN CENTRAL *BETA* CORTICAL OSCILLATIONS EVOKED BY BIMANUAL FINGER MOVEMENT

Objective: To design more effective interventions for stroke rehabilitation, there is a need for understanding the neuroplastic changes that take place. We aimed to study changes in neurophysiology following an ischemic stroke, both at rest and with motor planning and execution. *Methods*: We included 10 post-stroke patients, between 7 and 10 days after stroke, and 20 age-matched controls to assess changes in cortical excitability via transcranial magnetic stimulation and in dynamics of oscillations, by recording electroencephalography. *Results*: We found significant differences in cortical oscillatory patterns comparing stroke patients with healthy participants, particularly on *beta* rhythm during motor planning ($p = 0.011$) and execution ($p = 0.004$) of a complex movement with fingers from both hands simultaneously. A stroke lesion induced a decrease in event-related desynchronization in patients, in comparison to controls, providing evidence for increased inhibition. We did not detect significant inter-hemispheric asymmetries in patients ($p > 0.570$). *Conclusions*: After a stroke lesion, the dynamics of cortical oscillations is changed, with an increasing neural *beta* synchronization in the course of motor preparation and performance of complex bimanual finger tasks. *Significance*: The observed patterns may provide a potential functional biomarker that could be used to predict motor recovery in subacute stages.

6.1. INTRODUCTION

Stroke represents the third major cause of death and is one of the leading sources of disability, contributing to a decline in the global quality of life. Although several approaches are applied to the rehabilitation of patients, current interventions lack efficacy (Dionísio *et al.* 2018).

In order to develop new and more effective interventions for neurorehabilitation, and particularly, for the rehabilitation of stroke patients, it is fundamental to understand neuroplastic changes following the event. After a brain lesion, neural networks are damaged, which triggers the reorganization of the connections. Plastic changes occur not only on the lesioned but also in the contralateral hemisphere (Alia *et al.* 2017). It is frequently reported in the literature that the activity of the unaffected hemisphere increases in the first days after the cerebrovascular accident (Caleo 2015, Alia *et al.* 2017). After this period, at 3 to 6 months following the event, a relative increase in the activity of the areas adjacent to the lesion, is frequently observed, concurrent with functional improvements (Caleo 2015).

Functional techniques to assess brain changes include electroencephalography, magnetoencephalography and functional magnetic resonance imaging (Alia *et al.* 2017). Electroencephalography (EEG) has been a major contributor to the understanding of the physiology of brain reorganization (Iyer 2017) in particular in which concerns the study of dynamics of oscillations (Stępień *et al.* 2011).

The visual *alpha* rhythm is known to respond to a stimulus or instruction with a decrease in amplitude or power, resulting in an event-related desynchronization (ERD). Synchronization (ERS) occurs in the absence of stimuli or idle states. It is therefore believed that *alpha* ERS is associated to cortical inhibition, whereas ERD is related to the reduction of inhibition, in turn (Assenza *et al.* 2017). Also, performing a voluntary movement or receiving instructions to execute a motor task are generally associated to a decrease in *beta* rhythms (Assenza *et al.* 2017). Changes in neural synchronization and oscillatory activities can play a role in the pathophysiology of distinct disorders, such as in stroke (Assenza *et al.* 2017).

Here, we determined motor thresholds as a measure of cortical excitability and assessed ERD and ERS in the course of motor tasks, both in healthy subjects and in post-stroke patients. To the best of our knowledge, this is the first time that the

neurophysiology of stroke patients is analysed by EEG preceding and during motor tasks performed with both the affected and unaffected arms and hands, individual and simultaneously, and compared with a control healthy sample that did the same experiment. Our aim was to study the impact of ischemic stroke in brain neurophysiology at rest and during motor preparation and execution.

6.2. STATISTICAL DATA TREATMENT

Statistical tests were computed on the SPSS Statistics software, version 24 (IBM SPSS Statistics, IBM Corporation, Chicago, IL), and we adopted a significance level of 5% for all tests. We ran Mann-Whitney U test to address differences between healthy individuals and stroke patients, in cortical excitability and oscillatory patterns. Moreover, we applied the same test to investigate differences between groups of participants in age and handedness. For differences in gender we used Fisher's exact test. Hemispheric asymmetries in patients were tested with the Wilcoxon test. To check for correlations between changes in ERS/ERD and the severity of the motor deficits, as evaluated by NIHSS and WMFT scores, we assessed normality of data with Shapiro Wilk tests and determined Pearson coefficients.

6.3. RESULTS

The demographic characteristics of the stroke patients who were included in our sample did not differ significantly from those pertaining to the healthy participants, concerning age (U = 67.000, p = 0.150), gender (p = 0.700) or handedness as assessed by an adapted Edinburgh Handedness Inventory questionnaire (Oldfield 1971) (U = 80.000, p = 0.272).

As described in the methods' section (**Chapter 5**), we measured individual active motor threshold for both healthy subjects and patients. Patients showed no significant differences in aMT values on the unaffected hemisphere, when comparing with healthy participants (U = 70.500, p = 0.785), thereby showing that these hemispheres were matched, and enabling a fair comparison of neurophysiological profiles.

Concerning changes in neurophysiology following the stroke event, we assessed *alpha* rhythm at rest and motor rhythms, namely *mu* and *beta* bands, during motor

planning and execution. One patient was not able to complete the EEG recording; therefore, for EEG analysis we had a sample size of 9 patients and 20 healthy volunteers.

Differences between healthy participants and stroke patients in *alpha* power of the posterior area were not significant, either when the subjects had the eyes opened (U = 68.000, p = 0.317) or closed (U = 72.000, p = 0.417). *Mu* rhythm did not show significant group differences when performing motor tasks with each upper-limb (healthy or stroke-affected) individually or both simultaneously, either on arm elevation (p ≥ 0.183) or thumb opposition (p ≥ 0.077). *Beta* rhythm was not significantly altered in stroke patients comparing with healthy participants for arm elevation (p ≥ 0.216). However, we found significantly increased *beta* power levels on the central motor areas (see **Figure 5.5.4**, **Chapter 5**, for selection of electrode clusters) in patients comparing with healthy participants during simultaneous bimanual finger opposition, both during pre-movement/preparation and on time-locked beginning of movement (U = 37.000, p = 0.011, **Figure 6.3.1a** and U = 31.000, p = 0.004, **Figure 6.3.1b**, respectively) – individual data in *Appendix A5*. The differences in the *beta* band during the thumb opposition of both hands in simultaneous coexisted with changes in the topography of individuals after a cerebrovascular lesion.

Central *beta* bimanual finger opposition
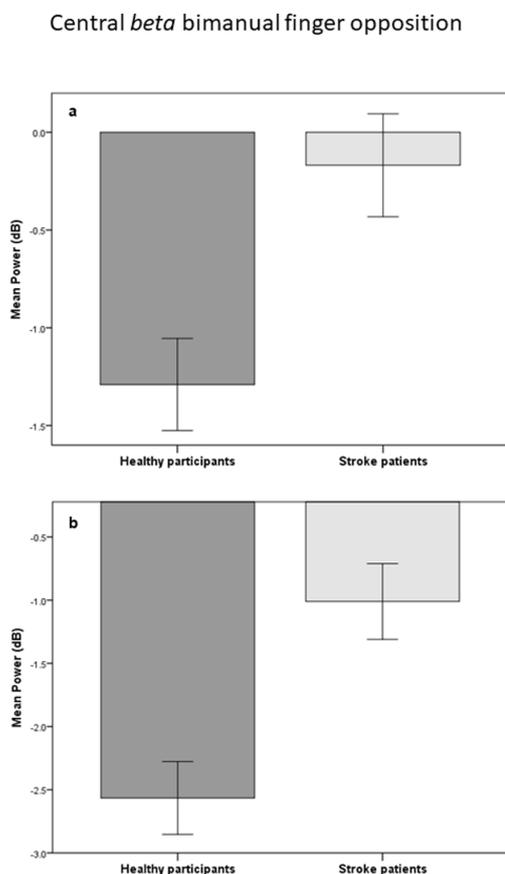
Figure 6.3.1 – Significant differences (p<0.05) are observed between healthy participants and stroke patients in power of the *beta* rhythm in the pre-movement and preparation (a) and in the time-locked beginning (b) of bimanual finger opposition. Error bars represent +/- 1 SE.

In **Figure 6.3.2** we present an example of scalp ERS/ERD mapping of *beta* power at rest (a) and during bimanual thumb opposition task (b) from a healthy individual and from a patient who had a stroke lesion on the right middle cerebral artery.

In patients, *beta* power in selected central electrodes (C3 and C4) did not show significant asymmetries between the affected and the unaffected hemispheres on the preparation ($Z = - 0.652$, $p = 0.570$) or execution ($Z = - 0.178$, $p = 0.910$) of bimanual thumb opposition.

We found a significant moderate negative correlation between *beta* power during the execution of bimanual thumb opposition and the velocity of execution in WMFT tasks ($r_s = - 0.675$, $p = 0.046$).
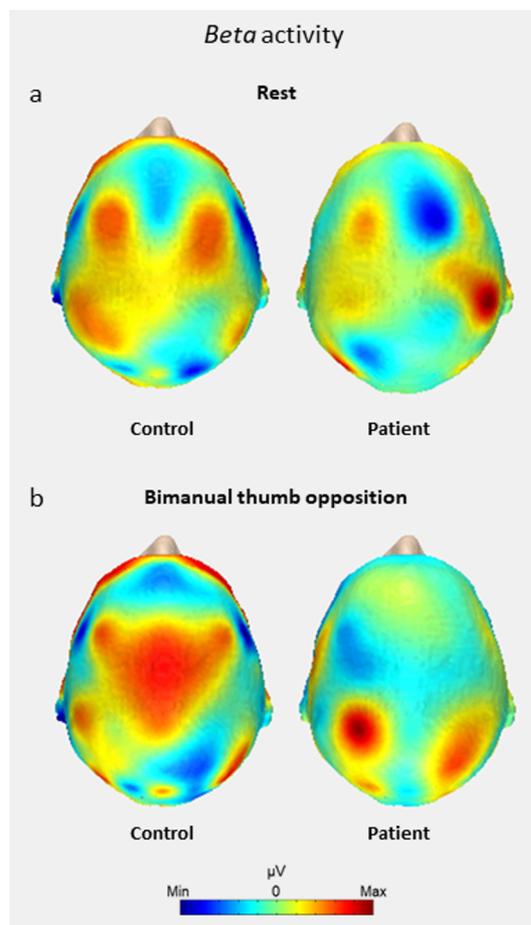
Figure 6.3.2 – Topographic maps for the *beta* rhythm of a healthy participant and a patient who had a stroke lesion on the right hemisphere (middle cerebral artery), at rest (a) and during motor preparation and execution of thumb opposition of both hands in simultaneous (b). Each scalp map represents the mean of ERS/ERD on the corresponding time period.

6.4. DISCUSSION

The study of the hemisphere contralateral to the stroke lesion seems to be critical for the investigation of post-stroke alterations (Prashantha *et al.* 2013). The active motor threshold was assessed on the unaffected hemisphere, in patients, and randomly on the right or left hemisphere of healthy participants. After stroke, the hemisphere contralateral to the lesion is known to become overactive, which raises the hypothesis that the aMT in this hemisphere would be reduced. Our results however indicated only a non significant trend for lower active motor threshold, suggesting that the hemisphere contralateral to the lesion was still relatively preserved. This is consistent with other findings. For example, Prashantha *et al*. analysed changes in the resting motor threshold of the non-affected hemisphere compared with healthy controls and reported no differences at baseline (2 weeks after stroke onset), a trend for a decrease after 4 weeks of the lesion and a significant reduction on the second follow-up, at 6 weeks post-stroke (Prashantha *et al.* 2013).

We found significant differences between patients and healthy participants on motor rhythms during thumb opposition, when performing the task with both hands simultaneously. These were observed as higher *beta* power for patients, which suggests a more inhibited state on central motor areas of stroke patients, when comparing to healthy subjects. We suggest that post-stroke changes in oscillatory activity during bimanual thumb opposition were not circumscribed to the areas located near the lesion, which is supported by our results showing no significant asymmetries between power on the electrode located in affected *versus* unaffected hemispheres. Besides, patients who had more severe deficits (with slower execution in WMFT tasks), showed a correlated decrease in desynchronization during bimanual thumb opposition, as shown by higher *beta* power. This significant moderate correlation suggests that future studies, with large sample sizes, should further explore the potential of *beta* levels as biomarkers for stroke recovery of motor deficits. Interestingly, Fu *et al*. (2006) studied shoulder-elbow movement of the affected limb and also reported a significant decrease post-stroke in peak ERD% in the *mu* range (8–12 Hz), comparing with healthy participants.

Regarding arm elevation task, we were not able to detect significant differences between groups. This is consistent with the notion that movement complexity can influence the brain activation of the lesioned primary motor cortex (Foltys *et al.* 2003).

Puh *et al.* (2007) pointed out finger movements as being the most suitable instruction when the focus is motor rehabilitation. The higher complexity involved in thumb opposition, associated to the motor control required for the transitions between fingers (Puh *et al.* 2007), can possibly explain the specificity of our results. This also provides insights into task dependence when probing neurophysiological changes in stroke.

6.5. CONCLUSIONS

We found that cerebrovascular lesions induced by ischemic stroke alter neurophysiological motor response status in both hemispheres translating into an alteration in event-related synchronization and desynchronization, particularly at *beta* frequencies during motor planning and execution of complex bimanual movements.

RESULTS

CONTINUOUS THETA BURST STIMULATION INCREASES CONTRALATERAL *MU* AND *BETA* RHYTHMS WITH ARM ELEVATION: IMPLICATIONS FOR NEUROREHABILITATION

The study of the physiological effects underlying brain response to transcranial magnetic stimulation is important to understand its impact on neurorehabilitation. We aim to analyse the impact of a transcranial magnetic stimulation protocol, the continuous theta burst (cTBS), on human neurophysiology, particularly on contralateral motor rhythms. cTBS was applied in 20 subjects over the primary motor cortex. We recorded brain electrical activity pre- and post-cTBS with electroencephalography both at rest and while performing motor tasks, to evaluate changes in brain oscillatory patterns such as *mu* and *beta* rhythms. Moreover, we measured motor-evoked potentials before and after cTBS to assess its impact on brain's excitability. On the hemisphere contralateral to the protocol, we did observe a significant increase in *mu* (p = 0.027) and *beta* (p = 0.006) rhythms from pre- to post-cTBS, at the beginning of arm elevation. The topology of action planning and motor execution suggests that cTBS produced an inhibitory effect that propagated to the contralateral hemisphere, thereby precluding the expected/desired excitation for therapy purposes. This novel approach provides support for the notion that this protocol induces inhibitory changes in contralateral motor rhythms, by decreasing desynchronization, contradicting the ipsilateral inhibition *vs.* contralateral disinhibition hypothesis. Our results have implications for personalized cTBS usage as a rehabilitation intervention, suggesting that an unexpected propagation of inhibition can occur.

7.1. INTRODUCTION

Transcranial magnetic stimulation (TMS) is a well-known non-invasive neuronal stimulation technique (Amassian and Maccabee 2006, Groppa *et al.* 2012) which has been applied to the study of several neurologic and psychiatric disorders, including the investigation of its therapeutic potential (George *et al.* 1999, Kobayashi and Pascual-Leone 2003, Chipchase *et al.* 2012, Heaton 2012).

Repetitive TMS allows the modulation of excitability for a period exceeding stimulation duration (Heaton 2012). Depending on the selected parameters, it can produce either excitatory or inhibitory modulation (Kobayashi and Pascual-Leone 2003, Rossi *et al.* 2009).

Despite its undoubted potential, large variability has actually been reported in terms of stimulation responses, even in which concerns response polarity (Heaton 2012), with some individuals showing inhibition and others excitation following the same protocol. Substantial effort is still required to understand the underlying brain responses, compare protocols and confirm their efficacy (Heaton 2012).

Here, we aimed to analyse a TMS protocol, seeking to unravel its effects on brain activity and complex network responses, as expressed by cortical oscillatory responses. In this study we focus on continuous theta burst stimulation (cTBS), a patterned form of repetitive TMS first proposed by Huang *et al.* (2005), where 3 pulses at 50 Hz are applied every 200 ms (5 Hz) for a total duration of 40 s (Sandrini *et al.* 2011). The cTBS protocol is an inhibitory protocol with the effect lasting up to 1 h when it is performed for 40 s (Sandrini *et al.* 2011). Still, the variability of the responses, including duration of the effects, associated with other repetitive TMS protocols has also been repeatedly reported by several authors investigating cTBS applications (Jannati *et al.* 2017, Lowe and Hall 2018, Rocchi *et al.* 2018).

It is widely accepted that motor brain activity is controlled between hemispheres in a task-dependent manner, in healthy individuals. This push-pull mechanism is believed to occur through interhemispheric inhibition. Some pathologies can affect such control of activity across hemispheres. TMS can be used as a therapeutic strategy, by applying high or low frequencies to increase or decrease the excitability on the stimulated hemisphere, respectively, with the goal to restore normal activity patterns (Dionísio *et al.* 2018). Some theories postulate that hemispheric inhibition can help to

boost activity in the contralateral (lesioned) hemisphere. Therefore, it remains an important question whether the repetitive TMS protocols can affect not only the stimulation site but also the contralateral areas, through interhemispheric connections, and whether this leads to increased/decreased activity in the contralateral hemisphere. To test this hypothesis, we applied cTBS to healthy volunteers to evaluate its impact on human neurophysiology, and to test its contralateral effects. A general *a priori* expectation would be that such effects should be excitatory, through disinhibition due to ipsilateral inhibition, but this remains controversial. It is also important to recognize that most studies just look at motor-evoked potentials (MEPs); whereas, local and remote EEG effects of cTBS in the context of a motor task are rarely investigated and might be more complex than expected. Actually, Rocchi *et al.* (2018) point out the possibility of MEP's amplitude information being incomplete and not reflecting all cortical outputs. It has been reported that action planning and motor execution involve different processing mechanisms, indexed by distinct frequency bands (in intervals such as 8-10, 10-12 and 15-25 Hz) (Pfurtscheller and Lopes Da Silva 1999, Pfurtscheller *et al.* 2000, Pineda 2005, Ilmoniemi and Kičić 2010, Ramos-Murguialday and Birbaumer 2015). Therefore, we studied cortical oscillatory patterns (namely *mu* and *beta* rhythms) with electroencephalography (EEG), before and after the stimulation. We aimed to study if the stimulation protocol affects contralateral motor rhythms, as hypothesized according to the above-mentioned ipsilateral inhibition *vs.* contralateral disinhibition hypothesis. We recorded electrical cerebral activity at rest to evaluate the physiological state and during motor execution to study brain oscillatory patterns (event-related synchronization (ERS) and desynchronization (ERD)). Increased synchronization and amplitude of such oscillatory patterns reflect idle states characterized by inhibited processing of visual information, somatosensory input or motor output, as a response to a stimulus or event (Pfurtscheller *et al.* 1996, 1997). These inhibition-related rhythms are referred to as occipital *alpha* rhythm, for visual areas, or central *mu* rhythm or *beta*, concerning sensorimotor areas (Pfurtscheller *et al.* 1996, 1997). However, these rhythms can be blocked in an activated state (such as in motor readiness/movement preparation), where cortical neurons are excited and neuronal assemblies are likely to work individually, by a phenomenon described as ERD (Pfurtscheller *et al.* 1997). The extent of ERD is proportional to the extent into which neural networks are recruited during the execution of a given task (Pfurtscheller *et al.*

1996). On the other hand, the resting or idling of those areas is associated to a decrease of excitability or inhibition of neuronal populations which remain in a more synchronous mode (Pfurtscheller *et al.* 1997). Therefore, such large-scale idle synchrony, translates into an ERS (Pfurtscheller *et al.* 1997). Motor-evoked potentials, quantified by electromyography (EMG), were also evaluated, as a measure of motor cortex output.

To the best of our knowledge, this is the first study that so far assesses the effects of cTBS applied to the primary motor cortex, using both EMG for measuring motor output and EEG for studying brain oscillation patterns during motor tasks in healthy subjects, to predict physiological effects and their implications for neurorehabilitation. We found an increase in motor rhythms (*mu* and *beta*) of the non-stimulated hemisphere, after continuous theta burst stimulation, which we interpret as an indication that inhibitory ipsilateral effects might actually propagate to the contralateral hemisphere instead of the prediction raised by the ipsilateral inhibition *vs.* contralateral disinhibition hypothesis.

7.2. STATISTICAL DATA TREATMENT

The statistical analysis of the data was performed on the SPSS Statistics software, version 24 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). We adopted a confidence interval of 95%. Normality of data was assessed by the Shapiro-Wilk Test. Differences in the occurrence of EEG artefacts associated with eye movements and blinks were evaluated with Paired t student test. To study intergroup differences in demographic data, we used the Mann-Whitney U test for age, handedness and education, and Fisher's exact test, for gender. The Wilcoxon test was applied to evaluate the effects of the cTBS protocol, comparing the post- to the pre-stimulation measures.

7.3. RESULTS

There were no statistically significant differences between subgroups concerning age (U = 40.500, p = 0.490), gender (p = 1.000), handedness assessed by an adapted Edinburgh Handedness Inventory questionnaire (Oldfield 1971) (U = 39.500, p = 0.458) or education (U = 37.000, p = 0.336). Severe adverse events were not observed.

Motor-evoked potentials

We found a bimodal effect of the protocol, with some participants showing an amplitude increase and the others revealing a decrease (positive and negative peaks, with scarce near null responses). Indeed, the direction of the effects was balanced across participants, with 40% of subjects exhibiting an increase of the peak-to-peak amplitude of the MEPs on the stimulated hemisphere. Differences between pre- and post-cTBS were not statistically significant, in line with the bimodal effect ($Z = -0.511$, $p = 0.639$).

Electroencephalography

Independent Component Analysis (ICA) was computed and components including eye movements and blinks were removed. In any case, prior to removal, the rate of occurrence of these artefacts was similar between pre- and post-stimulation conditions, for both tasks (arm elevation: $t = -0.029$, $p = 0.977$; thumb opposition: $t = 1.259$, $p = 0.223$).

Differences in visual *alpha* power between pre- and post-cTBS were, as expected, not significant in the control condition, either when the subjects had the eyes opened ($Z = -0.933$, $p = 0.368$) or closed ($Z = -0.597$, $p = 0.571$).

Concerning the motor rhythms, we found significant differences in power between pre- and post-cTBS. Changes are visible in the topography maps shown in **Figure 7.3.1** (example participant allocated to the RH group), during the beginning of arm elevation for both *mu* and *beta* rhythms, pre- and post-stimulation. These maps illustrate notable changes induced by the protocol, showing an interesting inversion of the signal polarity after cTBS and a bilateral mirror symmetric activity pattern in central areas (suggesting similar effects across hemispheres).
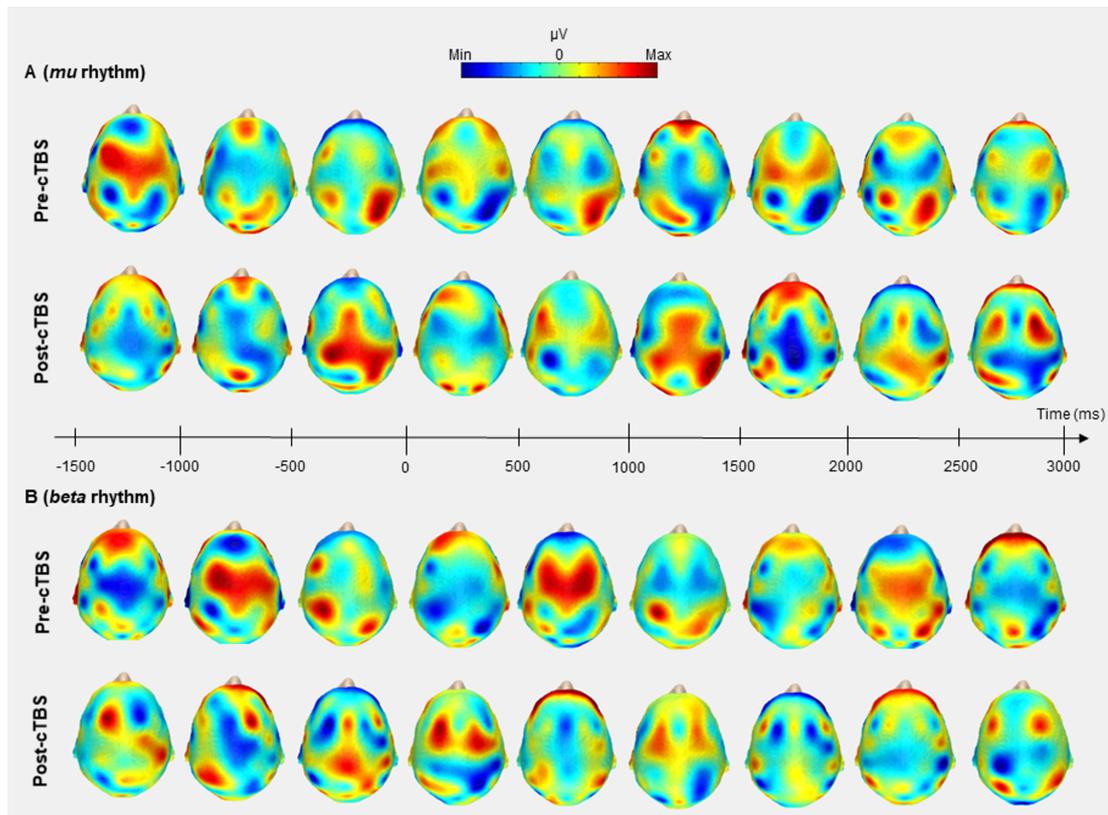
Figure 7.3.1 – Example of scalp ERS/ERD mapping. *Mu* (A) and *beta* (B) rhythms are presented from a participant who received continuous theta burst stimulation on the right hemisphere, during elevation of the arm ipsilateral to the stimulation, pre- and post-cTBS. Each scalp map represents the mean of ERS/ERD on the corresponding time period.

The above-mentioned differences in the *mu* band were significant for the simple arm elevation task (and not the complex thumb opposition), on the hemisphere contralateral to the protocol, both for pre-movement and preparation (Z = - 1.979, p = 0.048, **Figure 7.3.2a**) and when beginning elevation (Z = - 2.203, p = 0.027, **Figures 7.3.2a** and **7.3.2b**). These were translated into a significant increase of the mean *mu* power on the contralateral hemisphere, after stimulation. Similarly, regarding *beta* power, we observed a significant increase between pre- and post-cTBS on the hemisphere contralateral to the protocol, when beginning arm elevation (Z = - 2.688, p = 0.006, **Figures 7.3.2c** and **7.3.2d**). No significant differences were found for the *beta* rhythm on pre-movement and preparation. For individual data, please see *Appendix A6*.
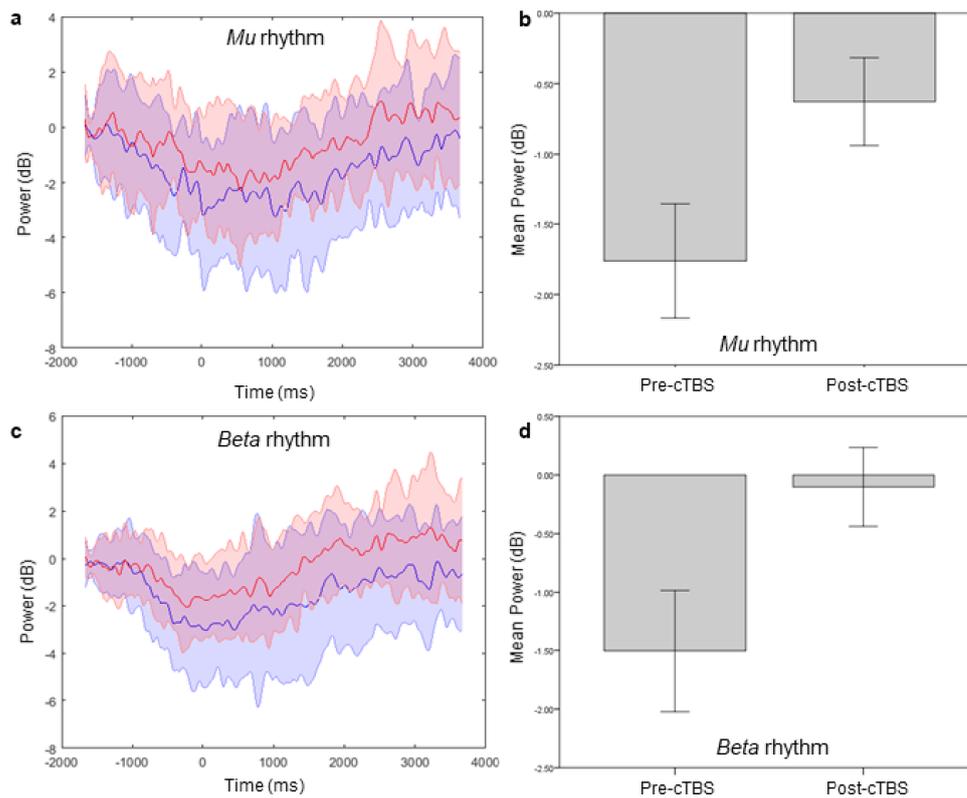
Figure 7.3.2 – Time-response plots showing changes in *mu* (a) and *beta* (c) rhythms following cTBS, during pre-movement and preparation, and beginning of the arm elevation, on the hemisphere contralateral to the protocol. Blue represents pre-cTBS and red illustrates post-cTBS data. The significant differences (p value < 0.05) on mean power of *mu* (b) and *beta* (d) rhythms for the beginning of the arm elevation are also depicted. Error bars represent +/- 1 SE.

7.4. DISCUSSION

In this study, we found a bimodal effect of the cTBS protocol in terms of motor-evoked responses as indicators of modulation of excitability and inhibition, and more consistent effects in motor related rhythms, which reflect also non-idle *versus* idle states. It is well known that increases in power of *mu* oscillations (ERS) reflect a motor inhibitory effect and a more idle state, which also occurs for *alpha* and *beta* oscillations (Jannati *et al.* 2017). The latter was the most important finding of this study. Concerning the bimodal pattern in motor-evoked potentials, a similar effect was described by Hamada *et al.* (2013). According to those authors, it could have been caused by differences in the recruitment of cortical neurons, as suggested by changes observed when the MEP's latency was analysed (Hamada *et al.* 2013). Moreover, Rocchi *et al.* (2018) also reported conflicting results, since they observed a facilitation of MEPs or no effect at all, after the application of cTBS. It might be that some participants are non-

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responders, and in those cases cTBS effects are not observed (Lowe and Hall 2018). However, we cannot disregard that the intensity for the application of the cTBS protocol was here selected as a function of the active motor threshold, as it is usual practice, with this measure being established following a voluntary muscle contraction. It is possible that the activation of the target muscle before, during or after stimulation could influence the modulation of plasticity, being able to cancel or even invert the effects detected by motor-evoked potentials (Goldsworthy *et al.* 2014, Opie *et al.* 2017). In fact, it is known that a higher number of descending volleys and a reduction of spinal motoneurons threshold do occur following muscular activation pre-stimulation (Lepage *et al.* 2008). At the same time, some authors suggest that MEPs may not express all cortical outputs, reflecting exclusively those destined to the spinal cord (Rocchi *et al.* 2018). Although both MEPs and EEG are considered reliable, and although the amplitude of motor-evoked potentials is, in part, influenced by spinal processes or other events remote to the brain, these are not expected to affect EEG data (Lepage *et al.* 2008, Rocchi *et al.* 2018). In this concern, our EEG recordings, and the nature of their neural sources are much less susceptible to be influenced by these types of effects.

The arm elevation task showed significant differences between pre- and post-intervention in the contralateral hemisphere. This is potentially interesting in terms of potential application in neurorehabilitation, because it was possible to detect an effect of the protocol on the *mu* and *beta* rhythms. This effect was specifically observed in a mirror symmetric way on the hemisphere contralateral to the protocol, possibly reflecting the topology of action planning and execution. The robustness of this finding could be attributed to the fact that there was less inter-subject variability on the contralateral hemisphere's response to cTBS. Actually, in this hemisphere, the majority of the volunteers showed a power increase in *mu* (13 out of 20) and *beta* (16 out of 20) rhythms, when beginning arm elevation after stimulation. On the pre-stimulation condition, we observed the expected event-related desynchronization when the participant was performing the movement, translating to negative values for the power (dB), comparing to the baseline. After cTBS, the power increased on the contralateral hemisphere, becoming less negative. The protocol decreased the desynchronization (in other words more relative synchronization). This increase in power suggests an inhibitory response on the sensorimotor cortical areas associated with an event-related synchronization. Moreover, on the corresponding topographic maps, we observed an

inversion of the signal polarity after the application of continuous theta burst stimulation, with both hemispheres responding in a more congruent manner. Hence, cTBS was able to influence the brain's neurophysiology by inducing a change in motor cortex that propagated to the contralateral hemisphere, corroborating our hypothesis that the protocol affects the contralateral motor rhythms. However, this change is not in the opposite direction, as expected in our initial hypothesis, but instead congruent with the manipulation in the ipsilateral hemisphere. In other words, the spreading of inhibition would render this protocol problematic for therapeutic modulation of a lesioned contralateral hemisphere. Other interpretations are, however, possible, namely nonlinear effects of artificial stimulation on signal-to-noise levels. This result substantiates the need for future studies that further analyse the electrophysiological changes underlying brain responses to the continuous theta burst protocol.

Remarkably, we did observe significant protocol-related differences only for the arm elevation task and not for the more fine-tuned thumb opposition, possibly because the former involves simpler motor programs that can be more easily targeted with our protocol. Also, it has been reported that more complex tasks lead augmented effort and attentional effects known to modulate ERDs (Pfurtscheller *et al.* 1996, Pfurtscheller and Lopes Da Silva 1999), which might cancel other effects.

In this study, EEG was more sensitive to detect neural modulation changes than EMG. It was already suggested in the literature that EEG can help in clarifying the effects of TMS (Rocchi *et al.* 2018). We suggest that this finding can be related to differences in the intrinsic variability of both techniques. It has been reported that the combination of TMS with EEG provides evoked responses that are less variable and more consistent, in comparison with MEPs (Ilmoniemi and Kičić 2010, Rocchi *et al.* 2018), considering that EEG measures, such as oscillations, are not affected by spinal cord excitability (Rocchi *et al.* 2018). Moreover, we chose to measure brain rhythms with relatively high signal-to-noise ratios (*alpha*, *mu* and *beta*) involved in either sensory or motor responsiveness. Our results suggest that it would be valuable to explore the potential of EEG in evaluating brain responses to TMS protocols, by including this technique on the design of future studies.

7.5. CONCLUSIONS

As far as we are aware, this is a novel study on the evaluation of the physiological effects of continuous theta burst stimulation applied to the primary motor cortex, which measures motor-evoked potentials with EMG and *mu* and *beta* rhythms with EEG during simple and complex motor execution tasks, in healthy subjects. EEG showed more reliable and consistent effects than MEP recordings. Our findings suggest that the cTBS protocol changes brain's neurophysiology, by decreasing the desynchronization of the contralateral *mu* and *beta* rhythms, with a direct impact on increased synchronization levels and inhibition. This propagation of inhibition has strong implications for the design of neurorehabilitation protocols, since it shows that contralateral excitation of a lesioned hemisphere might not occur following the application of an inhibitory protocol in the healthy ipsilateral hemisphere.

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Chapter

8

RESULTS

THE ROLE OF CONTINUOUS THETA BURST TMS ON THE NEUROREHABILITATION OF SUBACUTE STROKE PATIENTS: A LONGITUDINAL PLACEBO CONTROLLED STUDY

Background: Transcranial magnetic stimulation, in particular continuous theta burst (cTBS), has been proposed for stroke rehabilitation, based on the concept that inhibition of the healthy hemisphere helps promote the recovery of the lesioned one. *Aims*: We aimed to study its effects on cortical excitability, oscillatory patterns and motor function. *Methods*: We applied real or placebo stimulation over the unaffected primary motor cortex of ten subacute post-stroke patients. Neurophysiological measurements were performed using electroencephalography and electromyography. Motor function was assessed with the Wolf Motor Function Test (WMFT). We performed a longitudinal study with the recordings taken pre-, post-cTBS and at 3 months' follow-up. *Results*: We investigated changes in motor rhythms during arm elevation and thumb opposition tasks and found significant changes in *beta* power of the affected thumb's opposition, specifically after real cTBS ($p = 0.039$). Our results are consistent with an excitatory response (increase in event-related desynchronization) on the sensorimotor cortical areas of the affected hemisphere, after stimulation. *Conclusions*: Consistently with the theoretical prediction, this contralateral inhibitory stimulation paradigm changes neurophysiology, leading to a significant excitatory impact on the cortical oscillatory patterns of the contralateral hemisphere. Our results provide evidence for the potential role of continuous TBS in the neurorehabilitation of post-stroke patients.

8.1. INTRODUCTION

Stroke is the third most frequent cause of death (Yang *et al.* 2015) and one of the most prevalent causes of disability (Abo *et al.* 2014, Du, Tian, *et al.* 2016, Rastgoo *et al.* 2016). Motor deficits occur quite often in stroke and affect up to 75% of patients for several months (Sasaki *et al.* 2013, Abo *et al.* 2014, Rose *et al.* 2014, Wang, Tsai, *et al.* 2014). In spite of the available interventions, search for alternative therapeutic solutions is quite relevant (Higgins *et al.* 2013, Lüdemann-Podubecká *et al.* 2015).

Transcranial magnetic stimulation (TMS) is under investigation for this purpose, becoming attractive for the study, diagnosis and treatment of various diseases given its non-invasive nature with rare adverse effects (Kobayashi and Pascual-Leone 2003, Chipchase *et al.* 2012). When applied in its repetitive form, it can produce effects that last beyond the stimulation period (Kobayashi and Pascual-Leone 2003, Heaton 2012). Given these effects it might act as a neuromodulatory tool, providing a potential tool to restore the balance of activity between the hemispheres, through the modulation of plasticity. In fact, following stroke, it has been postulated that the lesioned hemisphere decreases its activity while the excitability of the contralesional hemisphere becomes pathologically increased (Ameli *et al.* 2009, Lin *et al.* 2015, Du, Tian, *et al.* 2016). Hence, repetitive TMS can be applied to augment the excitability of the stroke-affected hemisphere or to reduce the contralesional activity, depending on stimulation parameters (Lin *et al.* 2015, Yang *et al.* 2015, Du, Tian, *et al.* 2016, Rastgoo *et al.* 2016).

Although this technique is becoming popular, several issues remain to be elucidated. These including the variability of responses and the unknown mechanisms behind its application (Heaton 2012, Dionísio *et al.* 2018). One of the inhibitory protocols that are currently being studied is continuous theta burst stimulation (cTBS), a recent form of patterned TMS that consists of 3 pulses at 50 Hz repeated every 200 milliseconds during 40 seconds, inducing inhibitory effects that last up to 60 minutes (Huang *et al.* 2005, Sandrini *et al.* 2011).

In our previous work in healthy individuals (Dionísio *et al.* 2020), we observed that cTBS induced an unexpected inhibition in the contralateral hemisphere during arm elevation, contradicting the ipsilateral inhibition *versus* contralateral disinhibition theory. We hypothesized that it was a result of propagation of effects from the stimulation site, which might have implications for neurorehabilitation. However, it is

still possible that such effects only occur in the presence of two healthy hemispheres, and that the theory still holds when one hemisphere is lesioned.

Here we aim to study the impact of cTBS when applied to the unaffected hemisphere of stroke patients. Cortical activity was evaluated at rest to study baseline physiological state and during motor tasks, in which concerns brain oscillatory patterns. When sensory information or motor output are absent, there is an inhibition of cortical activity that is observed as an increase in oscillatory activity (event-related synchronization, ERS). In opposition, motor readiness induces an activation observed as a decrease in brain rhythms, designated by event-related desynchronization (ERD) in the *beta* band (Pfurtscheller and Neuper 1994, Pfurtscheller *et al.* 1996, 1997, Pfurtscheller and Lopes Da Silva 1999, Takemi *et al.* 2013). To accomplish our goals, we recorded brain activity using electroencephalography (EEG) to analyse *alpha*, *mu* and *beta* rhythms, before (T0) and after (T1) one session of real (experimental group: group E) or sham (control group: group C) cTBS and at 3-months follow-up (T2). Moreover, we evaluated motor-evoked potentials, using electromyography (EMG), and motor function, with the Wolf Motor Function Test (WMFT), at the same time points.

8.2. STATISTICAL DATA TREATMENT

Statistical analysis was carried out on SPSS Statistics software v.24 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). For all data, we adopted a 95% confidence interval. Differences between experimental and control groups related to clinical and demographic data were assessed by Mann-Whitney U test, for age, handedness, time-since-stroke onset, National Institutes of Health Stroke Scale at admission, and WMFT baseline measurements, and by the Fisher's exact test, for gender and lesion side. Friedman and Wilcoxon tests were computed to evaluate changes in WMFT, MEPs' amplitude and mean power of brain rhythms, throughout the three time points (T0, T1 and T2).

8.3.   RESULTS

Experimental and control groups were matched. They did not differ significantly regarding age (U = 10.500, p = 0.730), gender (p = 0.524), handedness assessed by Edinburgh Handedness Inventory (Oldfield 1971) (U = 12.500, p = 1.000), lesion side (p = 0.524), time-since-stroke (U = 10.000, p = 1.000), score in the National Institutes of Health Stroke Scale (U = 11.500, p = 0.881), or WMFT at baseline (log performance time: U = 10.000, p = 0.690; FAS: U = 12.000, p = 0.952).

Wolf Motor Function Test

WMFT log performance time showed a non-significant trend in decay (Group E: $\chi2$ = 4.800, p = 0.124; Group C: $\chi2$ = 0.500, p = 0.931). We observed marginally significant score difference between pre- and post-intervention in Group E (Z = - 2.023, p = 0.063). Changes in FAS were not significant (experimental group: $\chi2$ = 3.125, p = 0.259; control group: $\chi2$ = 2.286, p = 0.370).

Motor-Evoked Potentials

Differences were not statistically significant at any time point, concerning MEPs' amplitude of the affected (experimental group: $\chi2$ = 4.667, p = 0.194; control group: $\chi2$ = 4.000, p = 0.167) or the unaffected hemisphere (experimental group: $\chi2$ = 0.400, p = 0.954; control group: $\chi2$ = 0.667, p = 0.944).

Electroencephalography

Concerning bilateral arm elevation, the Wilcoxon test identified a trend towards a significant increase in *beta* power from pre- to post-cTBS in pre-movement and preparation (Group E: Z = - 2.023, p = 0.063; Group C: Z = - 1.461, p = 0.250), and at the beginning of movement (Group E: Z = - 2.023, p = 0.063; Group C: Z = 0.000, p = 1.000), only in the experimental group.

Regarding the thumb opposition task, we found a statistically significant change of *beta* rhythm across the three assessment points, in the pre-movement and preparation for movement performed with the affected limb only in the real-stimulation

group (Group E: χ2 = 6.400, p = 0.039, **Figure 8.3.1**; Group C: χ2 = 0.667, p = 0.944) – individual data in *Appendix A7*. Wilcoxon test also detected, for this group, a trend towards a decrease in *beta* rhythm between T0 and T1, when preparing for the task with the affected limb (Group E: Z = - 2.023, p = 0.063; Group C: Z = - 1.461, p = 0.250).
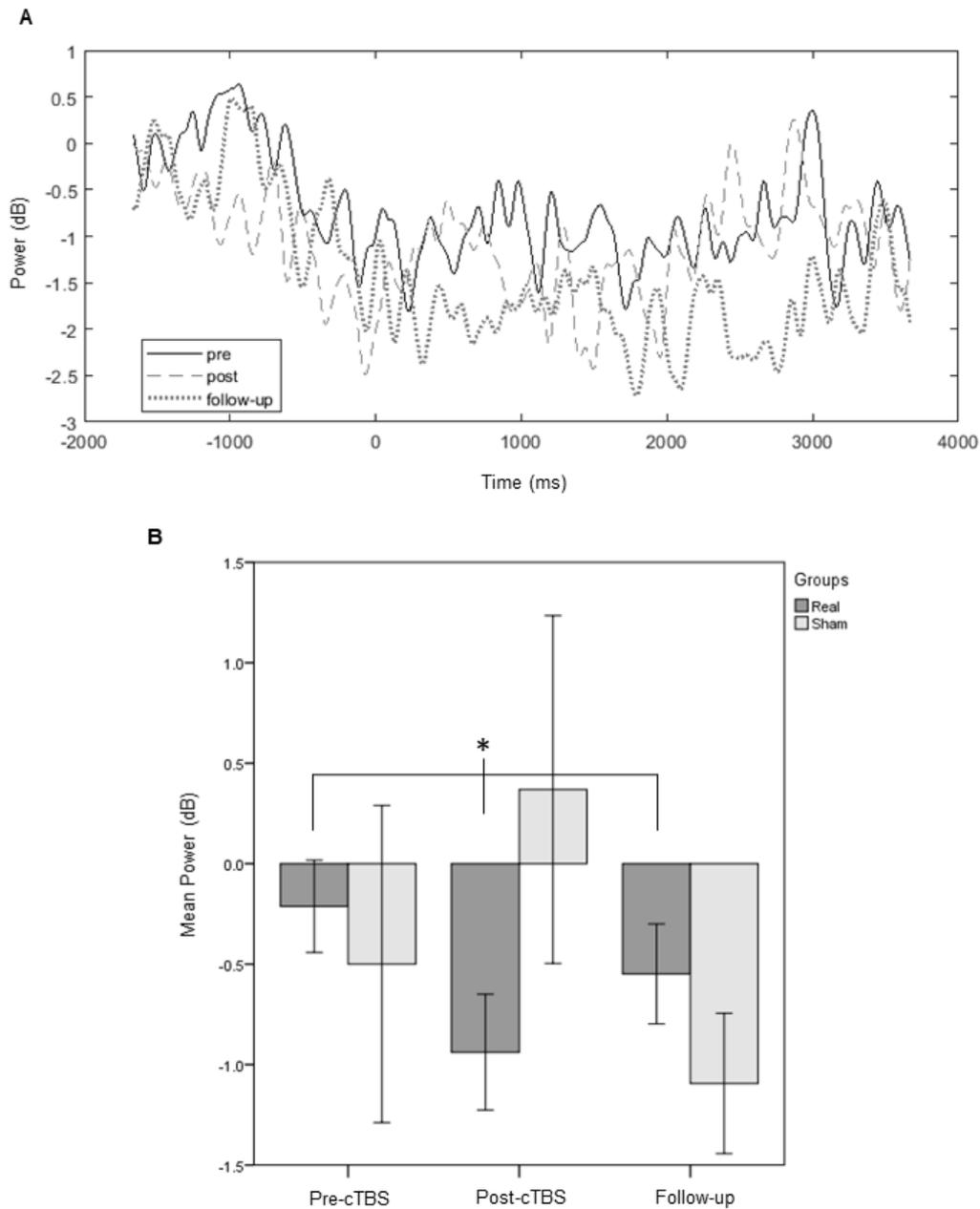
Figure 8.3.1 – Time-response plots of the mean *beta* power for the experimental group, throughout the three assessment points. Pre-movement and preparation of the affected thumb opposition reveal changes induced by the protocol on *beta* power of the affected hemisphere (A). Significant differences (*, p < 0.05) are also illustrated in the bar charts (B). Error bars represent ± 1 SE.

8.4. DISCUSSION

This interventional study is based on the hypothesis that applying an inhibitory TMS protocol to the unaffected hemisphere in stroke will release the lesioned hemisphere from such inhibition. The predicted increase in excitability might potentially help promote recovery (Lin *et al.* 2015, Yang *et al.* 2015, Du, Tian, *et al.* 2016).

Analysing our findings, we observed that significant neurophysiological effects were obtained indeed only for the experimental group, with no measure showing statistical effects for participants who received placebo stimulation. Even marginally significant effects were observed only for the former group. We only found trends concerning behavioural data, which may be due to the fact that this study mainly aimed at a short term proof-of-concept in patients with a recent episode of stroke, at a subacute stage.

Thumb opposition task revealed significant differences across time measurements for *beta* rhythm, only for the experimental group, in the pre-movement and preparation for movements performed with the affected hand. A trend towards a significant decrease in *beta* power at T1, in Group E, was suggestive of an excitatory response to the protocol (increase in ERD) (Pfurtscheller *et al.* 1997, Takemi *et al.* 2013) from the affected hemisphere, as expected. Regarding the arm elevation task, we did not detect statistically significant differences following the application of cTBS. We hypothesize that more complex movements potentiate stronger activation of the motor areas (Tinazzi *et al.* 2003) in the affected hemisphere, leading to better detectability of TMS effects.

Interestingly, motor rhythms did not change significantly during arm elevation or thumb opposition of the unaffected limb alone, after stimulation, which indicates that the protocol can have a larger impact in the hemisphere contralateral to the stimulation thus potentially improving the lesioned hemisphere functional status. This finding is supported by our results in healthy individuals, where we found a significant impact of the cTBS protocol only on the contralateral hemisphere (Dionísio *et al.* 2020).

There is nevertheless an important distinction with the effects observed in healthy participants and subacute stroke patients. While in healthy subjects we had observed a significant and paradoxical inhibition of the contralateral hemisphere, for the arm elevation task, in stroke patients we found instead significant excitation expected

from the above-mentioned conceptual framework, with thumb opposition. This suggests that changes in cortical excitability in responses to distinct neuromodulation protocols may be task-dependent and, more importantly, might be different in health and in disease.

8.5. CONCLUSIONS

The neurophysiology of subacute post-stroke patients was changed, consistently with the hypothesis that inhibitory cTBS over the unaffected hemisphere leads to increased excitation of the lesioned hemisphere. This was reflected in changes in brain cortical oscillations (ERD), particularly *beta* rhythms during motor preparation and execution. We suggest that this stimulation protocol may be useful in stroke neurorehabilitation by altering the ERS/ERD pattern and potentially improving the motor functions, when applied for several sessions.

Chapter **9**

GLOBAL
CONSIDERATIONS

This thesis focused on the investigation of neurophysiological mechanisms underlying the application of continuous theta burst stimulation to the human brain. This paradigm has been being studied as a potential therapeutic intervention. Yet, regardless of the promising results that are being reported for several different conditions, more efforts need to be devoted to the understanding of the changes produced by this protocol at the physiological level. In this work, we assessed its impact in the healthy brain and stroke afflicted patients, this condition being one of the most relevant clinical applications of transcranial magnetic stimulation.

Foremost, we have analysed neurophysiological alterations that could possibly be attributed to the stroke event (**Chapter 6**). It is believed that *beta* oscillations may have implications in the pathology of different diseases, including stroke (Rossiter *et al.* 2014, Assenza *et al.* 2017, Cassidy *et al.* 2020). The findings from Rossiter *et al.* (2014) point out the possibility that altered cortical oscillations have a great impact in motor functionality. Actually, studies in stroke patients have already revealed a decrease in movement-related *beta* desynchronization in the affected hemisphere (Rossiter *et al.* 2014). Similarly, comparing brain oscillatory activity of stroke patients with healthy controls, we observed in our study significant differences, with patients showing more elevated power of *beta* (larger synchrony) during motor planning and execution of bimanual thumb opposition. We suggest that this finding is related to the inhibition of cerebral activity after the brain lesion. Moreover, we found a moderate negative correlation between *beta* power during bimanual thumb opposition and velocity of performance in WMFT tasks, which suggests that patients with a stronger inhibition of activity, represented by higher levels of *beta*, show worse performance in execution of motor tasks. These results also suggest that the study of brain rhythms as potential biomarkers predicting stroke functional recovery is a promising avenue of research (Cassidy *et al.* 2020, Popa *et al.* 2020).

Afterwards, we have applied continuous theta burst stimulation to both healthy participants (see **Chapter 7** for results) and stroke patients (results in **Chapter 8**) in order to understand how the human brain responds to the protocol, in health and disease. The literature suggests that the cTBS paradigm decreases the amplitude of motor-evoked potentials on the stimulated hemisphere (Sandrini *et al.* 2011), possibly by weakening the strength of synaptic connections, through LTD-like mechanisms (Goldsworthy *et al.* 2012). Wischnewski & Schutter (2015) conducted a review on the

efficacy of TBS and observed that the application of continuous theta burst stimulation for 20 seconds suppresses cortical excitability for 20 minutes up to - 27.84 ± 4.15% (mean ± SEM), whereas when applied for 40 seconds cortical excitability is reduced up to - 22.81 ± 2.86% for a maximum of 50 minutes.

As a measure of motor cortical output, we quantified the peak-to-peak amplitude of motor-evoked potentials at the beginning of the experiment and following stimulation. Surprisingly, we did not detect any statistically significant change produced by cTBS in either the healthy participants or patients. We hypothesize that this absence of significant changes can be attributed to the inter-individual variability latent to TMS protocols. Opie *et al.* (2017) measured MEPs' amplitude changes following priming stimulation with cTBS and iTBS in healthy young and old subjects and did not find significant differences, as well. Moreover, several studies reported having modest, null or even opposite effects of this protocol when applied over M1, which was attributed to the high variability (Goldsworthy *et al.* 2014, Opie *et al.* 2017) and small sample sizes (Goldsworthy *et al.* 2014). Chung *et al*. (2016) performed a systematic review and meta-analysis and described that studies with larger number of participants also reported relevant inter- and intra-subject variability that hindered the findings of significant changes in MEPs' amplitude after cTBS. Also, it is claimed that some individuals may be non-responders, concerning the cTBS protocol (Lowe and Hall 2018). Furthermore, the active contraction of the muscle for defining the intensity prior to the application of the protocol can have an impact on the motor-evoked potentials measurement post-stimulation, which could possibly mask the effects (Goldsworthy *et al.* 2014, Opie *et al.* 2017).

Transcranial magnetic stimulation can also have an effect on brain rhythmic activity, being able to generate phenomena such as ERS or ERD (Ilmoniemi and Kičić 2010, Assenza *et al.* 2017). The use of neurophysiological techniques, such as EEG, can be useful in giving extended information regarding the effects of cTBS on motor and non-motor regions (Chung *et al.* 2016, Assenza *et al.* 2017). Moreover, the information provided by TMS-EEG might be valuable for the optimization of the stimulation protocols (Chung *et al.* 2017). The relevance of cortical oscillatory activity to the effects of cTBS should be given more attention (McAllister *et al.* 2013). In fact, there are few works focusing the impact of TBS on network oscillations, since most part of studies investigating the effects of TBS concentrate mostly on the evaluation of the amplitude of

motor-evoked potentials (Noh *et al.* 2012, Assenza *et al.* 2017), in part due to its ease of measurement (Assenza *et al.* 2017).

Shafi *et al.* (2014) noted that the impact of this protocol depends not only on frequency bands but also on brain regions. In their study, the cTBS paradigm over M1 acted mainly in those connections anterior/inter-regional and between hemispheres, which was observed in the resting state, with the participants having the eyes closed. McAllister *et al.* (2011), in turn, measured electrical activity over the motor cortex at C3 with EEG and failed to observe an effect from cTBS on the power spectra (0.5 to 40 Hz) (McAllister *et al.* 2011).

Concerning the visual *alpha* rhythm, we did not detect, as expected, significant changes after stimulation in occipital power of healthy subjects or stroke patients, during eyes opening or closure. Along with motor preparation and execution we did find significant alterations in oscillatory patterns, particularly in *mu* and *beta* rhythms, after the stimulation with continuous TBS. Some studies (Noh *et al.* 2012, 2015, Vernet *et al.* 2013, Shafi *et al.* 2014) have also reported alterations in the *beta* band, following stimulation with continuous theta burst.

Our results on healthy participants point out a significant change in *mu* and *beta* rhythms on the hemisphere that was not stimulated, during elevation of the arm ipsilateral to the protocol. Thumb opposition task did not reveal significant changes after stimulation in healthy subjects but did show a significant change in *beta* of the non-stimulated (affected) hemisphere, across the three assessment points for the stroke patients who received active but not sham stimulation. Therefore, the significant results obtained by us both in health and in stroke were confined to the non-stimulated hemisphere, which suggests not only that this paradigm of stimulation plays a role on this hemisphere, but also that the magnitude of the effect might be superior on the contralateral hemisphere. We also hypothesize that the effects of continuous theta burst stimulation might be task-dependent (Tinazzi *et al.* 2003, Fling and Seidler 2012). The fact that significant effects for the thumb opposition task were circumscribed to the affected hemisphere of patients led us to hypothesize that complex tasks potentiate stronger activation of the motor areas on the lesioned hemisphere comparing to the unaffected side or to a healthy brain.

Brain topographic maps allow the visualization of the effects of TMS at both local and distant levels (Ilmoniemi and Kičić 2010). Brain topology can be affected by

transcranial magnetic stimulation, at a widespread level (Shafi *et al.* 2014). Indeed, TMS can act on the interregional cortical connections, by changing their strength (Shafi *et al.* 2014). The stimulation of one hemisphere induces changes in activity that spread ipsilaterally through association fibres, to the contralateral hemisphere along transcallosal pathways and to subcortical regions through projection fibres (Ilmoniemi and Kičić 2010). On ERS/ERD scalp maps of healthy subjects, we saw an inversion of the signal polarity and bilateral activity pattern on the central areas, following stimulation. We suggest that the effect of the cTBS protocol has actually spread to the contralateral hemisphere. Shafi *et al.* (2014) reported that continuous theta burst changed the pattern of functional connectivity in the healthy brain, by modulating the connections between hemispheres and between different regions, even to a greater probability comparing to local intra-hemispheric connections. In their study, the magnitude of the changes in intra-hemispheric local connections was not significantly different, comparing the stimulated to the contralateral non-stimulated hemisphere, which was proposed by these authors to be due to greater interhemispheric coupling and recruitment of contralateral areas (Shafi *et al.* 2014).

Taken together, our results suggest that, in healthy individuals, the inhibitory effect of the continuous theta burst stimulation protocol propagates to the contralateral hemisphere, translating into an increase in synchronization and reduced desynchronization of oscillatory activity. These observations are supported by the study from Hu *et al.* (2017), where they detected a surprising decrease of the peak-to-peak amplitude of motor-evoked potentials on the hemisphere contralateral to the cTBS protocol, besides the expected suppression on the stimulated hemisphere. The results from magnetic resonance imaging in their study also corroborated this bilateral inhibitory response (Hu *et al.* 2017). According to these authors, the inhibition of the contralateral hemisphere could be attributed to excitatory projections to this side or the intra-cortical inhibitory circuit. Also, the decreased excitability on the stimulated hemisphere could have produced a homeostatic balancing effect on the contralateral side. Regardless of the mechanism, they believe that the corpus callosum plays a relevant role, by mediating the inter-hemispheric communication (Hu *et al.* 2017).

In stroke, the pattern we saw on EEG was a decrease in power of the affected hemisphere, associated to an augmented event-related desynchronization, indicating an increase in the excitability of this hemisphere, unlike in healthy participants. Therefore,

the direction of the responses to the protocol might also be different in the presence of a brain lesion. This way, cTBS effects in stroke were actually as predicted. The mechanisms underlying this observation are worth of further investigation; nevertheless, our findings support the potential of this paradigm as a rehabilitative intervention for post-stroke patients.

The relatively low sample of our studies can be explained by the extremely challenging design, in particular in patients, because it demanded a strong effort and commitment from the participants, who, even though were clinically stable, were still in the sub-acute stage of the disease and trying to cope with their new reality. Our eligibility criteria were very restricting to guarantee safety, in the first place, and also the greatest homogeneity possible and, therefore, reduce the inter-subject variability underlying transcranial magnetic stimulation. Several patients, although meeting the criteria and being willing to participate, had to be excluded because they were not clinically stable or developed a post-stroke respiratory tract infection. Even though we recognize this is a weakness in our work, the nature of these studies does make it difficult to achieve larger sample sizes, as it can be observed in the literature. Also, the estimated duration of the cTBS effects – one hour for a 40-seconds protocol – restricted the post-intervention measurements. This way, we could not include other assessments that would have been interesting to perform, such as the paired-pulse paradigm. Moreover, it limited the time we had to carry out electroencephalography, hindering the inclusion of additional experimental trials, which would have been beneficial.

Although our results are encouraging for the understanding of the mechanisms of action of continuous theta burst stimulation, with potential implications in its clinical application, the variability associated to this technique cannot be disregarded.

Intra-individual variability exists between sessions, with some participants responding differently, and even showing contrary direction of the effects, from one session to another (Sasaki *et al.* 2018). These changes in response can be associated to circumstantial factors such as time of the day, level of physical activity or attention pre- and during stimulation (Hordacre *et al.* 2017, Sasaki *et al.* 2018) or the physiological state of brain activity at the moment of the TMS application (Vernet *et al.* 2014).

Differences between individuals on the response to the protocol can be attributed, in part, to age factors (Hordacre *et al.* 2017, Sasaki *et al.* 2018). In healthy elderly, the neuroplastic capacity becomes decreased and the literature describes

weaker responses to TBS protocols, associated with aging (Opie *et al.* 2017). Priming stimulation with continuous or intermittent TBS was effective in building up plastic responses in young but not in old participants, in the study from Opie *et al.* (2017). Genetic differences (Hordacre *et al.* 2017, Sasaki *et al.* 2018), related mainly to changes in brain-derived neurotrophic factor (BDNF) alleles (Wischnewski and Schutter 2015) also play a role for inter-subject variability. Furthermore, following TMS, direct (D)-waves or indirect (I)-waves can be recruited associated to the activation of cortical network (Hordacre *et al.* 2017) (for more information on the origin of these waves please refer to **Chapter 2**, **section 2.3.** – Basic principles of functioning). However, this neuromodulatory technique promotes the recruitment of I-waves rather than D-waves, since it stimulates preferentially tangential cortical fibres (Bolay *et al.* 2000). Some authors described a stronger response to brain stimulation for those individuals who held more probability for recruiting late I-waves following TMS (Hordacre *et al.* 2017). Hordacre *et al.* (2017) described that the inhibition induced by continuous TBS protocol was more pronounced in those subjects who exhibited higher variability on the peak-to-peak amplitude of motor-evoked potentials at baseline. In turn, in participants with less variability on this measure there was a trend for an excitatory effect (Hordacre *et al.* 2017). The authors put forward a combined contribution of 31% for late I-wave recruitment and MEPs' variability to the cTBS response inconsistency, in their study (Hordacre *et al.* 2017).

Methodological issues regarding the technique, such as the selection of parameters, also account for the different responses across studies, even when the changes appear to be minor (Goldsworthy *et al.* 2012, Vernet *et al.* 2013, 2014, Sasaki *et al.* 2018). One of the most determining factors is the intensity selected for stimulation. Sasaki *et al.* (2018) described the expected inhibitory response in just 32% of participants, following cTBS applied with a biphasic current at 80% of aMT. They decided to decrease the intensity from 80 to 65%, in participants who showed a facilitatory response, and obtained the expected decrease in MEPs' peak-to-peak amplitude in half of them, after changing the intensity (Sasaki *et al.* 2018). Also, the intensity for the application of the cTBS protocol is usually selected as a function of the active motor threshold, with this measure being established following a voluntary muscle contraction, at a given force. However, it is believed that the activation of the target muscle before, during or after stimulation influences the modulation of plasticity,

being able to cancel or even invert the effects detected by motor-evoked potentials (Goldsworthy *et al.* 2014, Opie *et al.* 2017). In fact, Goldsworthy *et al.* (2014) stated that contraction of the target muscle decreases the consistency of MEP suppression, increasing the inter-subject variability of the responses to the paradigm. The authors propose that prior activation of M1 induces non-homeostatic metaplasticity, which raises the threshold for later LTD induction by continuous TBS (Goldsworthy *et al.* 2014). Iezzi *et al.* (2008) also noted that phasic voluntary movements reversed the direction of the effects, with iTBS inducing inhibitory and cTBS producing excitatory responses. Stimulation frequency might also have a relevant impact (Vernet *et al.* 2014). The majority of the cTBS works applied bursts of 3 pulses at a frequency of 50 Hz, repeated at 5 Hz. However, some authors used 30 Hz repeated at 6 Hz, instead. It is yet to be established if changing the frequency to 30 Hz results in a superior alternative (Wischnewski and Schutter 2015). Wu *et al.* (2012) observed comparable results for both 30 and 50 Hz TBS. The coil orientation (Vernet *et al.* 2014) and type may also influence the effects. In fact, the use of a round coil allows the stimulation of wider regions, comparing with the figure-of-eight, although less focused. This way, a round geometry enables the stimulation of more neurons (Brückner and Kammer 2016).

Taking the wide variability into account, the application of the same parameters to different individuals, and particularly to stroke rehabilitation, wherein there is a great heterogeneity, may prevent consistent and effective results (Plow *et al.* 2016). In this context, a personalized use of stimulation, with well-adjusted parameters should be a target for future studies.

Chapter

10
CLOSURE

10.1. CONCLUSIONS

In this thesis we focused on the use of transcranial magnetic stimulation as a neuromodulation tool. Although it has been applied to the study of several pathologies, searching for a therapeutic solution, the mechanisms underlying its action are not fully uncovered, yet. Here, we studied the functioning of continuous theta burst stimulation, when applied to the primary motor cortex, and its impact on the human brain, both in healthy individuals and in a clinical sample of patients who had suffered from a stroke event. We observed that cTBS plays a significant role on cortical oscillations during motor preparation and execution, by changing event-related synchronization and desynchronization patterns, both in health and in stroke. Notably, these changes were task-dependent and most prominent in the contralateral hemisphere. Moreover, our results suggest that the responses to transcranial magnetic stimulation, particularly to cTBS protocol, might be different in health and in pathological conditions. Our findings can have an impact in personalised neurorehabilitation.

10.2. FUTURE WORK

In the future, it would be valuable to recruit more patients to achieve higher statistical power and larger stratification of patient groups, taking into account important individual characteristics such as lesion extension and localization. Moreover, larger sample sizes with different levels of motor impairment would indeed enable the evaluation of the impact of deficits' severity on the response to the rehabilitation program.

As noted by O'Brien *et al.* (2018), it would be valuable to discover biomarkers that could allow a personalized usage of stimulation applied to motor rehabilitation. Efforts should be devoted to study the hypothesis of electroencephalographic data being used as a stratification biomarker in the rehabilitation of stroke patients and as a prognostic measure in the response to magnetic brain stimulation, helping on the selection of the subjects that would benefit the most from each protocol.

After finding answers to these issues, the same procedures should be applied for several sessions, at least 10 sessions over two weeks. This would allow assessing the

impact of the number of sessions on neurophysiological markers of plasticity. It would also be relevant to study the effects of cTBS as a co-adjuvant to traditional motor therapies, by randomizing stroke patients into two groups: one receiving both physical therapy and cTBS and the other receiving physiotherapy alone.

Subsequently to the thorough study of continuous theta burst stimulation, other protocols could also be subjected to the same tests to compare the efficacy between them in different sub-populations.

Additionally, although TMS has been attracting a lot of attention among non-invasive neuromodulation methods (Sánchez-Kuhn *et al.* 2017), it would be interesting to run the same experiments with transcranial direct current stimulation (tDCS) and compare both techniques, both in terms of mechanisms and neuroplastic effects.

SCIENTIFIC PRODUCTION

Published articles

→ **Dionísio A**[*], Gouveia R[*], Duarte IC, Castelhano J, Duecker F and Castelo-Branco M. (2020) Continuous theta burst stimulation increases contralateral *mu* and *beta* rhythms with arm elevation: implications for neurorehabilitation. *Journal of Neural Transmission.* 127: 17-25. ([*]equal contribution).
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→ **Dionísio A**, Duarte IC, Patrício M and Castelo-Branco M. (2018) Transcranial Magnetic Stimulation as an intervention tool to recover from language, swallowing and attentional deficits after stroke: a systematic review. *Cerebrovascular Diseases.* 46(3-4): 176-183.
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→ **Dionísio A**, Duarte IC, Patrício M and Castelo-Branco M. (2018) The use of repetitive Transcranial Magnetic Stimulation for stroke rehabilitation: a systematic review. *Journal of Stroke and Cerebrovascular Diseases.* 27(1): 1-31.
DOI: http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.09.008.

Under review

→ **Dionísio A**, Gouveia R, Castelhano J, Duarte IC, Santo G, Sargento-Freitas J and Castelo-Branco M. The neurophysiological impact of subacute stroke: changes in central *beta* cortical oscillations evoked by bimanual finger movement.

→ **Dionísio A**, Gouveia R, Castelhano J, Duarte IC, Santo G, Sargento-Freitas J, Duecker F and Castelo-Branco M. The role of continuous theta burst TMS on the neurorehabilitation of subacute stroke patients: a longitudinal placebo controlled study.

Conferences

→ **Dionísio A***, Castelhano J*, Gouveia R, Xavier C, Duecker F, Duarte IC, Santo G, Sargento-Freitas J, Lains J, Carvalho F, Abrunhosa A, Castelo-Branco M. (2020) The Role of Continuous Theta Burst TMS on the Neurophysiology of Stroke: a Multimodal Study. 2020 OHBM Annual Meeting (23 June – 3 July 2020, virtual meeting) (*equal contribution)

→ Bernardino I, **Dionísio A**, Espírito A and Castelo-Branco M. (2019) Como funciona o cérebro na NF1. 16th National meeting of the Portuguese Association for Neurofibromatosis (4 May 2019, Lisbon, Portugal)

→ **Dionísio A***, Gouveia R*, Duarte IC, Castelhano J and Castelo-Branco M. (2018) The impact of continuous theta burst TMS on cortical oscillatory patterns across hemispheres: implications for neurorehabilitation. In 11th FENS Forum of Neuroscience (7-11 July 2018, Berlin, Germany) (*equal contribution)

→ Bernardino I, **Dionísio A**, Monteiro R, Violante I and Castelo-Branco M. (2018) Cortical inhibitory alterations in autism spectrum disorders: a TMS study. In INSAR 2018 Annual Meeting (9-12 May 2018, Rotterdam, Netherlands). Available at: https://insar.confex.com/insar/2018/webprogram/Paper28450.html

SHORT CV

Ana Mendes Dionísio was born in Oporto, Portugal, on the 13th of January, 1989. She completed her Master in Biomedical Engineering, given by the Faculty of Biotechnology of Portuguese Catholic University, in January 2013. Her master thesis, *Thyroid Imaging Using Two Collimators: Parallel-Hole and 'Pinhole'*, supervised by Professor Durval Campos Costa MD, MSc, PhD, FRCR and by Diogo Borges Faria MSc, provided her first work experience at a hospital environment. She designed and constructed phantoms and conducted experiments in a gamma camera to determine the ideal parameters for performing a thyroid's scintigraphy. This work reinforced her desire of increasing her knowledge on the human system and continuing her studies in the biomedical field. Afterwards, she enrolled a PhD program in Biomedical Engineering and started learning neurosciences at the University of Coimbra, where she has been investigating, under the supervision of Professor Miguel Castelo-Branco MD, PhD, the application of non-invasive stimulation to the study of the human brain, in both health and disease. In this regard, she is exploring the use of transcranial magnetic stimulation (TMS) in health, stroke, type 1 neurofibromatosis and autism spectrum disorders, and transcranial direct current stimulation (tDCS) in epilepsy and tuberous sclerosis. Besides TMS and tDCS, she is also making use of electroencephalography, electromyography and magnetic resonance spectroscopy, to study neurophysiological changes, mechanisms of brain plasticity and brain responses to therapeutic interventions, in clinical populations. She is now interested in several branches of neuroscience, including neurorehabilitation, non-invasive stimulation, brain imaging and human neurophysiology, particularly in the context of disease.

REFERENCES

Abo, M., Kakuda, W., Momosaki, R., Harashima, H., Kojima, M., Watanabe, S., Sato, T., Yokoi, A., Umemori, T., and Sasanuma, J., 2014. Randomized, multicenter, comparative study of NEURO versus CIMT in poststroke patients with upper limb hemiparesis: The NEURO-VERIFY Study. *International Journal of Stroke*, 9 (5), 607–612.

Abo, M., Kakuda, W., Watanabe, M., Morooka, A., Kawakami, K., and Senoo, A., 2012. Effectiveness of low-frequency rTMS and intensive speech therapy in poststroke patients with aphasia: A pilot study based on evaluation by fMRI in relation to type of aphasia. *European Neurology*, 68 (4), 199–208.

Ackerley, S.J., Stinear, C.M., Barber, P.A., and Byblow, W.D., 2010. Combining theta burst stimulation with training after subcortical stroke. *Stroke*, 41, 1568–1572.

Agosta, S., Herpich, F., Miceli, G., Ferraro, F., and Battelli, L., 2014. Contralesional rTMS relieves visual extinction in chronic stroke. *Neuropsychologia*, 62, 269–276.

Alia, C., Spalletti, C., Lai, S., Panarese, A., Lamola, G., Bertolucci, F., Vallone, F., Di Garbo, A., Chisari, C., Micera, S., and Caleo, M., 2017. Neuroplastic Changes Following Brain Ischemia and their Contribution to Stroke Recovery: Novel Approaches in Neurorehabilitation. *Frontiers in Cellular Neuroscience*, 11.

Allart, E., Viard, R., Lopes, R., Devanne, H., and Delval, A., 2020. Influence of Motor Deficiency and Spatial Neglect on the Contralesional Posterior Parietal Cortex Functional and Structural Connectivity in Stroke Patients. *Brain Topography*, 33, 176–190.

Amantea, D. and Bagetta, G., 2017. Excitatory and inhibitory amino acid neurotransmitters in stroke: from neurotoxicity to ischemic tolerance. *Current Opinion in Pharmacology*, 35, 111–119.

Amassian, V.E. and Maccabee, P.J., 2006. Transcranial magnetic stimulation. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference*, 1, 1620–1623.

Ameli, M., Grefkes, C., Kemper, F., Riegg, F.P., Rehme, A.K., Karbe, H., Fink, G.R., and Nowak, D.A., 2009. Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. *Annals of Neurology*, 66 (3), 298–309.

Arroyo, S., Lesser, R.P., Gordon, B., Uematsu, S., Jackson, D., and Webber, R., 1993. Functional significance of the mu rhythm of human cortex: an electrophysiologic study with subdural electrodes. *Electroencephalography and Clinical Neurophysiology*, 87 (3), 76–87.

Assenza, G., Capone, F., di Biase, L., Ferreri, F., Florio, L., Guerra, A., Marano, M., Paolucci, M., Ranieri, F., Salomone, G., Tombini, M., Thut, G., and Di Lazzaro, V., 2017. Oscillatory activities in neurological disorders of elderly: Biomarkers to target for neuromodulation. *Frontiers in Aging Neuroscience*, 9, 1–18.

Athanasiou, A., Klados, M.A., Styliadis, C., Foroglou, N., Polyzoidis, K., and Bamidis, P.D., 2018. Investigating the Role of Alpha and Beta Rhythms in Functional Motor Networks. *Neuroscience*, 378, 54–70.

Avenanti, A., Coccia, M., Ladavas, E., Provinciali, L., and Ceravolo, M.G., 2012. Low-frequency rTMS promotes use-dependent motor plasticity in

chronic stroke: a randomized trial. *Neurology*, 78 (4), 256–264.

Barros, M.G.R.G., 2012. Encargos com o Acidente Vascular Cerebral no Alto Minho. Instituto Politécnico de Viana do Castelo.

Barwood, C., Murdoch, B., Whelan, B., Lloyd, D., Riek, S., O' Sullivan, J., Coulthard, A., and Wong, A., 2011. Improved language performance subsequent to low-frequency rTMS in patients with chronic non-fluent aphasia post-stroke. *European Journal of Neurology*, 18 (7), 935–943.

Barwood, C., Murdoch, B., Whelan, B., Lloyd, D., Riek, S., O'Sullivan, J., Coulthard, A., Wong, A., Aitken, P., and Hall, G., 2011. The effects of low frequency Repetitive Transcranial Magnetic Stimulation (rTMS) and sham condition rTMS on behavioural language in chronic non-fluent aphasia: Short term outcomes. *NeuroRehabilitation*, 28 (2), 113–128.

Barwood, C.H.S., Murdoch, B.E., Riek, S., O'Sullivan, J.D., Wong, A., Lloyd, D., and Coulthard, A., 2013. Long term language recovery subsequent to low frequency rTMS in chronic non-fluent aphasia. *NeuroRehabilitation*, 32 (4), 915–928.

Barwood, C.H.S., Murdoch, B.E., Whelan, B.M., Lloyd, D., Riek, S., O'Sullivan, J.D., Coulthard, A., and Wong, A., 2012. Improved receptive and expressive language abilities in nonfluent aphasic stroke patients after application of rTMS: An open protocol case series. *Brain Stimulation*, 5 (3), 274–286.

Benjamin, E.J., Virani, S.S., Callaway, C.W., Chamberlain, A.M., Chang, A.R., Cheng, S., Chiuve, S.E., Cushman, M., Delling, F.N., Deo, R., De Ferranti, S.D., Ferguson, J.F., Fornage, M., Gillespie, C., Isasi, C.R., Jiménez, M.C., Jordan, L.C., Judd, S.E., Lackland, D., Lichtman, J.H., Lisabeth, L., Liu, S., Longenecker, C.T., Lutsey, P.L., MacKey, J.S., Matchar, D.B., Matsushita, K., Mussolino, M.E., Nasir, K., O'Flaherty, M., Palaniappan, L.P., Pandey, A., Pandey, D.K., Reeves, M.J., Ritchey, M.D., Rodriguez, C.J., Roth, G.A., Rosamond, W.D., Sampson, U.K.A., Satou, G.M., Shah, S.H., Spartano, N.L., Tirschwell, D.L., Tsao, C.W., Voeks, J.H.,

Willey, J.Z., Wilkins, J.T., Wu, J.H.Y., Alger, H.M., Wong, S.S., and Muntner, P., 2018. Heart disease and stroke statistics - 2018 update: A report from the American Heart Association. *Circulation*.

Bernardino, I., Castelhano, J., Farivar, R., Silva, E.D., and Castelo-Branco, M., 2013. Neural correlates of visual integration in Williams syndrome: Gamma oscillation patterns in a model of impaired coherence. *Neuropsychologia*, 1287–1295.

Binnie, C.D. and Prior, P.F., 1994. Electroencephalography. *Journal of neurology, neurosurgery, and psychiatry*, 57 (11), 1308–1319.

Blesneag, A. V, Slavoaca, D.F., Popa, L., Stan, A.D., Jemna, N., Isai Moldovan, F., and Muresanu, D.F., 2015. Low-frequency rTMS in patients with subacute ischemic stroke: clinical evaluation of short and long-term outcomes and neurophysiological assessment of cortical excitability. *Journal of medicine and life*, 8 (3), 378–387.

Bliss, T.V.P. and Cooke, S.F., 2011. Long-term potentiation and long-term depression: a clinical perspective. *Clinics*, 66 (S1), 3–17.

Boddington, L.J. and Reynolds, J.N.J., 2017. Targeting interhemispheric inhibition with neuromodulation to enhance stroke rehabilitation. *Brain Stimulation*, 10, 214–222.

Bohle, H., Rimpel, J., Schauenburg, G., Gebel, A., Stelzel, C., Heinzel, S., Rapp, M., and Granacher, U., 2019. Behavioral and neural correlates of cognitive-motor interference during multitasking in young and old adults. *Neural Plasticity*.

Bolay, H., Gürsoy-Özdemir, Y., Ünal, I., and Dalkara, T., 2000. Altered mechanisms of motor-evoked potential generation after transient focal cerebral ischemia in the rat: Implications for transcranial magnetic stimulation. *Brain Research*, 873, 26–33.

Bonnì, S., Ponzo, V., Caltagirone, C., and Koch, G., 2014. Cerebellar theta burst stimulation in stroke patients with ataxia. *Functional Neurology*, 29 (1), 41–45.

Boonzaier, J., van Tilborg, G.A.F., Neggers,

S.F.W., and Dijkhuizen, R.M., 2018. Noninvasive Brain Stimulation to Enhance Functional Recovery After Stroke: Studies in Animal Models. *Neurorehabilitation and Neural Repair*, 32 (11), 927–940.

Brodie, S.M., Meehan, S., Borich, M.R., and Boyd, L. a, 2014. 5 Hz repetitive transcranial magnetic stimulation over the ipsilesional sensory cortex enhances motor learning after stroke. *Frontiers in Human Neuroscience*, 8 (143), 1–10.

Brückner, S. and Kammer, T., 2016. Modulation of visual cortex excitability by continuous theta burst stimulation depends on coil type. *PLoS ONE*, 11 (7).

Burghaus, L., Hilker, R., Dohmen, C., Bosche, B., Winhuisen, L., Galldiks, N., Szelies, B., and Heiss, W.D., 2007. Early electroencephalography in acute ischemic stroke: Prediction of a malignant course? *Clinical Neurology and Neurosurgery*, 109, 45–49.

Caleo, M., 2015. Rehabilitation and plasticity following stroke: Insights from rodent models. *Neuroscience*.

Carter, A.R., Connor, L.T., and Dromerick, A.W., 2010. Rehabilitation after stroke: Current state of the science. *Current Neurology and Neuroscience Reports*, 10 (3), 158–166.

Caschera, S., Petti, M., Mattia, D., and Astolfi, L., 2017. EEG source estimation accuracy in presence of simulated cortical lesions. *In*: *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*. 544–547.

Cassidy, J.M., Wodeyar, A., Wu, J., Kaur, K., Masuda, A.K., Srinivasan, R., and Cramer, S.C., 2020. Low-Frequency Oscillations Are a Biomarker of Injury and Recovery After Stroke. *Stroke*, 51, 1442–1450.

Castelhano, J., Bernardino, I., Rebola, J., Rodriguez, E., and Castelo-Branco, M., 2015. Oscillations or synchrony? Disruption of neural synchrony despite enhanced gamma oscillations in a model of disrupted perceptual coherence. *Journal of Cognitive Neuroscience*, 27 (12), 2416–2426.

Castelhano, J., Duarte, I.C., Abuhaiba, S.I., Rito, M., Sales, F., and Castelo-Branco, M., 2017. Cortical functional topography of high-frequency gamma activity relates to perceptual decision: An Intracranial study. *PLoS ONE*, 12 (10), e0186428.

Castelhano, J., Rebola, J., Leitão, B., Rodriguez, E., and Castelo-Branco, M., 2013. To Perceive or Not Perceive: The Role of Gamma-band Activity in Signaling Object Percepts. *PLoS ONE*, 8 (6).

Castelhano, J., Tavares, P., Mouga, S., Oliveira, G., and Castelo-Branco, M., 2018. Stimulus dependent neural oscillatory patterns show reliable statistical identification of autism spectrum disorder in a face perceptual decision task. *Clinical Neurophysiology*, 129, 981–989.

Cazzoli, D., Müri, R.M., Schumacher, R., von Arx, S., Chaves, S., Gutbrod, K., Bohlhalter, S., Bauer, D., Vanbellingen, T., Bertschi, M., Kipfer, S., Rosenthal, C.R., Kennard, C., Bassetti, C.L., and Nyffeler, T., 2012. Theta burst stimulation reduces disability during the activities of daily living in spatial neglect. *Brain*, 135 (Pt 11), 3426–3439.

Cha, H.-G., Kim, M.-K., Nam, H.-C., and Ji, S.-G., 2014. Effects of high frequency repetitive transcranial magnetic stimulation on function in subacute stroke patients. *Journal of Magnetics*, 19 (2), 192–196.

Cha, H.G. and Kim, M.K., 2016. Effects of repetitive transcranial magnetic stimulation on arm function and decreasing unilateral spatial neglect in subacute stroke: a randomized controlled trial. *CLINICAL REHABILITATION*, 30 (7), 649–656.

Chang, W.H., Kim, Y.-H., Yoo, W.-K., Goo, K.-H., Park, C.-H., Kim, S.T., and Pascual-Leone, A., 2012. rTMS with motor training modulates cortico-basal ganglia-thalamocortical circuits in stroke patients. *Restorative Neurology and Neuroscience*, 30 (3), 179–89.

Chang, W.H., Kim, Y.H., Bang, O.Y., Kim, S.T., Park, Y.H., and Lee, P.K., 2010. Long-term effects of rTMS on motor recovery in patients after subacute stroke. *Journal of Rehabilitation*

Medicine, 42 (8), 758–764.

Cheng, I.K.Y., Chan, K.M.K., Wong, C.-S., Li, L.S.W., Chiu, K.M.Y., Cheung, R.T.F., and Yiu, E.M.L., 2017. Neuronavigated high-frequency repetitive transcranial magnetic stimulation for chronic post-stroke dysphagia: A randomized controlled study. *Journal of rehabilitation medicine*, 49 (6), 475–481.

Chervyakov, A. V., Chernyavsky, A.Y., Sinitsyn, D.O., and Piradov, M.A., 2015. Possible Mechanisms Underlying the Therapeutic Effects of Transcranial Magnetic Stimulation. *Frontiers in Human Neuroscience*, 9.

Chieffo, R., Ferrari, F., Battista, P., Houdayer, E., Nuara, A., Alemanno, F., Abutalebi, J., Zangen, A., Comi, G., Cappa, S.F., and Leocani, L., 2014. Excitatory deep transcranial magnetic stimulation with H-coil over the right homologous Broca's region improves naming in chronic post-stroke aphasia. *Neurorehabilitation and Neural Repair*, 28 (3), 291–298.

Chieffo, R., De Prezzo, S., Houdayer, E., Nuara, A., Di Maggio, G., Coppi, E., Ferrari, L., Straffi, L., Spagnolo, F., Velikova, S., Sessa, M., Comola, M., Zangen, A., Comi, G., and Leocani, L., 2014. Deep repetitive transcranial magnetic stimulation with H-coil on lower limb motor function in chronic stroke: A pilot study. *Archives of Physical Medicine and Rehabilitation*, 95 (6), 1141–1147.

Chipchase, L., Schabrun, S., Cohen, L., Hodges, P., Ridding, M., Rothwell, J., Taylor, J., and Ziemann, U., 2012. A checklist for assessing the methodological quality of studies using transcranial magnetic stimulation to study the motor system: An international consensus study. *Clinical Neurophysiology*, 123 (9), 1698–1704.

Chung, S.W., Hill, A.T., Rogasch, N.C., Hoy, K.E., and Fitzgerald, P.B., 2016. Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*.

Chung, S.W., Lewis, B.P., Rogasch, N.C., Saeki, T., Thomson, R.H., Hoy, K.E., Bailey, N.W., and Fitzgerald, P.B., 2017. Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. *Clinical Neurophysiology*, 128 (7), 1117–1126.

Compumedics NeuroScan, 2015. Quik-Cap Electrode System; Synamps 2/RT 64-channel EEG/EP/ERP [online]. Available from: http://compumedicsneuroscan.com/quik-cap-electrode-system/; http://compumedicsneuroscan.com/synamps-rt-64-channel-eegeperp/ [Accessed 9 Jul 2015].

Conforto, A.B., Anjos, S.M., Saposnik, G., Mello, E.A., Nagaya, E.M., Santos, W., Ferreiro, K.N., Melo, E.S., Reis, F.I., Scaff, M., and Cohen, L.G., 2012. Transcranial magnetic stimulation in mild to severe hemiparesis early after stroke: A proof of principle and novel approach to improve motor function. *Journal of Neurology*, 259 (7), 1399–1405.

Conforto, A.B., Marie, S.K.N., Cohen, L.G., and Scaff, M., 2003. Estimulação magnética transcraniana. *Arquivos de Neuro-Psiquiatria*, 61 (1), 146–152.

Cooper, R., Binnie, C.D., and Billings, R., 2005. *Techniques in Clinical Neurophysiology: A Practical Manual*. 1st ed. Elsevier Churchill Livingstone.

Costa, F.A. da, Silva, D.L.A. da, and Rocha, V.M. da, 2011. Estado neurológico e cognição de pacientes pós-acidente vascular cerebral. *Revista da Escola de Enfermagem da U S P*, 45 (5), 1083–1088.

Coupland, A.P., Thapar, A., Qureshi, M.I., Jenkins, H., and Davies, A.H., 2017. The definition of stroke. *Journal of the Royal Society of Medicine*, 110 (1), 9–12.

Dafotakis, M., Grefkes, C., Eickhoff, S.B., Karbe, H., Fink, G.R., and Nowak, D. a, 2008. Effects of rTMS on grip force control following subcortical stroke. *Experimental Neurology*, 211 (2), 407–12.

Davidson, R.J., Jackson, D.C., and Larson, C.L., 2007. Human electroencephalography. *In*: *Handbook of psychophysiology*. Cambridge University Press, 27–52.

Davila-Pérez, P., Jannati, A., Fried, P.J., Cudeiro, J., and Pascual-Leone, A., 2018. The Effects of Waveform and Current Direction on the Efficacy and Test–Retest Reliability of Transcranial Magnetic Stimulation. *Neuroscience*, 393, 97–109.

Delorme, A. and Makeig, S., 2004. EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, 134 (1), 9–21.

Dionísio, A., Duarte, I.C., Patrício, M., and Castelo-Branco, M., 2018. The Use of Repetitive Transcranial Magnetic Stimulation for Stroke Rehabilitation: A Systematic Review. *Journal of Stroke and Cerebrovascular Diseases*, 27 (1), 1–31.

Dionísio, A., Gouveia, R., Duarte, I.C., Castelhano, J., Duecker, F., and Castelo-Branco, M., 2020. Continuous theta burst stimulation increases contralateral mu and beta rhythms with arm elevation: implications for neurorehabilitation. *Journal of Neural Transmission*, 127 (1), 17–25.

Direcção-Geral da Saúde, 2017. Programa Nacional para as Doenças Cérebro-Cardiovasculares 2017. *DGS*, 20.

Du, J., Tian, L., Liu, W., Hu, J., Xu, G., Ma, M., Fan, X., Ye, R., Jiang, Y., Yin, Q., Zhu, W., Xiong, Y., Yang, F., and Liu, X., 2016. Effects of repetitive transcranial magnetic stimulation on motor recovery and motor cortex excitability in patients with stroke: a randomized controlled trial. *European journal of neurology*, 23 (11), 1666–1672.

Du, J., Yang, F., Liu, L., Hu, J., Cai, B., Liu, W., Xu, G., and Liu, X., 2016. Repetitive transcranial magnetic stimulation for rehabilitation of poststroke dysphagia: A randomized, double-blind clinical trial. *CLINICAL NEUROPHYSIOLOGY*, 127 (3), 1907–1913.

Duarte, I.C., Castelhano, J., Sales, F., and Castelo-Branco, M., 2016. The anterior versus posterior hippocampal oscillations debate in human spatial navigation: evidence from an electrocorticographic case study. *Brain and Behavior*, 6 (9).

Duncan, H., Spillane, K., and Morrison, I., 2014. Electroencephalography – An Overview. *Scottish Universities Medical Journal*, 3 (1), 47–53.

Emara, T.H., Moustafa, R.R., ElNahas, N.M., Elganzoury, A.M., Abdo, T.A., Mohamed, S.A., and Eletribi, M.A., 2010. Repetitive transcranial magnetic stimulation at 1Hz and 5Hz produces sustained improvement in motor function and disability after ischaemic stroke. *European Journal of Neurology*, 17 (9), 1203–1209.

Etoh, S., Noma, T., Ikeda, K., Jonoshita, Y., Ogata, A., Matsumoto, S., Shimodozono, M., and Kawahira, K., 2013. Effects of repetitive transcranial magnetic stimulation on repetitive facilitation exercises of the hemiplegic hand in chronic stroke patients. *Journal of Rehabilitation Medicine*, 45 (9), 843–847.

Fling, B.W. and Seidler, R.D., 2012. Task-dependent effects of interhemispheric inhibition on motor control. *Behavioural Brain Research*, 226 (1), 211–217.

Foltys, H., Krings, T., Meister, I.G., Sparing, R., Boroojerdi, B., Thron, A., and Töpper, R., 2003. Motor representation in patients rapidly recovering after stroke: A functional magnetic resonance imaging and transcranial magnetic stimulation study. *Clinical Neurophysiology*, 114 (12), 2404–2415.

Fregni, F., Boggio, P.S., Valle, A.C., Rocha, R.R., Duarte, J., Ferreira, M.J.L., Wagner, T., Fecteau, S., Rigonatti, S.P., Riberto, M., Freedman, S.D., and Pascual-Leone, A., 2006. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. *Stroke*, 37 (8), 2115–2122.

Freitas, C., Farzan, F., and Pascual-Leone, A., 2013. Assessing brain plasticity across the lifespan with transcranial magnetic stimulation: Why, how, and what is the ultimate goal? *Frontiers in Neuroscience*, 7 (42), 1–17.

Fu, M.J., Daly, J.J., and Çavuşoğlu, M.C., 2006. Assessment of EEG event-related desynchronization in stroke survivors performing shoulder-elbow

movements. *In*: *Proceedings - IEEE International Conference on Robotics and Automation*. 3158–3164.

Fu, W., Song, W., Zhang, Y., Yang, Y., Huo, S., Zhang, R., and Wang, M., 2015. Long-term effects of continuous theta-burst stimulation in visuospatial neglect. *The Journal of International Medical Research*, 43 (2), 196–203.

g.tec medical engineering, 2015. No Title [online]. Available from: http://www.gtec.at/var/plain_site/storage/images/media/images/support/mount_eeg_10_20_system/10664-3-eng-GB/mount_eeg_10_20_system.png [Accessed 10 Jul 2015].

Galvão, S.C.B., Dos Santos, R.B.C., Dos Santos, P.B., Cabral, M.E., and Monte-Silva, K., 2014. Efficacy of coupling repetitive transcranial magnetic stimulation and physical therapy to reduce upper-limb spasticity in patients with stroke: a randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, 95 (2), 222–229.

Gammeri, R., Iacono, C., Ricci, R., and Salatino, A., 2020. Unilateral spatial neglect after stroke: Current insights. *Neuropsychiatric Disease and Treatment*, 16, 131–152.

George, M.S., Lisanby, S.H., and Sackeim, H.A., 1999. Transcranial magnetic stimulation: applications in neuropsychiatry. *Archives of general psychiatry*, 56 (4), 300–11.

Goldsworthy, M.R., Müller-Dahlhaus, F., Ridding, M.C., and Ziemann, U., 2014. Inter-subject variability of LTD-like plasticity in human motor cortex: A matter of preceding motor activation. *Brain Stimulation*, 7 (6), 864–870.

Goldsworthy, M.R., Pitcher, J.B., and Ridding, M.C., 2012. A comparison of two different continuous theta burst stimulation paradigms applied to the human primary motor cortex. *Clinical Neurophysiology*, 123 (11), 2256–2263.

Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L.G., Mall, V., Kaelin-Lang, A., Mima, T., Rossi, S., Thickbroom, G.W., Rossini, P.M., Ziemann, U., Valls-Solé, J., and Siebner, H.R., 2012. A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee. *Clinical Neurophysiology*, 123 (5), 858–882.

Hallett, M., 2001. Plasticity of the human motor cortex and recovery from stroke. *Brain Research Reviews*, 36 (2–3), 169–174.

Hamada, M., Murase, N., Hasan, A., Balaratnam, M., and Rothwell, J.C., 2013. The role of interneuron networks in driving human motor cortical plasticity. *Cerebral Cortex*, 23 (7), 1593–1605.

Hanajima, R., Furubayashi, T., Kobayashi Iwata, N., Shiio, Y., Okabe, S., Kanazawa, I., and Ugawa, Y., 2003. Further evidence to support different mechanisms underlying intracortical inhibition of the motor cortex. *Experimental Brain Research*, 151, 427–434.

Hanakawa, T., Mima, T., Matsumoto, R., Abe, M., Inouchi, M., Urayama, S.I., Anami, K., Honda, M., and Fukuyama, H., 2009. Stimulus-response profile during single-pulse transcranial magnetic stimulation to the primary motor cortex. *Cerebral Cortex*, 19, 2605–2615.

Hara, T., Abo, M., Kakita, K., Mori, Y., Yoshida, M., and Sasaki, N., 2017. The Effect of Selective Transcranial Magnetic Stimulation with Functional Near-Infrared Spectroscopy and Intensive Speech Therapy on Individuals with Post-Stroke Aphasia. *European Neurology*, 77 (3–4), 186–194.

Hara, Y., 2015. Brain plasticity and rehabilitation in stroke patients. *Journal of Nippon Medical School*, 82, 4–13.

He, B., Dai, Y., Astolfi, L., Babiloni, F., Yuan, H., and Yang, L., 2011. EConnectome: A MATLAB toolbox for mapping and imaging of brain functional connectivity. *Journal of Neuroscience Methods*, 195 (2), 261–269.

Heart and Stroke Foundation of Canada, 2015. No Title [online]. Available from: http://heart.arizona.edu/%0Dsites/heart.arizona.edu/files/spotlight/stroke_hem_iso.jpg [Accessed 3 Jun 2015].

Heaton, J., 2012. Repetitive Transcranial Magnetic Stimulation: A comparative trial of low frequency treatments.

University of Otago.

Heiss, W.-D., Hartmann, A., Rubi-Fessen, I., Anglade, C., Kracht, L., Kessler, J., Weiduschat, N., Rommel, T., and Thiel, A., 2013. Noninvasive brain stimulation for treatment of right- and left-handed poststroke aphasics. *Cerebrovascular Diseases*, 36 (5–6), 363–372.

Herrmann, L.L. and Ebmeier, K.P., 2009. Transcranial magnetic stimulation. *Psychiatry*, 8 (4), 130–134.

Higgins, J., Koski, L., and Xie, H., 2013. Combining rTMS and task-oriented training in the rehabilitation of the arm after stroke: a pilot randomized controlled trial. *Stroke Research and Treatment*, 2013.

Hordacre, B., Goldsworthy, M.R., Vallence, A.M., Darvishi, S., Moezzi, B., Hamada, M., Rothwell, J.C., and Ridding, M.C., 2017. Variability in neural excitability and plasticity induction in the human cortex: A brain stimulation study. *Brain Stimulation*, 10 (3), 588–595.

Hosomi, K., Morris, S., Sakamoto, T., Taguchi, J., Maruo, T., Kageyama, Y., Kinoshita, Y., Goto, Y., Shimokawa, T., Koyama, T., and Saitoh, Y., 2016. Daily Repetitive Transcranial Magnetic Stimulation for Poststroke Upper Limb Paresis in the Subacute Period. *JOURNAL OF STROKE & CEREBROVASCULAR DISEASES*, 25 (7), 1655–1664.

Hu, R., Zhu, Y., Tang, X., Du, X., Zhang, H., Liu, Q., Wu, J., Fan, S., Hao, Y., and Wu, Y., 2017. Continuous theta burst stimulation inhibits the bilateral hemispheres. *Neuroscience Letters*, 657, 134–139.

Huang, Y.Z., Edwards, M.J., Rounis, E., Bhatia, K.P., and Rothwell, J.C., 2005. Theta burst stimulation of the human motor cortex. *Neuron*, 45 (2), 201–206.

Huerta, P.T. and Volpe, B.T., 2009. Transcranial magnetic stimulation, synaptic plasticity and network oscillations. *Journal of NeuroEngineering and Rehabilitation*, 6 (7).

Hummel, F.C. and Cohen, L.G., 2005. Drivers of brain plasticity. *Current opinion in neurology*, 18 (6), 667–74.

Iezzi, E., Conte, A., Suppa, A., Agostino, R., Dinapoli, L., Scontrini, A., and Berardelli, A., 2008. Phasic Voluntary Movements Reverse the Aftereffects of Subsequent Theta-Burst Stimulation in Humans. *Journal of Neurophysiology*, 100 (4), 2070–2076.

Ilmoniemi, R.J. and Kičić, D., 2010. Methodology for combined TMS and EEG. *Brain Topography*.

Ilmoniemi, R.J., Ruohonen, J., and Karhu, J., 1999. Transcranial magnetic stimulation-a new tool for functional imaging of the brain. *Critical reviews in biomedical engineering*, 27 (3–5), 241–84.

Iyer, K.K., 2017. Effective assessments of electroencephalography during stroke recovery: contemporary approaches and considerations. *Journal of Neurophysiology*, jn.00206.2017.

Jannati, A., Block, G., Oberman, L.M., Rotenberg, A., and Pascual-Leone, A., 2017. Interindividual variability in response to continuous theta-burst stimulation in healthy adults. *Clinical Neurophysiology*, 128 (11), 2268–2278.

Janssen, A., 2016. *Transcranial Magnetic Stimulation: Measuring and Modeling in Health and Disease*. Nijmegen, the Netherlands: Gildeprint Drukkerijen.

Johansson, B.B., 2000. Brain plasticity and stroke rehabilitation. The Willis lecture. *Stroke; a journal of cerebral circulation*, 31 (1), 223–230.

Johnston, M. V., 2009. Plasticity in the developing brain: implications for rehabilitation. *Developmental Disabilities Research Reviews*, 15 (2), 94–101.

Kakuda, W., Abo, M., Kaito, N., Ishikawa, A., Taguchi, K., and Yokoi, A., 2010. Six-day course of repetitive transcranial magnetic stimulation plus occupational therapy for post-stroke patients with upper limb hemiparesis: a case series study. *Disability and Rehabilitation*, 32 (10), 801–7.

Kakuda, W., Abo, M., Kobayashi, K., Momosaki, R., Yokoi, A., Fukuda, A., Ishikawa, A., Ito, H., and Tominaga, A., 2010. Low-frequency repetitive transcranial magnetic stimulation and intensive occupational therapy for poststroke patients with upper limb

hemiparesis: preliminary study of a 15-day protocol. *International Journal of Rehabilitation Research*, 33 (4), 339–345.

Kakuda, W., Abo, M., Kobayashi, K., Momosaki, R., Yokoi, A., Fukuda, A., Ito, H., and Tominaga, A., 2011. Combination treatment of low-frequency rTMS and occupational therapy with levodopa administration: an intensive neurorehabilitative approach for upper limb hemiparesis after stroke. *The International Journal of Neuroscience*, 121 (7), 373–8.

Kakuda, W., Abo, M., Kobayashi, K., Momosaki, R., Yokoi, A., Fukuda, A., Ito, H., Tominaga, A., Umemori, T., and Kameda, Y., 2011. Anti-spastic effect of low-frequency rTMS applied with occupational therapy in post-stroke patients with upper limb hemiparesis. *Brain Injury*, 25 (5), 496–502.

Kakuda, W., Abo, M., Kobayashi, K., Momosaki, R., Yokoi, A., Fukuda, A., and Umemori, T., 2011. Application of combined 6-Hz primed low-frequency rTMS and intensive occupational therapy for upper limb hemiparesis after stroke. *NeuroRehabilitation*, 29 (4), 365–71.

Kakuda, W., Abo, M., Kobayashi, K., Takagishi, T., Momosaki, R., Yokoi, A., Fukuda, A., Ito, H., and Tominaga, A., 2011. Baseline severity of upper limb hemiparesis influences the outcome of low-frequency rTMS combined with intensive occupational therapy in patients who have had a stroke. *PM & R*, 3 (6), 516–522.

Kakuda, W., Abo, M., Momosaki, R., Yokoi, A., Fukuda, A., Ito, H., Tominaga, A., Umemori, T., and Kameda, Y., 2012. Combined therapeutic application of botulinum toxin type A, low-frequency rTMS, and intensive occupational therapy for post-stroke spastic upper limb hemiparesis. *European Journal of Physical and Rehabilitation Medicine*, 48 (1), 47–55.

Kakuda, W., Abo, M., Nakayama, Y., Kiyama, A., and Yoshida, H., 2013. High-frequency rTMS using a double cone coil for gait disturbance. *Acta Neurologica Scandinavica*, 128 (2),

100–106.

Kakuda, W., Abo, M., Sasanuma, J., Shimizu, M., Okamoto, T., Kimura, C., Kakita, K., and Hara, H., 2016. Combination Protocol of Low-Frequency rTMS and Intensive Occupational Therapy for Post-stroke Upper Limb Hemiparesis: a 6-year Experience of More Than 1700 Japanese Patients. *TRANSLATIONAL STROKE RESEARCH*, 7 (3), 172–179.

Kakuda, W., Abo, M., Shimizu, M., Sasanuma, J., Okamoto, T., Yokoi, A., Taguchi, K., Mitani, S., Harashima, H., Urushidani, N., Urashima, M., and Investigators, T.N., 2012. A multi-center study on low-frequency rTMS combined with intensive occupational therapy for upper limb hemiparesis in post-stroke patients. *Journal of NeuroEngineering and Rehabilitation*, 9 (1), 4.

Kakuda, W., Abo, M., Watanabe, S., Momosaki, R., Hashimoto, G., Nakayama, Y., Kiyama, A., and Yoshida, H., 2013. High-frequency rTMS applied over bilateral leg motor areas combined with mobility training for gait disturbance after stroke: a preliminary study. *Brain Injury*, 27 (9), 1080–1086.

Kalitzin, S., Petkov, G., Suffczynski, P., Grigorovsky, V., Bardakjian, B.L., Lopes da Silva, F., and Carlen, P.L., 2019. Epilepsy as a manifestation of a multistate network of oscillatory systems. *Neurobiology of Disease*, 130.

Kammer, T., Beck, S., Thielscher, A., Laubis-Herrmann, U., and Topka, H., 2001. Motor thresholds in humans: A transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. *Clinical Neurophysiology*, 112, 250–258.

Keser, Z. and Francisco, G.E., 2015. Neuropharmacology of Poststroke Motor and Speech Recovery. *Physical Medicine and Rehabilitation Clinics of North America*, 26, 671–689.

Khedr, E.M., Abdel-Fadeil, M.R., Farghali, A., and Qaid, M., 2009. Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. *European Journal of Neurology*, 16 (12),

1323–1330.

Khedr, E.M. and Abo-Elfetoh, N., 2010. Therapeutic role of rTMS on recovery of dysphagia in patients with lateral medullary syndrome and brainstem infarction. *Journal of Neurology, Neurosurgery, and Psychiatry*, 81 (5), 495–499.

Khedr, E.M., Abo-Elfetoh, N., and Rothwell, J.C., 2009. Treatment of post-stroke dysphagia with repetitive transcranial magnetic stimulation. *Acta Neurologica Scandinavica*, 119 (3), 155–161.

Khedr, E.M., Ahmed, M.A., Fathy, N., and Rothwell, J.C., 2005. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology*, 65 (3), 466–468.

Khedr, E.M., El-Fetoh, N.A., Ali, A.M., El-Hammady, D.H., Khalifa, H., Atta, H., and Karim, A.A., 2014. Dual-hemisphere repetitive transcranial magnetic stimulation for rehabilitation of poststroke aphasia: a randomized, double-blind clinical trial. *Neurorehabilitation and Neural Repair*, 28 (8), 740–750.

Khedr, E.M., Etraby, A.E., Hemeda, M., Nasef, A.M., and Razek, A.A.E., 2010. Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke. *Acta Neurologica Scandinavica*, 121 (1), 30–37.

Kilavik, B.E., Zaepffel, M., Brovelli, A., MacKay, W.A., and Riehle, A., 2013. The ups and downs of beta oscillations in sensorimotor cortex. *Experimental Neurology*, 245, 15–26.

Kim, B.R., Chun, M.H., Kim, D.Y., and Lee, S.J., 2013. Effect of high- and low-frequency repetitive transcranial magnetic stimulation on visuospatial neglect in patients with acute stroke: A double-blind, sham-controlled trial. *Archives of Physical Medicine and Rehabilitation*, 94 (5), 803–807.

Kim, C., Choi, H.E., Jung, H., Lee, B.-J., Lee, K.H., and Lim, Y.-J., 2014. Comparison of the Effects of 1 Hz and 20 Hz rTMS on Motor Recovery in Subacute Stroke Patients. *Annals of Rehabilitation Medicine*, 38 (5), 585–591.

Kim, W., Jung, S., Oh, M., Min, Y., Lim, J., and Paik, N., 2014. Effect of repetitive transcranial magnetic stimulation over the cerebellum on patients with ataxia after posterior circulation stroke: a pilot study. *Journal of Rehabilitation Medicine*, 46 (5), 418–23.

Kim, Y.-H., You, S.H., Ko, M.-H., Park, J.-W., Lee, K.H., Jang, S.H., Yoo, W.-K., and Hallett, M., 2006. Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. *Stroke*, 37 (6), 1471–1476.

Kim, Y., Jung, J., and Shin, S., 2015. A comparison of the effects of repetitive transcranial magnetic stimulation (rTMS) by number of stimulation sessions on hemispatial neglect in chronic stroke patients. *Experimental Brain Research*, 233 (1), 283–289.

Kimiskidis, V.K., Valentin, A., and Kälviäinen, R., 2014. Transcranial magnetic stimulation for the diagnosis and treatment of epilepsy. *Current opinion in neurology*, 27 (2), 236–41.

Kindler, J., Schumacher, R., Cazzoli, D., Gutbrod, K., Koenig, M., Nyffeler, T., Dierks, T., and Müri, R.M., 2012. Theta burst stimulation over the right Broca's homologue induces improvement of naming in aphasic patients. *Stroke*, 43 (8), 2175–2179.

Klomjai, W., Katz, R., and Lackmy-Vallée, A., 2015. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of Physical and Rehabilitation Medicine*, 58 (4), 208–213.

Kobayashi, M. and Pascual-Leone, A., 2003. Transcranial magnetic stimulation in neurology. *Lancet Neurology*, 2 (3), 145–156.

Koganemaru, S., Mima, T., Thabit, M.N., Ikkaku, T., Shimada, K., Kanematsu, M., Takahashi, K., Fawi, G., Takahashi, R., Fukuyama, H., and Domen, K., 2010. Recovery of upper-limb function due to enhanced use-dependent plasticity in chronic stroke patients. *Brain*, 133 (11), 3373–3384.

Kokinovic, B. and Medini, P., 2018. Loss of GABAB-mediated interhemispheric synaptic inhibition in stroke periphery.

Journal of Physiology, 596 (10), 1949–1964.

Koyama, S., Tanabe, S., Warashina, H., Kaneko, T., Sakurai, H., Kanada, Y., Nagata, J., and Kanno, T., 2014. NMES with rTMS for moderate to severe dysfunction after stroke. *NeuroRehabilitation*, 35 (3), 363–368.

Kubis, N., 2016. Non-invasive brain stimulation to enhance post-stroke recovery. *Frontiers in Neural Circuits*, 10.

Kwon, T.G., Kim, Y.-H., Chang, W.H., Bang, O.Y., and Shin, Y.-I., 2014. Effective method of combining rTMS and motor training in stroke patients. *Restorative Neurology and Neuroscience*, 32 (2), 223–32.

Lachaux, J.P., Rodriguez, E., Martinerie, J., and Varela, F.J., 1999. Measuring phase synchrony in brain signals. *Human Brain Mapping*.

Langhorne, P., Stott, D.J., Robertson, L., MacDonald, J., Jones, L., McAlpine, C., Dick, F., Taylor, G.S., and Murray, G., 2000. Medical complications after stroke: a multicenter study. *Stroke; a journal of cerebral circulation*, 31 (6), 1223–1229.

Di Lazzaro, V., Pilato, F., Saturno, E., Oliviero, A., Dileone, M., Mazzone, P., Insola, A., Tonali, P.A., Ranieri, F., Huang, Y.Z., and Rothwell, J.C., 2005. Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. *Journal of Physiology*, 565 (3), 945–950.

Lee, J., Kim, S., Lee, K., Lee, S., and Lee, J., 2015. Effect of Repetitive Transcranial Magnetic Stimulation According to the Stimulation Site in Stroke Patients With Dysphagia. *Annals of Rehabilitation Medicine*, 39 (3), 432–439.

Legg, L.A., Lewis, S.R., Schofield-Robinson, O.J., Drummond, A., and Langhorne, P., 2017. Occupational therapy for adults with problems in activities of daily living after stroke. *Cochrane Database of Systematic Reviews*, (7).

Lepage, J.F., Saint-Amour, D., and Théoret, H., 2008. EEG and neuronavigated single-pulse TMS in the study of the observation/execution matching system: Are both techniques measuring the same process? *Journal of Neuroscience Methods*.

Liepert, J., Zittel, S., and Weiller, C., 2007. Improvement of dexterity by single session low-frequency repetitive transcranial magnetic stimulation over the contralesional motor cortex in acute stroke: a double-blind placebo-controlled crossover trial. *Restorative Neurology and Neuroscience*, 25 (5–6), 461–465.

Light, G.A., Williams, L.E., Minow, F., Sprock, J., Rissling, A., Sharp, R., Swerdlow, N.R., and Braff, D.L., 2010. Electroencephalography (EEG) and event-related potentials (ERPs) with human participants. *Current Protocols in Neuroscience*.

Lim, J.Y., Kang, E.K., and Paik, N.-J., 2010. Repetitive transcranial magnetic stimulation to hemispatial neglect in patients after stroke: an open-label pilot study. *Journal of Rehabilitation Medicine*, 42 (5), 447–452.

Lin, Y., Hu, C., Chi, J., Lin, L., Yen, T., Lin, Y., and Liou, T., 2015. Effects of repetitive transcranial magnetic stimulation of the unaffected hemisphere leg motor area in patients with subacute stroke and substantial leg impairment: a pilot study. *Journal of Rehabilitation Medicine*, 47 (4), 305–310.

Lioumis, P., 2012. Transcranial magnetic stimulation in assessment of cortical network properties. Aalto University.

Lokk, J., Salman Roghani, R., and Delbari, A., 2011. Effect of methylphenidate and/or levodopa coupled with physiotherapy on functional and motor recovery after stroke - a randomized, double-blind, placebo-controlled trial. *Acta Neurologica Scandinavica*, 123, 266–273.

Lopes da Silva, F., 2013. EEG and MEG: Relevance to Neuroscience. *Neuron*, 80, 1112–1128.

Lopes da Silva, F.H., 1990. A critical review of clinical applications of topographic mapping of brain potentials. *Journal of Clinical Neurophysiology*, 7 (4), 535–551.

Lowe, C.J. and Hall, P.A., 2018.

Reproducibility and sources of interindividual variability in the responsiveness to prefrontal continuous theta burst stimulation (cTBS). *Neuroscience Letters*, 687, 280–284.

Ludemann-Podubecka, J., Bosl, K., and Nowak, D.A., 2016. Inhibition of the contralesional dorsal premotor cortex improves motor function of the affected hand following stroke. *EUROPEAN JOURNAL OF NEUROLOGY*, 23 (4), 823–830.

Lüdemann-Podubecká, J., Bösl, K., Theilig, S., Wiederer, R., and Nowak, D.A., 2015. The effectiveness of 1Hz rTMS over the primary motor area of the unaffected hemisphere to improve hand function after stroke depends on hemispheric dominance. *Brain Stimulation*, 8 (4), 823–830.

van Lutterveld, R., Houlihan, S.D., Pal, P., Sacchet, M.D., McFarlane-Blake, C., Patel, P.R., Sullivan, J.S., Ossadtchi, A., Druker, S., Bauer, C., and Brewer, J.A., 2017. Source-space EEG neurofeedback links subjective experience with brain activity during effortless awareness meditation. *NeuroImage*, 151, 117–127.

MagVenture, 2016. MagPro magnetic stimulators [online]. Available from: http://www.magventure.com/en-gb/Products/MagPro-magnetic-stimulators [Accessed 26 Jan 2016].

Malcolm, M.P., Triggs, W.J., Light, K.E., Rothi, L.J.G., Wu, S., Reid, K., and Nadeau, S.E., 2007. Repetitive transcranial magnetic stimulation as an adjunct to constraint-induced therapy. *American Journal of Physical Medicine & Rehabilitation*, 86 (9), 707–715.

Mälly, J. and Dinya, E., 2008. Recovery of motor disability and spasticity in post-stroke after repetitive transcranial magnetic stimulation (rTMS). *Brain Research Bulletin*, 76, 388–395.

Mansur, C., Fregni, F., Boggio, P., Riberto, M., Gallucci-Neto, J., Santos, C., Wagner, T., Rigonatti, S., Marcolin, M., and Pascual-Leone, A., 2005. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. *Neurology*, 64 (10), 1802–4.

Matsuura, A., Onoda, K., Oguro, H., and Yamaguchi, S., 2015. Magnetic stimulation and movement-related cortical activity for acute stroke with hemiparesis. *EUROPEAN JOURNAL OF NEUROLOGY*, 22 (12), 1526–1532.

McAllister, C.J., Ronnqvist, K.C., Stanford, I.M., Woodhall, G.L., Furlong, P.L., and Hall, S.D., 2013. Oscillatory Beta Activity Mediates Neuroplastic Effects of Motor Cortex Stimulation in Humans. *Journal of Neuroscience*, 33 (18), 7919–7927.

McAllister, S.M., Rothwell, J.C., and Ridding, M.C., 2011. Cortical oscillatory activity and the induction of plasticity in the human motor cortex. *European Journal of Neuroscience*, 33 (10), 1916–1924.

Medina, J., Norise, C., Faseyitan, O., Coslett, H.B., Turkeltaub, P.E., and Hamilton, R.H., 2012. Finding the right words: Transcranial magnetic stimulation improves discourse productivity in non-fluent aphasia after stroke. *Aphasiology*, 26 (9), 1153–1168.

Medithe, J.W.C. and Nelakuditi, U.R., 2016. Study of Normal and Abnormal EEG. *In*: *3rd International Conference on Advanced Computing and Communication Systems*.

Melloni, L., Molina, C., Pena, M., Torres, D., Singer, W., and Rodriguez, E., 2007. Synchronization of Neural Activity across Cortical Areas Correlates with Conscious Perception. *Journal of Neuroscience*.

Moezzi, B., Pratti, L.M., Hordacre, B., Graetz, L., Berryman, C., Lavrencic, L.M., Ridding, M.C., Keage, H.A.D., McDonnell, M.D., and Goldsworthy, M.R., 2019. Characterization of Young and Old Adult Brains: An EEG Functional Connectivity Analysis. *Neuroscience*, 422, 230–239.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., and The PRISMA Group, 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, 6 (7), e1000097.

Morris, D.M., Uswatte, G., Crago, J.E., Cook, E.W., and Taub, E., 2001. The reliability of the wolf motor function test for assessing upper extremity function

after stroke. *Archives of Physical Medicine and Rehabilitation*.

Mozaffarian, D., Benjamin, E., Go, A., Arnett, D., Blaha, M., Cushman, M., de Ferranti, S., Després, J., Fullerton, H., Howard, V., Huffman, M., Judd, S., Kissela, B., Lackland, D., Lichtman, J., Lisabeth, L., Liu, S., Mackey, R., Matchar, D., McGuire, D., Mohler, E. 3rd, Moy, C., Muntner, P., Mussolino, M., Nasir, K., Neumar, R., Nichol, G., Palaniappan, L., Pandey, D., Reeves, M., Rodriguez, C., Sorlie, P., Stein, J., Towfighi, A., Turan, T., Virani, S., Willey, J., Woo, D., Yeh, R., and Turner, MB American Heart Association Statistics Committee, S.S.S., 2015. Heart Disease and Stroke Statistics – 2015 Update: A Report From the American Heart Association. *Circulation*, 131 (4), e29–322.

Müller, V.T., Santos, P.P. dos, Carnaval, T., Gomes, M. da M., and Fregni, F., 2013. O que é estimulação magnética transcraniana? *Revista Brasileira de Neurologia*, 49 (1), 20–31.

Murty, D.V.P.S., Manikandan, K., Kumar, W.S., Ramesh, R.G., Purokayastha, S., Javali, M., Rao, N.P., and Ray, S., 2020. Gamma oscillations weaken with age in healthy elderly in human EEG. *NeuroImage*, 215.

Naeser, M.A., Martin, P.I., Theoret, H., Kobayashi, M., Fregni, F., Nicholas, M., Tormos, J.M., Steven, M.S., Baker, E.H., and Pascual-Leone, A., 2011. TMS suppression of right pars triangularis, but not pars opercularis, improves naming in aphasia. *Brain and Language*, 119 (3), 206–213.

Naghdi, S., Ansari, N.N., Rastgoo, M., Forogh, B., Jalaie, S., and Olyaei, G., 2015. A pilot study on the effects of low frequency repetitive transcranial magnetic stimulation on lower extremity spasticity and motor neuron excitability in patients after stroke. *Journal of bodywork and movement therapies*, 19 (4), 616–623.

Nakamura, H., Kitagawa, H., Kawaguchi, Y., and Tsuji, H., 1997. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. *The Journal of physiology*, 498 (Pt 3, 817–823.

Neuper, C., Wörtz, M., and Pfurtscheller, G., 2006. ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Progress in brain research*, 159, 211–222.

Niedermeyer, E., 1999. The Normal EEG of the Waking Adult. *In*: E. Niedermeyer and F. Lopes da Silva, eds. *Electroencephalography: Basic Principles, Clinical Applications and Related Fields*. Baltimore: Lippincott Williams & Wilkins, 149–173.

Niemann, N., Wiegel, P., Kurz, A., Rothwell, J.C., and Leukel, C., 2018. Assessing TMS-induced D and I waves with spinal H-reflexes. *Journal of Neurophysiology*, 119, 933–943.

Noh, N.A., Fuggetta, G., and Manganotti, P., 2015. Theta-burst transcranial magnetic stimulation alters the functional topography of the cortical motor network. *Malaysian Journal of Medical Sciences*, 22, 36–44.

Noh, N.A., Fuggetta, G., Manganotti, P., and Fiaschi, A., 2012. Long lasting modulation of cortical oscillations after continuous theta burst transcranial magnetic stimulation. *PLoS ONE*, 7 (4).

Nowak, D.A., Grefkes, C., Dafotakis, M., Eickhoff, S., Küst, J., Karbe, H., and Fink, G.R., 2008. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. *Archives of Neurology*, 65 (6), 741–747.

O'Brien, A.T., Bertolucci, F., Torrealba-Acosta, G., Huerta, R., Fregni, F., and Thibaut, A., 2018. Non-invasive brain stimulation for fine motor improvement after stroke: a meta-analysis. *European Journal of Neurology*, 25, 1017–1026.

O'Shea, J. and Walsh, V., 2007. Transcranial magnetic stimulation. *Current Biology*, 17 (6), R196–R199.

Oldfield, R.C., 1971. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, 9 (1), 97–113.

Oliveri, M., 2011. Brain stimulation procedures for treatment of contralesional spatial neglect.

Restorative Neurology and Neuroscience, 29, 421–425.

Opie, G.M., Vosnakis, E., Ridding, M.C., Ziemann, U., and Semmler, J.G., 2017. Priming theta burst stimulation enhances motor cortex plasticity in young but not old adults. *Brain Stimulation*, 10 (2), 298–304.

Paiva, W.S., 2012. Avaliação da estimulação magnética transcraniana navegada no mapeamento anatômico e funcional não invasivo do córtex motor. Universidade de São Paulo.

Park, E., Kim, M.S., Chang, W.H., Oh, S.M., Kim, Y.K., Lee, A., and Kim, Y.H., 2017. Effects of Bilateral Repetitive Transcranial Magnetic Stimulation on Post-Stroke Dysphagia. *Brain Stimulation*, 10 (1), 75–82.

Park, J.W., Oh, J.C., Lee, J.W., Yeo, J.S., and Ryu, K.H., 2013. The effect of 5Hz high-frequency rTMS over contralesional pharyngeal motor cortex in post-stroke oropharyngeal dysphagia: A randomized controlled study. *Neurogastroenterology and Motility*, 25 (4), 324–331.

Pekna, M., Pekny, M., and Nilsson, M., 2012. Modulation of Neural Plasticity as a Basis for Stroke Rehabilitation. *Stroke*, 43 (10), 2819–2828.

Pfurtscheller, G., Brunner, C., Schlögl, A., and Lopes da Silva, F.H., 2006. Mu rhythm (de)synchronization and EEG single-trial classification of different motor imagery tasks. *NeuroImage*, 31, 153–159.

Pfurtscheller, G. and Lopes Da Silva, F.H., 1999. Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clinical Neurophysiology*.

Pfurtscheller, G. and Neuper, C., 1994. Event-related synchronization of mu rhythm in the EEG over the cortical hand area in man. *Neuroscience Letters*, 174 (1), 93–96.

Pfurtscheller, G., Neuper, C., Andrew, C., and Edlinger, G., 1997. Foot and hand area mu rhythms. *In*: *International Journal of Psychophysiology*. 121–135.

Pfurtscheller, G., Neuper, C., and Krausz, G., 2000. Functional dissociation of lower and upper frequency mu rhythms in relation to voluntary limb movement. *Clinical Neurophysiology*, 111 (10), 1873–1879.

Pfurtscheller, G., Stancák, A., and Neuper, C., 1996. Event-related synchronization (ERS) in the alpha band - An electrophysiological correlate of cortical idling: A review. *International Journal of Psychophysiology*, 24 (1–2), 39–46.

Pineda, J., 2005. The functional significance of mu rhythms: translating 'seeing' and 'hearing' into 'doing'. *Brain Research. Brain Research Reviews*, 50 (1), 57–68.

Platz, T., Kim, I.H., Pintschovius, H., Winter, T., Kieselbach, A., Villringer, K., Kurth, R., and Mauritz, K.H., 2000. Multimodal EEG analysis in man suggests impairment-specific changes in movement-related electric brain activity after stroke. *Brain : a journal of neurology*, 123 Pt 12 (12), 2475–2490.

Plow, E.B., Sankarasubramanian, V., Cunningham, D.A., Potter-Baker, K., Varnerin, N., Cohen, L.G., Sterr, A., Conforto, A.B., and Machado, A.G., 2016. Models to tailor brain stimulation therapies in stroke. *Neural Plasticity*.

Popa, L.L., Dragos, H., Pantelemon, C., Rosu, O.V., and Strilciuc, S., 2020. The Role of Quantitative EEG in the Diagnosis of Neuropsychiatric Disorders. *Journal of medicine and life*, 13 (1), 8–15.

Prashantha, D.K., Sriranjini, S.J., Sathyaprabha, T.N., Nagaraja, D., and Pal, P.K., 2013. Evaluation of the motor cortical excitability changes after ischemic stroke. *Annals of Indian Academy of Neurology*, 16 (3), 394–7.

Puh, U., Vovk, A., Sevsek, F., and Suput, D., 2007. Increased cognitive load during simple and complex motor tasks in acute stage after stroke. *International Journal of Psychophysiology*, 63 (2), 173–180.

Ramos-Murguialday, A. and Birbaumer, N., 2015. Brain oscillatory signatures of motor tasks. *Journal of Neurophysiology*, 113 (10), 3663–3682.

Rangel, E.S.S., Belasco, A.G.S., and Diccini, S., 2013. Quality of life of patients with stroke rehabilitation. *Acta Paulista de Enfermagem*, 26 (2), 205–212.

Rastgoo, M., Naghdi, S., Nakhostin Ansari, N., Olyaei, G., Jalaei, S., Forogh, B., and Najari, H., 2016. Effects of repetitive transcranial magnetic stimulation on lower extremity spasticity and motor function in stroke patients. *Disability and rehabilitation*, 38 (19), 1918–1926.

Rocchi, L., Ibáñez, J., Benussi, A., Hannah, R., Rawji, V., Casula, E., and Rothwell, J., 2018. Variability and predictors of response to continuous theta burst stimulation: A TMS-EEG study. *Frontiers in Neuroscience*.

Rodriguez, E., George, N., Lachaux, J.P., Martinerie, J., Renault, B., and Varela, F.J., 1999. Perception's shadow: Long-distance synchronization of human brain activity. *Nature*.

Rose, D.K., Patten, C., McGuirk, T.E., Lu, X., and Triggs, W.J., 2014. Does Inhibitory Repetitive Transcranial Magnetic Stimulation Augment Functional Task Practice to Improve Arm Recovery in Chronic Stroke? *Stroke Research and Treatment*, 2014, 1–10.

Rossi, S., 2013. Safety of Transcranial Magnetic Stimulation: With a Note on Regulatory Aspects. *In*: C. Miniussi, W. Paulus, and P.M. Rossini, eds. *Transcranial Brain Stimulation*. Frontiers in Neuroscience, 415–425.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., Avanzini, G., Bestmann, S., Berardelli, A., Brewer, C., Canli, T., Cantello, R., Chen, R., Classen, J., Demitrack, M., Di Lazzaro, V., Epstein, C.M., George, M.S., Fregni, F., Ilmoniemi, R., Jalinous, R., Karp, B., Lefaucheur, J.P., Lisanby, S., Meunier, S., Miniussi, C., Miranda, P., Padberg, F., Paulus, W., Peterchev, A., Porteri, C., Provost, M., Quartarone, A., Rotenberg, A., Rothwell, J., Ruohonen, J., Siebner, H., Thut, G., Valls-Solè, J., Walsh, V., Ugawa, Y., Zangen, A., and Ziemann, U., 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, 120 (12), 2008–2039.

Rossini, P.M., Rossini, L., and Ferreri, F., 2010. Brain-behavior relations: transcranial magnetic stimulation: a review. *IEEE Eng Med Biol Mag*, 29 (1), 84–95.

Rossiter, H.E., Boudrias, M.-H., and Ward, N.S., 2014. Do movement-related beta oscillations change after stroke? *Journal of Neurophysiology*, 112 (9), 2053–2058.

Rubi-Fessen, I., Hartmann, A., Huber, W., Fimm, B., Rommel, T., Thiel, A., and Heiss, W.-D., 2015. Add-on Effects of Repetitive Transcranial Magnetic Stimulation on Subacute Aphasia Therapy: Enhanced Improvement of Functional Communication and Basic Linguistic Skills. A Randomized Controlled Study. *ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION*, 96 (11), 1935–1944.

Ruohonen, J., 1998. Transcranial Magnetic Stimulation: Modelling and New Techniques. Helsinki University of Technology.

Sacco, R., Kasner, S., Broderick, J., Caplan, L., Connors, J., Culebras, A., Elkind, M., George, M., Hamdan, A., Higashida, R., Hoh, B., Janis, L., Kase, C., Kleindorfer, D., Lee, J., Moseley, M., Peterson, E., Turan, T., Valderrama, A., Vinters, H., American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, and Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, C. on N.P.A. and M., 2013. An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals From the American Heart Association/ American Stroke Association. *Stroke*, 44 (7), 2064–2089.

Sampaio-Baptista, C., Sanders, Z.-B., and Johansen-Berg, H., 2018. Structural Plasticity in Adulthood with Motor Learning and Stroke Rehabilitation. *Annual Review of Neuroscience*, 41, 25–40.

Sánchez-Kuhn, A., Pérez-Fernández, C., Cánovas, R., Flores, P., and Sánchez-Santed, F., 2017. Transcranial direct current stimulation as a motor neurorehabilitation tool: An empirical review. *BioMedical Engineering Online*,

16 (Suppl 1).

Sandrini, M., Umiltà, C., and Rusconi, E., 2011. The use of transcranial magnetic stimulation in cognitive neuroscience: A new synthesis of methodological issues. *Neuroscience and Biobehavioral Reviews*, 35 (3), 516–536.

Sasaki, N., Kakuda, W., and Abo, M., 2014. Bilateral high- and low-frequency rTMS in acute stroke patients with hemiparesis: A comparative study with unilateral high-frequency rTMS. *Brain Injury*, 28 (13–14), 1682–6.

Sasaki, N., Mizutani, S., Kakuda, W., and Abo, M., 2013. Comparison of the effects of high- and low-frequency repetitive transcranial magnetic stimulation on upper limb hemiparesis in the early phase of stroke. *Journal of Stroke and Cerebrovascular Diseases*, 22 (4), 413–418.

Sasaki, T., Kodama, S., Togashi, N., Shirota, Y., Sugiyama, Y., Tokushige, S. ichi, Inomata-Terada, S., Terao, Y., Ugawa, Y., and Hamada, M., 2018. The intensity of continuous theta burst stimulation, but not the waveform used to elicit motor evoked potentials, influences its outcome in the human motor cortex. *Brain Stimulation*, 11, 400–410.

Schapkin, S.A., Raggatz, J., Hillmert, M., and Bockelmann, I., 2020. EEG correlates of cognitive load in a multiple choice reaction task. *Acta Neurobiologiae Experimentalis*, 80, 76–89.

Schaul, N., 1998. The fundamental neural mechanisms of electroencephalography. *Electroencephalography and Clinical Neurophysiology*, 106 (2), 101–107.

Schuster, C., Maunz, G., Lutz, K., Kischka, U., Sturzenegger, R., and Ettlin, T., 2011. Dexamphetamine improves upper extremity outcome during rehabilitation after stroke: A pilot randomized controlled trial. *Neurorehabilitation and Neural Repair*, 25 (8), 749– 755.

Seniów, J., Bilik, M., Lesniak, M., Waldowski, K., Iwanski, S., and Czlonkowska, A., 2012. Transcranial Magnetic Stimulation Combined With Physiotherapy in Rehabilitation of Poststroke Hemiparesis: A Randomized, Double-Blind, Placebo-Controlled Study. *Neurorehabilitation and Neural Repair*, 26 (9), 1072–1079.

Seniów, J., Waldowski, K., Leśniak, M., Iwański, S., Czepiel, W., and Członkowska, A., 2013. Transcranial magnetic stimulation combined with speech and language training in early aphasia rehabilitation: a randomized double-blind controlled pilot study. *Topics in Stroke Rehabilitation*, 20 (3), 250–261.

Shafi, M.M., Brandon Westover, M., Oberman, L., Cash, S.S., and Pascual-Leone, A., 2014. Modulation of EEG functional connectivity networks in subjects undergoing repetitive transcranial magnetic stimulation. *Brain Topography*, 27 (1), 172–191.

Shenoy Handiru, V., Vinod, A.P., and Guan, C., 2017. EEG source space analysis of the supervised factor analytic approach for the classification of multi-directional arm movement. *Journal of Neural Engineering*, 14.

Silva, G., Ribeiro, M.J., Costa, G.N., Violante, I., Ramos, F., Saraiva, J., and Castelo-Branco, M., 2016. Peripheral attentional targets under covert attention lead to paradoxically enhanced alpha desynchronization in neurofibromatosis type 1. *PLoS ONE*, 11 (2).

Simões, M., Monteiro, R., Andrade, J., Mouga, S., França, F., Oliveira, G., Carvalho, P., and Castelo-Branco, M., 2018. A novel biomarker of compensatory recruitment of face emotional imagery networks in autism spectrum disorder. *Frontiers in Neuroscience*, 12.

Song, W., Du, B., Xu, Q., Hu, J., Wang, M., and Luo, Y., 2009. Low-frequency transcranial magnetic stimulation for visual spatial neglect: A pilot study. *Journal of Rehabilitation Medicine*, 41 (3), 162–165.

Sousa-Uva, M. and Dias, C.M., 2014. Prevalência de Acidente Vascular Cerebral na população portuguesa: dados da amostra ECOS 2013. *Boletim Epidemiológico Observações*, 3 (9), 12–14.

Stępień, M., Conradi, J, Waterstraat, G., Hohlefeld, F.U., Curio, G., and Nikulin, V.

V, 2011. Event-related desynchronization of sensorimotor EEG rhythms in hemiparetic patients with acute stroke. *Neuroscience letters*, 488 (1), 17–21.

Steriade, M., Gloor, P., Llinás, R.R., Lopes de Silva, F.H., and Mesulam, M.M., 1990. Report of IFCN Committee on Basic Mechanisms. Basic mechanisms of cerebral rhythmic activities. *Electroencephalography and clinical neurophysiology*, 76, 481–508.

Sung, W.H., Wang, C.P., Chou, C.L., Chen, Y.C., Chang, Y.C., and Tsai, P.Y., 2013. Efficacy of coupling inhibitory and facilitatory repetitive transcranial magnetic stimulation to enhance motor recovery in hemiplegic stroke patients. *Stroke*, 44 (5), 1375–1382.

Szaflarski, J.P., Vannest, J., Wu, S.W., DiFrancesco, M.W., Banks, C., and Gilbert, D.L., 2011. Excitatory repetitive transcranial magnetic stimulation induces improvements in chronic post-stroke aphasia. *Medical Science Monitor*, 17 (3), CR132–CR139.

Takemi, M., Masakado, Y., Liu, M., and Ushiba, J., 2013. Event-related desynchronization reflects downregulation of intracortical inhibition in human primary motor cortex. *Journal of neurophysiology*, 110 (5), 1158–66.

Takeuchi, N., Chuma, T., Matsuo, Y., Watanabe, I., and Ikoma, K., 2005. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke*, 36 (12), 2681–2686.

Takeuchi, N., Tada, T., Toshima, M., Chuma, T., Matsuo, Y., and Ikoma, K., 2008. Inhibition of the unaffected motor cortex by 1 HZ repetitive transcranial magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. *Journal of Rehabilitation Medicine*, 40 (4), 298–303.

Takeuchi, N., Tada, T., Toshima, M., Matsuo, Y., and Ikoma, K., 2009. Repetitive transcranial magnetic stimulation over bilateral hemispheres enhances motor function and training effect of paretic hand in patients after stroke. *Journal of Rehabilitation Medicine*, 41 (13), 1049–1054.

Talelli, P., Greenwood, R.J., and Rothwell, J.C., 2007. Exploring Theta Burst Stimulation as an intervention to improve motor recovery in chronic stroke. *Clinical Neurophysiology*, 118 (2), 333–342.

Talelli, P., Wallace, A., Dileone, M., Hoad, D., Cheeran, B., Oliver, R., VandenBos, M., Hammerbeck, U., Barratt, K., Gillini, C., Musumeci, G., Boudrias, M.-H., Cloud, G.C., Ball, J., Marsden, J.F., Ward, N.S., Di Lazzaro, V., Greenwood, R.G., and Rothwell, J.C., 2012. Theta burst stimulation in the rehabilitation of the upper limb: a semirandomized, placebo-controlled trial in chronic stroke patients. *Neurorehabilitation and Neural Repair*, 26 (8), 976–987.

Teplan, M., 2002. Fundamentals of EEG measurement. *Measurement Science Review*, 2 (2), 1–11.

Thiel, A., Hartmann, A., Rubi-Fessen, I., Anglade, C., Kracht, L., Weiduschat, N., Kessler, J., Rommel, T., and Heiss, W.D., 2013. Effects of noninvasive brain stimulation on language networks and recovery in early poststroke aphasia. *Stroke*, 44 (8), 2240–2246.

Tinazzi, M., Farina, S., Tamburin, S., Facchini, S., Fiaschi, A., Restivo, D., and Berardelli, A., 2003. Task-dependent modulation of excitatory and inhibitory functions within the human primary motor cortex. *Experimental Brain Research*, 150, 222–229.

Tretriluxana, J., Kantak, S., Tretriluxana, S., Wu, A.D., and Fisher, B.E., 2015. Improvement in Paretic Arm Reach-to-Grasp following Low Frequency Repetitive Transcranial Magnetic Stimulation Depends on Object Size: A Pilot Study. *Stroke research and treatment*, 2015, 498169.

Tsai, P.-Y., Wang, C.-P., Ko, J.S., Chung, Y.-M., Chang, Y.-W., and Wang, J.-X., 2014. The persistent and broadly modulating effect of inhibitory rTMS in nonfluent aphasic patients: a sham-controlled, double-blind study. *Neurorehabilitation and Neural Repair*, 28, 779–787.

Tsujimoto, K., Mizuno, K., Kobayashi, Y., Tanuma, A., and Liu, M., 2020. Right as well as left unilateral spatial neglect influences rehabilitation outcomes and its recovery is important for determining discharge destination in subacute stroke patients. *European Journal of Physical and Rehabilitation Medicine*, 56 (1), 5–13.

Uhlhaas, P.J., Linden, D.E.J., Singer, W., Haenschel, C., Lindner, M., Maurer, K., and Rodriguez, E., 2006. Dysfunctional Long-Range Coordination of Neural Activity during Gestalt Perception in Schizophrenia. *Journal of Neuroscience*.

Vaziri, P.M., Bahrpeyma, F., Firoozabadi, M., Forough, B., Hatef, B., Sheikhhoseini, R., and Shamili, A., 2014. Low frequency repetitive transcranial magnetic stimulation to improve motor function and grip force of upper limbs of patients with hemiplegia. *Iranian Red Crescent Medical Journal*, 16 (8).

Verin, E. and Leroi, A.M., 2009. Poststroke dysphagia rehabilitation by repetitive transcranial magnetic stimulation: A noncontrolled pilot study. *Dysphagia*, 24 (2), 204–210.

Vernet, M., Bashir, S., Yoo, W.-K., Oberman, L., Mizrahi, I., Ifert-Miller, F., Beck, C.J., and Pascual-Leone, A., 2014. Reproducibility of the effects of theta burst stimulation on motor cortical plasticity in healthy participants. *Clinical neurophysiology*, 125 (2), 320–6.

Vernet, M., Bashir, S., Yoo, W.K., Perez, J.M., Najib, U., and Pascual-Leone, A., 2013. Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS-EEG. *European Journal of Neuroscience*, 37 (4), 598–606.

Vidal-Dourado, M., Conforto, a. B., Caboclo, L.O.S.F., Scaff, M., Guilhoto, L.M.D.F.F., and Yacubian, E.M.T., 2014. Magnetic Fields in Noninvasive Brain Stimulation. *The Neuroscientist*, 20 (2), 112–121.

Vidal, A.C., Banca, P., Pascoal, A.G., Cordeiro, G., Sargento-Freitas, J., and Castelo-Branco, M., 2014. Modulation of cortical interhemispheric interactions by motor facilitation or restraint.

Neural Plasticity, 2014.

Volz, L.J., Hamada, M., Rothwell, J.C., and Grefkes, C., 2015. What Makes the Muscle Twitch: Motor System Connectivity and TMS-Induced Activity. *Cerebral Cortex*, 25, 2346–2353.

Volz, L.J., Rehme, A.K., Michely, J., Nettekoven, C., Eickhoff, S.B., Fink, G.R., and Grefkes, C., 2016. Shaping Early Reorganization of Neural Networks Promotes Motor Function after Stroke. *CEREBRAL CORTEX*, 26 (6), 2882–2894.

Vongvaivanichakul, P., Tretriluxana, J., Bovonsunthonchai, S., Pakaprot, N., and Laksanakorn, W., 2014. Reach-to-grasp training in individuals with chronic stroke augmented by low-frequency repetitive transcranial magnetic stimulation. *Journal of the Medical Association of Thailand*, 97 (7), S45-49.

Wagner, T., 2006. Non Invasive Brain Stimulation: Modeling and Experimental Analysis of Transcranial Magnetic Stimulation and Transcranial DC Stimulation as a Modality for Neuropathology Treatment. Massachusetts Institute of Technology.

Waldowski, K., Seniów, J., Leśniak, M., Iwański, S., and Członkowska, A., 2012. Effect of low-frequency repetitive transcranial magnetic stimulation on naming abilities in early-stroke aphasic patients: a prospective, randomized, double-blind sham-controlled study. *ScientificWorldJournal*.

Wang, C.-C., Wang, C.-P., Tsai, P.-Y., Hsieh, C.-Y., Chan, R.-C., and Yeh, S.-C., 2014. Inhibitory repetitive transcranial magnetic stimulation of the contralesional premotor and primary motor cortices facilitate poststroke motor recovery. *Restorative Neurology and Neuroscience*, 32 (6), 825–835.

Wang, C.-P., Hsieh, C.-Y., Tsai, P.-Y., Wang, C.-T., Lin, F.-G., and Chan, R.-C., 2014. Efficacy of synchronous verbal training during repetitive transcranial magnetic stimulation in patients with chronic aphasia. *Stroke*, 45 (12), 3656–62.

Wang, C.P., Tsai, P.Y., Yang, T.F., Yang, K.Y., and Wang, C.C., 2014. Differential

Effect of Conditioning Sequences in Coupling Inhibitory/Facilitatory Repetitive Transcranial Magnetic Stimulation for PostStroke Motor Recovery. *CNS Neuroscience and Therapeutics*, 20 (4), 355–363.

Wang, R.-Y., Tseng, H.-Y., Liao, K.-K., Wang, C.-J., Lai, K.-L., and Yang, Y.-R., 2012. rTMS combined with task-oriented training to improve symmetry of interhemispheric corticomotor excitability and gait performance after stroke: a randomized trial. *Neurorehabilitation and Neural Repair*, 26 (3), 222–30.

Weiduschat, N., Thiel, A., Rubi-Fessen, I., Hartmann, A., Kessler, J., Merl, P., Kracht, L., Rommel, T., and Heiss, W.D., 2011. Effects of repetitive transcranial magnetic stimulation in aphasic stroke: a randomized controlled pilot study. *Stroke*, 42 (2), 409–415.

Wischnewski, M. and Schutter, D.J.L.G., 2015. Efficacy and time course of theta burst stimulation in healthy humans. *Brain Stimulation*, 8 (4), 685–692.

Wolf, S.L., Catlin, P.A., Ellis, M., Archer, A.L., Morgan, B., and Piacentino, A., 2001. Assessing Wolf Motor Function Test as outcome measure for research in patients after stroke. *Stroke*, 32, 1635–1639.

World Health Organization, 2015. Stroke, Cerebrovascular accident [online]. Available from: http://www.who.int/topics/cerebrovascular_accident/en/ [Accessed 22 Jun 2015].

Wu, S.W., Shahana, N., Huddleston, D.A., and Gilbert, D.L., 2012. Effects of 30Hz Theta Burst Transcranial Magnetic Stimulation on the primary motor cortex. *Journal of Neuroscience Methods*, 208 (2), 161–164.

Yamada, N., Kakuda, W., Kondo, T., Shimizu, M., Mitani, S., and Abo, M., 2013. Bihemispheric repetitive transcranial magnetic stimulation combined with intensive occupational therapy for upper limb hemiparesis after stroke: a preliminary study. *International Journal of Rehabilitation Research*, 36 (4), 323–9.

Yang, W., Liu, T.-T., Song, X.-B., Zhang, Y., Li, Z.-H., Cui, Z.-H., Hao, Q., Liu, H.L., Lei, C.L., and Liu, J., 2015. Comparison of different stimulation parameters of repetitive transcranial magnetic stimulation for unilateral spatial neglect in stroke patients. *JOURNAL OF THE NEUROLOGICAL SCIENCES*, 359 (1–2), 219–225.

Yoon, T., Han, S., Yoon, T., Kim, J., and Yi, T., 2015. Therapeutic effect of repetitive magnetic stimulation combined with speech and language therapy in post-stroke non-fluent aphasia. *NeuroRehabilitation*, 36 (1), 107–114.

Zandvliet, S.B., Kwakkel, G., Nijland, R.H.M., van Wegen, E.E.H., and Meskers, C.G.M., 2020. Is Recovery of Somatosensory Impairment Conditional for Upper-Limb Motor Recovery Early After Stroke? *Neurorehabilitation and Neural Repair*, 34 (5), 403– 416.

Zheng, C.-J., Liao, W.-J., and Xia, W.-G., 2015. Effect of combined low-frequency repetitive transcranial magnetic stimulation and virtual reality training on upper limb function in subacute stroke: a double-blind randomized controlled trail. *Journal of Huazhong University of Science and Technology Medical Sciences*, 35 (2), 248–54.

Zheng, C. and Colgin, L.L., 2015. Beta and gamma rhythms go with the flow. *Neuron*, 85 (2), 236–237.

Chapter A

APPENDIX

A1

Table A1.1 - Relevant data extracted from each reviewed study, including study design, sample size, details of the TMS protocol, outcome measures, and behavioral results

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(J Du et al., 2016)	Double-blind, randomized, controlled study	69 p. (23 HF-rTMS, 23 LF-rTMS, 23 sham)	(C) 90-mm figure-8, (A) HF-rTMS: lesional, LF-rTMS: nonlesional hemisphere, (S) 5, (F) HF-rTMS: 3 Hz, LF-rTMS: 1 Hz, (I) HF-rTMS: 80%-90% of rMT, LF-rTMS: 110%-120% of rMT, (D) HF-rTMS: 1200 pulses (40 trains of 10 s, 10 s intertrain int.), LF-rTMS: 1200 pulses (40 trains of 30 s, 2 s intertrain int.), (SM) the coil held at 90º to the scalp	FMA, MRC, NIHSS, BI, and modified RS	FMA: A significant improvement was observed only for the LF-rTMS group, on the UE subtest. For the lower limbs both real stimulation groups showed significant improvements compared with the sham stimulation. MRC: As for FMA, on the upper limb the 1-Hz group improved function significantly and both real stimulation groups improved significantly the lower limb function in comparison to sham group. NIHSS, BI, and modified RS: Real stimulation was more effective, showing marked improvements compared with sham stimulation. Both LF- and HF-rTMS improved motor function significantly compared with sham stimulation, and the effect was maintained at least 3 mo. The HF-rTMS group, however, did not demonstrate significant improvements regarding the upper limb motor function.
(Abo et al., 2014)	Randomized, multicenter, comparative study	66 p. (44 rTMS+OT, 22 CIMT)	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 22, (F) 1 Hz, (I) 90% of rMT (D) 1200 pulses (20 min), (SM) none: comparison with the CIMT group	FMA and WMFT (log performance time and functional ability score)	FMA showed a significant increase, with a mean increase of 5.39 ± 4.28 points in the rTMS+OT and of 3.09 ± 4.50 points in the CIMT group. The difference between groups was significant. WMFT log performance time decreased significantly in both groups with a mean decrease of 0.43 ± 0.59 points in the rTMS+OT and of 0.31 ± 0.42 points in the CIMT. The difference between groups was not significant. WMFT Functional Ability Score increased significantly with a mean increase of 3.98 ± 2.99 points in the rTMS+OT and of 2.09 ± 2.96 points in the CIMT group. The increase was significantly larger in the rTMS+OT group. It was observed a significant improvement of motor function in patients with upper limb hemiparesis; the rTMS+OT intervention demonstrated better results, compared with CIMT.
(Chieffo, De Prezzo, et al., 2014)	Double-blind, placebo-controlled crossover study	9 p.	(C) H-coil, (A) bilateral over the lower limb motor cortical areas, (S) 11 rTMS + 11 sham (4-wk washout period), (F) 20 Hz, (I) 90% of rMT or up to 82% maximal stimulation output, (D) 1500 pulses (30 min: 30 trains with 60 s intertrain int.), (SM) sham coil	FMA-LE, 10MWT and 6MWT	Sham stimulation did not show significant improvements in any measure. Real rTMS showed significant improvements of the FMA-LE; the difference in the % of improvement between rTMS and sham groups was even greater at 1-mo follow-up. rTMS intervention led to a significant amelioration in 10MWT at the end of treatment but this improvement was not significant after 1 mo. Real rTMS increased walking speed significantly, but it did not reach statistical significance compared with sham. High-frequency rTMS could improve lower limb motor function for at least 1 mo.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Galvão et al., 2014)	Randomized, double-blind, sham-controlled trial	20 p. (10 rTMS, 10 sham)	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 1500 pulses, (SM) 1 disconnected coil held over the scalp + 1 connected coil behind the head, without touching the scalp	Modified AS, FMA-UE, maximum passive range of motion of the paretic wrist joint and FIM	Modified AS decreased significantly with rTMS but not with sham. When real stimulation was applied, 90% of patients after intervention and 55.5% at follow-up experienced a clinically meaningful decrease (≥ 1). On the other hand, in the sham group 30% of patients after stimulation and 22.2% at follow-up showed clinically relevant differences. FMA, range of motion and FIM: there were no differences between rTMS and sham groups at any time. Low-frequency rTMS combined with physical therapy can decrease spastic hypertonia in the upper limb, with the improvement lasting at least 4 wk.
(E M Khedr et al., 2009)	Exploratory study	36 p. (12 group 1: 1Hz-rTMS, 12 group 2: 3Hz-rTMS), 12 group 3: sham)	(C) 90-mm figure-8, (A) Group 1: nonlesional, Group 2: lesional hemisphere, (S) 5, (F) Group 1: 1 Hz Group 2: 3 Hz, (I) Group 1: 100% of rMT, Group 2: 130% of rMT, (D) Group 1: 900 pulses (15 min), Group 2: 900 pulses (10 s, 30 trains with 2 s intertrain int.), (SM) the coil angled away from the head	Hand grip strength (MRC), KT, PPT, NIHSS, and BI	Hand grip strength did not show significant differences between groups. KT and PPT: real rTMS led to significant improvements in comparison with sham stimulation; 1-Hz rTMS demonstrated a significantly greater improvement than 3 Hz. NIHSS and BI were improved in all patients at 3 mo follow-up; nevertheless real rTMS led to significantly larger improvements than sham stimulation. For NIHSS, 1-Hz rTMS demonstrated a significantly greater improvement. Real intervention improved motor function more than sham stimulation; at 3 mo 1 Hz rTMS was more effective than 3 Hz rTMS, causing a more pronounced effect.
(E. M. Khedr et al., 2010)	Preliminary study	48 p. (16 group 1: 3 Hz, 16 group 2: 10 Hz, 16 group 3: sham)	(C) 90-mm figure-8, (A) lesional hemisphere over motor cortex, (S) 5, (F) Group 1: 3 Hz, Group 2: 10 Hz, (I) Group 1: 130% of rMT, Group 2: 100% of rMT, (D) Group 1: 750 pulses (5 s, 50 trains). Group 2: 750 pulses (2 s, 37 trains), (SM) the coil angled away from the head	Strength (hand grip, shoulder abduction, hip flexion and toes dorsiflexion), NIHSS and modified RS	Strength: real rTMS demonstrated a tendency to increase strength more than sham stimulation. NIHSS and modified RS: only the 3 Hz-rTMS showed better results than sham. 3 Hz-rTMS revealed a tendency to produce larger improvements in strength and rating scales, compared with 10 Hz-rTMS; however, this was not significant. rTMS significantly improved motor function, compared with sham stimulation; the observed improvements lasted until 1 y.
(Nowak et al., 2008)	Crossover investigation	15 p.	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 1 rTMS + 1 sham, (F) 1 Hz, (I) 100% of rMT, (D) 10 min, (SM) the coil over the vertex	Index finger tapping (movement frequency, velocity and amplitude) and reach-to-grasp task (peak of vertical wrist position and velocity, movement time, peak grip aperture, peak velocity of grasp aperture and time of peak grip aperture)	Index finger tapping: Real rTMS increased frequency and peak velocity of the affected hand to values comparable with the unaffected hand. Peak amplitudes did not show significant effects with the intervention. Reach-to grasp: After rTMS, movement times, peak wrist velocities, peak velocities of grasp aperture, and times of peak grasp aperture for movements of the affected hand all changed to values comparable with those of the unaffected hand. Low-frequency rTMS led to improvements on movement kinematics of the affected hand.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Sung et al., 2013)	Randomized, sham-controlled, double-blind parallel study	54 p. (15 group A: 1-Hz + iTBS, 12 group B: sham 1-Hz +iTBS, 13 group C: 1-Hz+sham iTBS, 14 group D: sham 1-Hz +sham iTBS)	(C) 70-mm figure-8, (A) 1 Hz rTMS: nonlesional over M1, iTBS: lesional hemisphere over M1, (S) 20 (10 first course + 10 second course), (F) 1 Hz-rTMS: 1 Hz, iTBS: Short bursts of 3 stimuli at 50 Hz, repeating at 5 Hz, (I) 1 Hz rTMS: 90% of rMT, iTBS: 80% of aMT, (D) 1 Hz rTMS: 600 pulses, iTBS: 600 pulses (2 s train repeated every 10 s for 190 s), (SM) sham coil	WMFT, FMA - UE, finger flexor MRC, simple RT, and index FTT	MRC, FMA, WMFT, FTT, and RT showed significantly greater improvements in patients who experienced real stimulation (groups A, B, and C), compared with those who just received sham stimulation (group D). MRC and FMA: A greater improvement was observed in group A, compared with the other groups. WMFT: A 68.8% improvement in group A was observed, 22.6% improvement in group B, and 17.1% improvement in group C. RT: An 83.9% improvement in group A was observed, 58.5% improvement in group B, and 49% improvement in group C. The poststroke patients who demonstrated larger improvements in motor performance were those who received real double-course conditioning (1Hz-rTMS + iTBS).
(Rastgoo et al., 2016)	Randomized, sham-controlled, cross-over trial	20 p. (10 rTMS + sham: AS group, 10 sham + rTMS: SA group)	(C) 90-mm figure-8, (A) nonlesional hemisphere over lower extremity motor cortex, (S) 5 rTMS + 5 sham (washout period: 1 mo), (F) 1 Hz, (I) 90% of MT, (D) 1000 pulses (20 min), (SM) sham coil	Modified Modified AS, TUG, FMA - LE	Modified Modified AS and FMA - LE: only patients who received real stimulation showed a significant improvement on the lower extremity but no significant difference was found between groups. TUG test: real and sham stimulation showed similar effects. The results did not present significant correlation between the improvement in spasticity, measured by modified modified AS, and the improvement on motor function, assessed by FMA. 1 Hz rTMS improved lower extremity motor function and spasticity but the improvement was modest.
(Rose et al., 2014)	Double-blind randomized sham-controlled trial	19 p. (9 rTMS, 10 sham)	(C) 70-mm air-cooled figure-8, (A) nonlesional hemisphere over M1, (S) 16, (F) 1 Hz, (I) 100% of rMT, (D) 1200 pulses, (SM) sham coil	WMFT, grip, lateral and palmar pinch, 3JC force, FMA-UE, ARAT, light touch sensation, modified AS, MAL (amount of use and how well) and LLFDI	The scores in WMFT (time and functional scale), UE FMA, grip force, ARAT, modified AS, MAL-amount of use and how well scales changed significantly between pre- and postintervention for all patients. Comparing postintervention with retention values, significant changes were not detected, except for grip force. None of the kinematic variables showed significant differences between real and sham stimulation at any time point. Low-frequency rTMS was not effective as an adjuvant to functional task practice.
(N. Sasaki et al., 2013)	Randomized, controlled trial	29 p. (9 HF-rTMS, 11 LF-rTMS, 9 sham)	(C) 70-mm figure-8, (A) HF-rTMS: lesional over M1, LF-rTMS: nonlesional hemisphere over M1, (S) 5, (F) HF-rTMS: 10 Hz, LF-rTMS: 1 Hz, (I) 90% of rMT, (D) HF-rTMS: 1000 pulses (10 min: 10 s trains + 50 s intertrain int.), LF-rTMS: 1800 pulses (30 min), (SM) the coil held at 90º to the scalp	Grip strength and tapping frequency	Grip strength and tapping frequency showed significant improvements with the real rTMS groups but not with the sham group. HF showed a significantly greater increase in scores than sham stimulation; however, a significant difference was not observed between the HF and LF results or between the LF-rTMS and sham results. Both high-frequency and low-frequency rTMS improved upper limb hemiparesis; however, 10 Hz-rTMS was more effective.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(C. P. Wang et al., 2014)	Randomized, sham-controlled, double-blinded parallel study	48 p. (17 group A: 1Hz+iTBS, 15 group B: iTBS + 1Hz, 16 group C: sham)	(C) 70-mm figure-8, (A) 1 Hz rTMS: nonlesional over M1, iTBS: lesional hemisphere over M1, (S) 20 (A and B: 10 1Hz-rTMS + 10 iTBS, C: 10 sham 1Hz-rTMS + 10 sham iTBS), (F) 1 Hz-rTMS: 1 Hz, iTBS: Short bursts of 3 stimuli at 50 Hz, repeating at 5 Hz, (I) 1 Hz rTMS: 90% of rMT, iTBS: 80% of aMT, (D) 1 Hz rTMS: 600 pulses (10 min), iTBS: 600 pulses (2 s train repeated every 10 s), (SM) sham coil	Muscle strength (MRC), FMA-UE and WMFT (functional ability scale)	All motor scores showed larger improvement for Group A, compared with Group B and sham. Real stimulation in Group A improved significantly all measures more than sham stimulation, in all assessments; the second course of conditioning provided additional gains to the first course. WMFT and proximal MRC scores improved significantly in Group B compared with sham; the other measures did not show such difference. For Group B, just WMFT and distal MRC scores showed a significant improvement after the second course, compared with the assessment at the end of the first course of conditioning. LF-rTMS followed by intermittent TBS was considered to be optimal to improve hand dexterity with long-term effects (at least 3 mo).
(Avenanti et al., 2012)	Prospective, randomized, parallel and factorial-design, sham-controlled, phase II trial	30 p. (8 got PT after rTMS: rTMS-PT, 8 PT before: PT-rTMS, 14 sham)	(C) 70-mm focal, (A) nonlesional hemisphere over M1, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 1500 pulses (25 min), (SM) coil perpendicular to the scalp	JFT, NHPT, and B&B (hand dexterity) and key grip, tip-pinch and power-grip (force)	JFT, NHPT, and B&B: dexterity improved significantly in both rTMS groups; sham stimulation led to a modest but significant improvement that returned to baseline level at follow-up 3-4. Dexterity was significantly greater in rTMS-PT group compared with PT-rTMS at follow-up 2-4. Key grip force: force performance improved significantly in both rTMS groups; sham led to a modest but significant improvement that returned to baseline level at follow-up 2-4. Tip-pinch and power-grip force: real stimulation significantly increased force at post-treatment and follow-up 1-4, without difference between both groups; sham stimulation increased significantly pinch-grip at post-treatment but not at follow-up and did not change power-grip. rTMS combined with physical therapy, either before or after, improves dexterity and force in the affected limb.
(Higgins et al., 2013)	Observer-blinded stratified block-randomized controlled trial	9 p. (4 rTMS, 5 sham)	(C) air-cooled figure-8, (A) nonlesional hemisphere over motor cortex, (S) 8, (F) 1 Hz, (I) 110% of MT, (D) 1200 pulses (20 min), (SM) sham coil	B&B, WMFT, MAL-14, grip and pinch strengths and SIS-16	B&B: There was no observed effect of rTMS compared with sham stimulation. WMFT and quality part of MAL showed trends for between-group effect sizes. There were observed improvements on B&B, in pinch strength, on the WMFT (functional score), and on the SIS with both interventions (real rTMS and sham). rTMS was not effective as an adjunct therapy to task-oriented training for arm rehabilitation, despite showing a transient effect on excitability.
(Ameli et al., 2009)	N.A.	29 p. (16 with subcortical, 13 with cortical stroke)	(C) 70-mm figure-8, (A) lesional hemisphere over M1, (S) 1 rTMS + 1 sham, separated by a minimum of 120 min., (F) 10 Hz, (I) 80% of rMT, (D) 1000 pulses (trains of 5 s stimulation + 25 s intertrain int.), (SM) the coil over the vertex	Movement frequency and peak movement amplitude for index finger and hand tapping movements	Movement frequency: rTMS did not increase movement frequency of index finger and hand tapping in only 2 of the 16 subcortical stroke patients. On the other hand, rTMS decreased frequencies in 7 of the 13 cortical stroke patients, suggesting deterioration. Movement amplitudes did not change significantly with rTMS. HF-rTMS, but not sham, led to a significant improvement of the affected hand function in subcortical stroke patients, but not in those with additional cortical stroke.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Lin et al., 2015)	Pilot study	32 p. (16 rTMS, 16 sham)	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 15, (F) 1 Hz, (I) 130% of MT (with upper limit of 80% of machine output), (D) 900 pulses (15 min), (SM) sham coil	PASS, POMA-balance subscale, TUG, BI, and FMA-LE	PASS increased from a median of 19.0 (9.5) to 28.5 (11.3) in the group that received real stimulation and from a median of 17.5 (10.5) to 24.0 (10.0) in the group which received sham stimulation. POMA-balance subscale showed an increase from a median of 2.0 (5.0) to 9.5 (8.0) after real rTMS and from 1.0 (4.0) to 4.0 (7.0) after sham. BI: median changed from 40.0 (16.3) to 50.0 (22.5) after real rTMS and from 32.5 (30.0) to 40.0 (20.0) after sham. FMA-LE: median score increased from 14.5 (6.8) to 21.0 (6.8) on the real rTMS group and from 15.0 (3.8) to 20.0 (8.0) on the sham group. For all outcome measures there were significant improvements in both groups; nevertheless, there were significant differences between them for PASS, POMA-balance subscale and BI, with greater improvement after real rTMS. TUG: although at baseline none of the participants was able to finish the test within 2 min, after intervention 11 patients from the experimental and 4 patients from the control group were able to do it, with a significant difference between groups. The 15 sessions of 1 Hz-rTMS, each followed by physical therapy, improved balance, mobility and independence more than physical therapy alone.
(Naoyuki Takeuchi et al., 2009)	Double-blind study	30 p. (10 U-rTMS, 10 A-rTMS, 10 B-rTMS)	(C) figure-8, (A) B-rTMS: both hemispheres (1 Hz to nonlesional + 10 Hz to lesional), U-rTMS: rTMS to nonlesional + sham to lesional; A-rTMS: rTMS to lesional + sham to nonlesional hemisphere (S) 1, (F) B-rTMS: 1 Hz + 10 Hz, U-rTMS: 1 Hz, A-rTMS: 10 Hz, (I) 90% of rMT, (D) 20 times, 1000 pulses in each hemisphere (B-rTMS: 50 s 1Hz + 5 s int. + 5 s 10Hz + 5 s int., U-rTMS: 50 s 1 Hz + 5 s int. + 5 s sham + 5 s int., A-rTMS: 50 s sham + 5 s int. + 5 s 10 Hz + 5 s int.), (SM) N.A.	Pinch force and acceleration	Acceleration: B-rTMS and U-rTMS groups showed significant improvements immediately after stimulation that was maintained for 1 wk. No additional improvement induced by motor training on these groups was observed. Bilateral rTMS increased acceleration during all sessions in comparison with rTMS over the unaffected hemisphere; however, this difference was not significant. It was not observed a significant improvement in the A-rTMS group, either after rTMS or motor training. Pinch force: B-rTMS and U-rTMS groups did not show significant improvements immediately after stimulation; nevertheless, motor training induced an improvement that was sustained for 1 wk. B-rTMS enhanced the effect of motor training after stimulation more than U-rTMS. There was no observed significant improvement in the A-rTMS group, either after rTMS or motor training. Both bilateral rTMS and rTMS applied over the unaffected hemisphere can improve the effect of motor training on the paretic hand; however, bilateral rTMS was more effective.
(J Ludemann-Podubecka et al., 2016)	Prospective randomized, double-blind, sham-controlled crossover trial	10 p.	(C) 70-mm figure-8, (A) nonlesional hemisphere over PMd, (S) 1 rTMS + 1 sham (minimum washout period: 48h), (F) 1 Hz, (I) 110% of rMT, (D) 900 pulses (15 min), (SM) zero stimulation output intensity	JFT and B&B	JFT of the affected hand decreased from 9.88 ± 6.07 to 9.27 ± 4.73 s subsequently to sham session and from 10.93 ± 6.90 to 9.56 ± 5.40 s after real rTMS session. B&B of the affected hand changed from 47.9 ± 13.7 to 47.9 ± 14.5 after sham stimulation and from 44.8 ± 14.2 to 49.4 ± 14.8 following real stimulation. LF-rTMS applied to the unaffected dorsal premotor cortex exhibited improvements of affected hand's motor function.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Fregni et al., 2006)	Longitudinal, randomized, parallel-design, sham-controlled, phase II trial	15 p. (10 rTMS, 5 sham)	(C) figure-8, (A) nonlesional hemisphere over M1, (S) 5, (F) 1 Hz, (I) 100% of MT, (D) 1200 pulses (20 min), (SM) sham coil	JFT, simple and choice RT and PPT	Real rTMS improved significantly motor function of the affected hand but not of the unaffected hand. On the other hand, sham stimulation did not. The results obtained for simple RT and choice RT were more stable than those verified for JFT. rTMS increased the magnitude of the affected hand motor function improvement; the improvement lasted 2 wk.
(Liepert et al., 2007)	Double-blind, placebo-controlled, crossover trial	12 p.	(C) figure-8, (A) nonlesional hemisphere over M1, (S) 1 rTMS + 1 sham (on the same day), (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses (20 min), (SM) sham coil	Grip strength and NHPT	Grip strength showed no significant change. NHPT: A significant difference between both interventions (real rTMS and sham) was observed; rTMS improved NHPT more than sham stimulation in the affected hand. A single session of low-frequency rTMS significantly improved dexterity in the paretic hand by approximately 10%.
(Y.-H. Kim et al., 2006)	Crossover, sham-controlled, single-blind study	15 p. (8 rTMS + sham, 7 sham + rTMS)	(C) 70-mm figure-8, (A) lesional hemisphere over M1, (S) 1 rTMS + 1 sham, (F) 10 Hz, (I) 80% of rMT, (D) 160 pulses (8 min: 8 trains of 20 pulses, 2 s each train + 58 s intertrain int. (40 s motor task + 18 s rest)), (SM) the coil held at 90º to the scalp	Movement accuracy and time	Movement accuracy and time scores were significantly more improved by real rTMS compared with sham stimulation; real rTMS increased movement accuracy and speed. HF-rTMS with motor practice improved motor performance, enhancing movement accuracy and speed.
(Emara et al., 2010)	Placebo-controlled pilot study	60 p. (20 HF-rTMS, 20 LF-rTMS, 20 sham)	(C) figure-8, (A) HF-rTMS: lesional, LF-rTMS: nonlesional hemisphere, (S) 10, (F) HF-rTMS: 5 Hz, LF-rTMS: 1 Hz, (I) HF-rTMS: 80-90% of MT, LF-rTMS: 110-120% of MT, (D) HF-rTMS: 750 pulses (2.5 min pulse train), LF-rTMS: 150 pulses (2.5 min pulse train), (SM) the coil held at 90º to the scalp	TIFT, AI and modified RS	TIFT: the paretic-to-contralateral ratio improved with rTMS but not with sham. AI: both rTMS interventions improved AI, whereas sham stimulation did not. Modified RS: A significant change with rTMS but not with sham stimulation was observed. Low-frequency or high-frequency rTMS can improve significantly motor function in hemiparetic patients.
(W Kakuda et al., 2013)	Randomized, double-blind, crossover study	18 p. (9 rTMS + sham, 9 sham + rTMS)	(C) double cone (each wing 80 mm-diameter), (A) bilateral over leg motor areas, (S) 1 rTMS + 1 sham (minimum washout period: 24h), (F) 10 Hz, (I) 90% of rMT, (D) 2000 pulses (20 min: 10 s bursts + 50 s intertrain int.), (SM) the coil held at 90º to the scalp	Walking velocity and PCI	Walking velocity showed a significant increase after rTMS that lasted until 20 min follow-up; sham stimulation did not increase significantly walking velocity immediately after session but it showed an increase at 10 min and 20 min follow-up compared with baseline. Walking velocity was significantly higher after rTMS than after sham. PCI showed a significant decrease after real stimulation that was maintained until 20 min follow-up; a significant decrease was also seen immediately after sham but not at follow-up. Real rTMS reduced PCI significantly compared with sham. High-frequency rTMS led to significant improvements in walking function.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Malcolm et al., 2007)	Prospective randomized, double-blind, sham-controlled, parallel group study	19 p. (9 rTMS, 10 sham)	(C) 70-mm figure-8, (A) lesional hemisphere over motor cortex, (S) 10, (F) 20 Hz, (I) 90% of MT, (D) 2000 pulses (50 trains of 40 pulses, each train: 2 s + 28 s intertrain int.), (SM) sham coil	WMFT, MAL (amount, and how well), and B&B	WMFT: real rTMS decreased 0.85 s less at 2 wk and 0.21 s less at 6 mo than sham stimulation, but the difference was not significant. MAL-Amount: real rTMS resulted in 0.7 points more at 2 wk and 0.1 points more at 6 mo compared with sham group; the differences between groups were marginally significant. MAL-How Well: both groups showed significant improvements, with no significant differences between them. B&B: real stimulation mean change was 3.6 points higher at 2 wk and 6.9 points higher at 6 mo compared with sham; the differences between groups were significant. rTMS did not demonstrate a significant effect as an adjunct to constraint-induced therapy.
(Naghdi et al., 2015)	Single-group, pretest-posttest clinical trial	7 p.	(C) figure-8, (A) nonlesional hemisphere over leg motor cortex, (S) 5, (F) 1 Hz, (I) 90% of MT, (D) 1000 pulses (20 min.), (SM) none	Modified Modified AS, TUG, FMA - LE	TUG decreased from 25.79 ± 15.82 to 23.33 ± 13.89 after rTMS, but it was not significant. FMA-LE showed a significant improvement and increased from 23.85 ± 4.37 to 25.42 ± 3.69. Modified Modified AS which had a median of 2 (1-3) for ankle plantar flexors at baseline revealed a significant improvement after treatment, scoring 1 (0-2). For knee extensors, a significant improvement after stimulation was also observed, changing from 1 (0-2) at baseline to 0 (0-0) after rTMS. rTMS improved significantly ankle plantar flexor and knee extensor spasticity.
(W H Chang et al., 2010)	Longitudinal, pseudo-randomized, parallel-design, sham-controlled trial	28 p. (18 rTMS, 10 sham)	(C) 70-mm figure-8, (A) lesional hemisphere over M1, (S) 10, (F) 10 Hz, (I) 90% of rMT, (D) 1000 pulses (20 blocks, each block: 5 s stimulus + 50 s motor training + 5 s rest), (SM) the coil held at 90º to the scalp	MI-arm and leg, FMA-UE and LE, grip strength, B&B, FAC, and modified BI	MI-arm and B&B: significant improvement in both groups immediately following intervention and at 3 mo follow-up. MI-arm: the difference was significantly larger in the real rTMS group immediately after treatment. FMA-UE and grip strength: immediately after intervention, a significant improvement only with the real rTMS was obtained. At 3 mo follow-up, a significant improvement in both groups for FMA-UE and in only the real rTMS group for grip strength was noticed. MI-leg and FMA-LE: significant improvement in both groups. FAC and modified BI: significant improvement in both groups. Motor function improved in both groups, without additional improvement from rTMS to the affected lower limb function, mobility or functional independence. However, rTMS treatment demonstrated additional improvements in the affected upper limb that lasted 3 mo.
(H.-G. Cha et al., 2014)	Randomized controlled study	24 p. (12 HF-rTMS, 12 LF-rTMS)	(C) 70-mm figure-8, (A) HF-rTMS: lesional, LF-rTMS: nonlesional hemisphere, (S) 20, (F) HF-rTMS: 10 Hz, LF-rTMS: 1 Hz, (I) 90% of rMT, (D) HF: 2000 pulses (20 min: 10 s trains + 50 s intertrain int.), LF: 1200 pulses (20 min), (SM) N.A.	Balance index and BBS	HF-rTMS led to significant differences in motor evoked potentials values, balance index and BBS. In the LF-rTMS group, significant differences were observed only in results of balance index and BBS. High-frequency rTMS conducted to significantly greater improvements compared with low-frequency rTMS.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Conforto et al., 2012)	Pilot, randomized, double-blinded clinical trial	29 p. (15 rTMS, 14 sham)	(C) figure-8, (A) nonlesional hemisphere, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 1500 pulses (25 min), (SM) the coil held at 90º to the vertex	JFT-UE, force of the lateral pinch of paretic hand, FMA, AS and modified RS	JFT-UE: significant improvements after rTMS but not after sham stimulation; at 1 mo follow-up an absolute improvement of 12.3% ± 16.9% with rTMS against 5.5% ± 10.3% with sham stimulation was observed. Force of the paretic hand: significant improvements after real but not sham stimulation; after 1 mo, there was a trend toward improvement in the real rTMS group. AS: no significant changes in either group. FMA and modified RS improved significantly in both groups. Low-frequency rTMS improved significantly the force of the paretic hand and the ability to perform daily living activities; the improvements lasted at least 1 mo.
(C. Kim et al., 2014)	N.A.	40 p. (20 HF-rTMS, 20 LF-rTMS)	(C) 97-mm figure-8, (A) HF-rTMS: lesional over M1, LF-rTMS: nonlesional hemisphere over M1, (S) 10, (F) HF-rTMS: 20 Hz, LF-rTMS: 1 Hz, (I) HF-rTMS: 90% of rMT, LF-rTMS: 120% of rMT, (D) HF-rTMS: 2000 pulses (20 times: 5 s stimulation + 50 s rest with exercise training); LF-rTMS: 1500 pulses (10 times: 150 s stimulation + 30 s rest with exercise training), (SM) none	MFT, FMA-UE, modified BI, BRS, and grip strength	FMA-UE, MFT, BRS, and modified BI were significantly improved between baseline and the end of treatment and between baseline and 1 mo follow-up, for both HF and LF groups. Grip strength: there was a tendency for improvement in both groups; in the HF group there was no significant difference between baseline and the end of treatment, although there was a significant difference between baseline and 1 mo follow-up; in the LF-rTMS group the difference was not significant in any period. Comparing HF-rTMS with LF-rTMS, there was no significant difference between them before and after intervention. There were significant improvements in motor function after stimulation with both high and low frequencies; it was not possible to conclude which of the interventions is more effective.
(Hosomi et al., 2016)	Randomized, double-blind, sham-controlled, parallel study	39 p. (18 HF-rTMS, 21 sham)	(C) figure-8, (A) lesional hemisphere over M1, (S) 10, (F) 5 Hz, (I) 90% of rMT, (D) 500 pulses (10 trains for 10 s with 50 s intertrain int.), (SM) the coil held at 90º to the scalp	BRS (for arm, hand and lower limb), FMA (total and UE), handgrip of both hands, NIHSS (total and motor arm), FIM (motor and cognitive) and finger tapping	BRS: even though HF-rTMS led to an earlier recovery of arm and hand in comparison to sham, a significant improvement following both was demonstrated. For hand function, HF group obtained significantly larger improvement than sham group at day 29, whereas arm and lower limb scores did not show significant differences between groups. FMA total and UE, NIHSS total and FIM: real and sham stimulation groups showed a significant improvement; FMA distal score, total NIHSS and FIM motor score revealed an earlier improvement after HF. NIHSS motor arm exhibited a significant change exclusively following HF-rTMS. Handgrip strength of the affected hand improved after real but not after sham stimulation. Finger tapping: the amount of taps was significantly increased in patients who received HF but not in those receiving sham. Total distance traveled, mean maximum amplitude, opening velocity, closing velocity or total consumed energy (estimation) did not show a significant effect. 5 Hz-rTMS had a modest effect in facilitating motor rehabilitation of the affected hand.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Ackerley et al., 2010)	Double-blind, crossover, sham-controlled study	10 p.	(C) figure-8, (A) iTBS: lesional hemisphere over M1; cTBS: nonlesional hemisphere over M1, (S) 1 iTBS + 1 cTBS + 1 sham for each patient, separated by 1 wk, (I) 90% of aMT, (D) 600 pulses, (SM) sham coil	Grip-lift kinetics (PF and PD) and ARAT	PF of the paretic-hand deteriorated after sham, but remained stable after real TBS. PD showed improvements after cTBS and a tendency to improve after iTBS, compared with sham. ARAT scores got worse after cTBS but remained stable after iTBS and sham. iTBS and cTBS with training showed task-specific improvements in grip-lift kinetics; however, cTBS led to an overall deterioration of upper-limb function.
(C.-C. Wang et al., 2014)	Double-blind, randomized study	44 p. (16 cM1, 14 cPMd, 14 sham)	(C) 70-mm figure-8, (A) cM1: nonlesional over M1, cPMd: nonlesional hemisphere over PMd, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 600 pulses, (SM) sham coil	FMA, WMFT, and MRC scale	Real stimulation significantly improved measures compared with sham. MRC: grip strength and shoulder abduction strength showed a higher improvement with rTMS over cPMd compared with sham; however, rTMS over cM1 led to a greater improvement than rTMS over cPMd. WMFT and FMA: higher improvement with rTMS over cPMd compared with sham; rTMS over cM1 led to a greater improvement in comparison with rTMS over cPMd. Low-frequency rTMS over the contralesional premotor and primary motor cortices improved motor recovery; nevertheless, contralesional primary motor cortex neuromodulation was more effective.
(P. Talelli et al., 2007)	N.A.	6 p.	(C) 70-mm figure-8, (A) cTBS: nonlesional, iTBS: lesional hemisphere, (S) 1 cTBS + 1 iTBS + 1 sham (minimum washout period: 10 d), (F) short bursts of 3 stimuli at 50 Hz, repeating at 5 Hz, (I) 80% of aMT, (D) cTBS: 300 pulses (continuous train of 100 bursts); iTBS: 600 pulses (20 trains of 10 bursts given with 8 sec. int.), (SM) 2-wings 90º positioning	Simple RT, simple reaction grip strength and choice RT	Simple RT was decreased by iTBS but tended to increase after cTBS and sham. cTBS and sham led to similar results. At 7 min after stimulation, RT was significantly lower after iTBS in comparison with cTBS and sham; however, in the last evaluations (20 and 30 min after treatment), iTBS showed a reduced RT compared with sham but not with cTBS. Grip strength and choice RT did not demonstrate significant changes. iTBS led to significant improvements of motor behavior compared with cTBS or sham stimulation.
(Blesneag et al., 2015)	Prospective, randomized, placebo-controlled, single-blind clinical study	16 p. (8 LF-rTMS, 8 sham)	(C) figure-8, (A) nonlesional hemisphere over M1, (S) 10, (F) 1 Hz, (I) 120% of rMT, (D) 1200 pulses (20 min), (SM) lower intensity (10% of rMT)	FMA-UE	FMA-UE: Real stimulation led to a significant improvement from baseline (29.63 ± 12.65 points), to the second evaluation (42.88 ± 16.81 points) and from baseline to the third evaluation (45.00 ± 13.40). Following sham stimulation a significant change in FMA was also reported. At 45 d the real atimulation showed greater improvement than sham stimulation, whereas at 90 d from stroke the variation was higher for the sham group; difference between groups was not significant. 1 Hz-rTMS led to a greater improvement at 45 d poststroke compared with sham stimulation, but not at 90 d after onset. The LF-rTMS group did not show long-term effects on motor function additional to those observed on the sham stimulation group.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Tretriluxana et al., 2015)	Prospective cohort within-subject pilot study	9 p.	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 1 rTMS + 1 sham (minimum washout period: 5 d), (F) 1 Hz, (I) 90% of MT, (D) 1200 pulses (20 min), (SM) sham coil	Reach-to-grasp kinematics and coordination	Transport kinematics: the velocity of reach-to-grasp movements was increased for both small and large objects after real stimulation but not after sham. This outcome was significant just for the small objects. For peak transport velocity and time of peak transport velocity the effect of real stimulation was not significant compared with sham stimulation. Grasp kinematics: The effect of active stimulation was modest for larger objects reach-to-grasp but significant for maximum grasp aperture of smaller objects compared with sham stimulation. Time to peak aperture was not significantly changed by TMS. Coordination of small but not large objects was improved by real rTMS. The application of LF-rTMS improved paretic limb performance, namely kinematics and coordination, for reach to grasp of small objects but not for larger ones.
(N Takeuchi et al., 2005)	Double-blind study	20 p. (10 rTMS, 10 sham)	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 1, (F) 1 Hz, (I) 90% of rMT, (D) 25 min, (SM) the coil held at 90º to the scalp	Pinch force and movement acceleration	Pinch force: No significant interaction between time and condition was observed. Acceleration: real rTMS, but not sham stimulation, led to an additional improvement immediately after treatment session, although it did not last for 30 min. A single session of low-frequency rTMS was able to improve motor function of the affected hand.
(Vongvaivanichakul et al., 2014)	N.A.	14 p. (7 LF-rTMS+RTG, 7 sham+RTG)	(C) figure-8 air-cooled, (A) nonlesional hemisphere over M1, (S) 6, (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses (20 min), (SM) the coil held at 90º to the scalp	WMFT, maximum aperture and total time of RTG actions	WMFT total time was significantly decreased in the rTMS group. Total time of RTG actions: A significant reduction after RTG in comparison with pretest and with post-rTMS (before RTG training) in patients that received LF-rTMS was observed. Maximum aperture did not change. In the sham stimulation group there were no significant changes detected. rTMS enhanced the effect of reach-to-grasp training in improving the performance of the paretic hand.
(L J Volz et al., 2016)	Sham-controlled, pseudo-randomized, single-blinded between-subject design	26 p. (13 rTMS, 13 sham)	(C) 70-mm figure-8, (A) lesional hemisphere over M1, (S) 5, (F) Short bursts of 3 stimuli at 50 Hz, repeating at 5 Hz, (I) 70% of rMT, (D) iTBS: 600 pulses (~3.5 min), (SM) the coil over the vertex	Maximum and relative grip strength and JFT	Grip strength was significantly more enhanced by real (21.38% ± 15.16% between sessions) than by sham stimulation (10.54% ± 8.82%). More than 3 mo after intervention, the relative grip strength was still significantly greater in the real TMS group. JFT did not show significant differences between groups. iTBS followed by PT significantly improved grip strength.
(Wataru Kakuda et al., 2012)	Multi-institutional study	204 p.	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 22, (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses (20 min), (SM) none	FMA and WMFT	FMA increased significantly from a mean of 44.6 points at baseline to a mean of 48.6 points after intervention. WMFT log performance time was significantly decreased from a mean of 2.93 at admission to a mean of 2.37 at the end of treatment. Both FMA and WMFT results were also significant at 4 wk follow-up. Low-frequency rTMS combined with intensive occupational therapy improved significantly motor function in patients with upper limb hemiparesis.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Penelope Talelli et al., 2012)	Small semi-randomized, placebo-controlled trial	41 p. (13 iTBS, 12 iSham, 12 cTBS, 12 cSham) (8 p. were common to both sham groups)	(C) 70-mm figure-8, (A) cTBS: nonlesional, iTBS: lesional hemisphere, (S) 10, (I) short bursts of 3 stimuli at 50 Hz, repeating at 5 Hz, (I) 80% of aMT, (D) cTBS: 600 pulses (continuous train of 200 bursts); iTBS: 600 pulses (20 trains of 10 bursts given with 8 s intervals), (SM) 2-wings 90º positioning	NHPT, JFT, and maximal grip strength (grasp and pinch grip dynamometry)	NHPT: there were observed improvements in all patients at 4 d after the end of the treatment period that were sustained until 30 d follow-up. JFT showed improvements in all patients at 4 d and 30 d. Grasp and Pinch-Grip: Pinch grip did not show effects. Significant improvements were identified for grasp only at 30 d after intervention for all groups. All patients demonstrated improvements, mostly in dexterity. Theta burst stimulation did not provide additional improvements.
(Wataru Kakuda et al., 2016)	Multi-institutional open-label study	1725 p. (326 BRS Stage 3, 552 Stage 4, 847 Stage 5)	(C) figure-8, (A) nonlesional hemisphere, (S) 22, (F) 1 Hz, (I) 90% of MT, (D) 1200 pulses (20 min), (SM) none	FMA and WMFT	FMA showed a significant improvement regardless of the BRS; considering all patients, it increased from 46.8 ± 12.2 points to 50.9 ± 11.4 after treatment with 1 Hz rTMS. WMFT log performance time and functional ability scale demonstrated a significant improvement regardless of the BRS; considering all patients log performance time decreased from 2.57 ± 1.32 points to 2.21 ± 1.33 after intervention and functional ability scale increased from 47.4 ± 14.1 points to 51.4 ± 14.3. The effect of the stimulation was superior for the FMA than for the remaining measures. 1Hz-rTMS combined with intensive occupational therapy can be a good option for upper limb rehabilitation in patients with Brunnstrom Recovery Stages 3, 4, and 5.
(Etoh et al., 2013)	Cross-over study	18 p. (9 rTMS+sham, 9 sham+rTMS)	(C) 70-mm figure-8, (A) nonlesional hemisphere over motor cortex, (S) 10 rTMS + 10 sham, (F) 1 Hz, (I) 90% of rMT, (D) 240 pulses (4 min), (SM) to a region 5-cm posterior to the contralesional motor cortex	FMA, ARAT, STEF and modified AS	FMA, ARAT and STEF scores improved significantly with the rTMS but not with the sham stimulation. Modified AS (for the elbow, wrist and finger flexors) did not improve significantly with any type of stimulation. LF-rTMS enhanced the effects of repetitive facilitation exercises, showing improvements in motor function, although it did not change spasticity.
(Wataru Kakuda et al., 2013)	Preliminary study	19 p.	(C) double cone (each wing 80 mm-diameter), (A) bilateral over leg motor areas, (S) 20, (F) 10 Hz, (I) 90% of rMT, (D) 2000 pulses (20 min: 10 s trains + 50 s intertrain int), (SM) none	Walking velocity, PCI and TUG	Walking velocity showed a significant increase from 0.898 ± 0.342 to 0.987 ± 0.320 m/s. A significant reduction in mean PCI from 0.265 ± 0.155 to 0.201 ± 0.132 beats/min was observed. TUG performance time also demonstrated significant decrease from 16.2 ± 7.0 to 14.3 ± 6.1 s. High-frequency rTMS combined with mobility training improved significantly mobility and can be applied in poststroke hemiparetic patients with gait disturbance.
(Wataru Kakuda, Abo, Kobayashi, Takagishi, et al., 2011)	Retrospective comparative study	52 p. (13 BRS Stage 3, 20 Stage 4, 19 Stage 5)	(C) 70-mm figure-8, (A) nonlesional hemisphere, (S) 22, (F) 1 Hz, (I) 90% of MT, (D) 1200 pulses (20 min), (SM) none	FMA and WMFT	FMA showed a significant increase for all groups; a mean increase of 2.1 ± 2.3 points for Stage 3 group, of 5.1 ± 2.9 points for Stage 4, and 2.3 ± 1.8 points for the Stage 5 group was observed. WMFT performance time was significantly shortened in Stage 4 and Stage 5 groups but not in the Stage 3; the mean decrease was 0.04 ± 0.07 for Stage 3, 0.41 ± 0.29 for Stage 4, and 0.35 ± 0.31 for Stage 5. The implemented protocol of low-frequency rTMS combined with intensive occupational therapy improved motor function; the intervention was more effective in patients with upper-limb hemiparesis Brunnstrom Stage 4 or 5 for hand-fingers.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Koyama et al., 2014)	Preliminary study	15 p.	(C) 90-mm air-cooled figure-8, (A) nonlesional hemisphere over M1, (S) 24, (F) 1 Hz, (I) 90% of rMT, (D) 880 pulses, (SM) none	FMA-UE, WMFT, and B&B	FMA-UE increased significantly from 23.3 ± 12.4 to 27.6 ± 14.0, in a clinically meaningful manner. WMFT performance time decreased significantly from 55.8 ± 39.3 s to 50.0 ± 38.4 s, in a clinically important manner. B&B demonstrated a statistically significant increase from 8.7 ± 13.2 to 10.9 ± 15.7, but it might not show a clinically meaningful difference. NMES combined with rTMS improved motor function in patients with moderate to severe dysfunction, in a clinically meaningful way.
(J. Seniów et al., 2012)	Randomized, placebo-controlled, double-blind, parallel-group study	40 p. (20 PT + rTMS, 20 PT + sham)	(C) 70-mm air-cooled figure-8, (A) nonlesional hemisphere over M1, (S) 15, (F) 1 Hz, (I) 90% of rMT, (D) 30 min, (SM) sham coil	WMFT (functional ability score and performance time)	WMFT functional ability score and performance time showed similar results for both interventions (real rTMS and sham), without significant differences between groups, after treatment and at follow-up. The results failed to demonstrate a significant effect of rTMS in hand function, both in quality of motor skills and performance time.
(Eman M. Khedr et al., 2005)	Therapeutic trial	52 p. (26 rTMS, 26 sham)	(C) 90-mm figure-8, (A) lesional hemisphere over motor cortex, (S) 10, (F) 3 Hz, (I) 120% of rMT, (D) 10 trains, each train 10 s + 50 s intertrain int., (SM) the coil angled away from the head	SSS, NIHSS, and BI	The observed improvement was larger for the real rTMS group than for the sham group. A higher percentage of the patients that received rTMS became independent compared with those who received sham stimulation. At follow-up, a higher percentage of patients having only mild disability in the real intervention group was observed. The worst improvement was identified in patients with massive infarcts (6 p. in the real rTMS group and 5 p. in the sham group), who did not benefit from the intervention. rTMS as an add-on to standard physical and medical therapies showed improvements in clinical outcome.
(Bonnì, Ponzo, Caltagirone, & Koch, 2014)	Preliminary study	6 p.	(C) 70-mm figure-8 flat, (A) lesional cerebellar hemisphere, (S) 10, (F) iTBS: Short bursts of 3 stimuli at 50 Hz, repeating at 5 Hz, (I) 80% of aMT, (D) 600 pulses (20 trains of 10 bursts with 8 s int.), (SM) none	MICARS (posture and gait, kinetic functions, speech and oculomotor disorders)	MICARS: iTBS improved mean total score from 53.4 ± 13.0 to 43.8 ± 12.1. The improvement was significant in only the posture and gait disturbances subscale. iTBS has potential to promote rehabilitation of cerebellar stroke patients.
(Brodie, Meehan, Borich, & Boyd, 2014)	Pseudo-crossover	15 p.	(C) 70-mm figure-8 air-cooled, (A) lesional hemisphere over S1, (S) 5 rTMS + 5 sham (minimum washout period: 4 wk), (F) 5 Hz, (I) 90% of rMT, (D) 1200 pulses (24 trains for 10 s, with 5 s intertrain int.), (SM) sham coil	STT, 2PD, WMFT, and B&B	STT: greater improvements in motor performance (response time, peak velocity and cumulative distance) in the rTMS group. Considering only baseline and retention, only the response time showed a significant improvement. 2PD: A significant improvement in cutaneous somatosensation with rTMS was observed. WMFT and B&B: no significant effect. rTMS combined with motor practice was able to enhance motor learning and cutaneous somatosensation, but not upper extremity function, in chronic stroke patients.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Won Hyuk Chang et al., 2012)	Single-blind, sham-controlled, parallel group trial	17 p. (9 rTMS, 8 sham)	(C) 70-mm figure-8, (A) lesional hemisphere over M1, (S) 10, (F) 10 Hz, (I) 80% of rMT, (D) 1000 pulses (20 min: 20 trains of 5 s (50 pulses) + 55 s intertrain int. (50 s motor training + 5 s rest)), (SM) one-wing sham method	Movement accuracy and time and JFT	Movement accuracy was significantly improved after rTMS and motor training but not after sham stimulation. Movement time did not change significantly in either group. JFT: rTMS led to improvements in performance time for the simulated feeding subtask that lasted 1 mo, whereas sham did not. Other subtasks and total scores did not show significant changes in any group. rTMS combined with motor training demonstrated additional improvements of motor performance compared with sham stimulation. However, the transfer effect to functional hand movement was limited.
(Dafotakis et al., 2008)	N.A.	12 p.	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 1 rTMS + 1 sham, (F) 1 Hz, (I) 100% of rMT, (D) 10 min., (SM) the coil over the vertex	Peak lift and grip forces, peak grip/peak lift ratio, and time lag between peak grip forces	Peak lift and peak grip forces: Peak grip forces for trials performed with the affected hand were reduced by rTMS. Peak lift forces showed a significant influence from hand (affected versus unaffected) but not from condition nor interaction condition × hand. Peak grip/peak lift ratio was reduced by rTMS, scaling grip force with more efficiency. Time lag between peak grip and lift forces was reduced by rTMS. The performance of the unaffected hand was not changed by rTMS. rTMS can improve dexterity of the affected hand in subcortical stroke patients.
(Wataru Kakuda, Abo, Kaito, et al., 2010)	Case series pilot study	5 p.	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 10, (F) 1 Hz, (I) 90% of MT, (D) 1200 pulses (20 min), (SM) none	FMA, WMFT, 10-second tests, FTT, grip strength and pinch force	FMA showed an increase in all patients that was maintained until 4 wk after treatment, except for 1 patient. WMFT: total performance time was decreased in all patients. 10-second tests: increased scores in all 3 categories for all patients; this test indicated an improvement of dexterity. Grip strength and pinch force increased for all patients. All patients showed some improvement of the affected upper limb motor function with the combined treatment.
(Wataru Kakuda, Abo, Kobayashi, et al., 2010)	Preliminary study	15 p.	(C) 70-mm figure-8, (A) nonlesional hemisphere, (S) 22, (F) 1 Hz, (I) 90% of MT, (D) 1200 pulses (20 min), (SM) N.A.	FMA, WMFT and modified AS	FMA improved in all patients, showing an increase of 1-12 points in patients with baseline Brunnstrom stage for hand-fingers of 4-5 and of 1-7 points in those participants with baseline stage 3. WMFT: the performance time was decreased in almost all patients, except in 3 patients with baseline Brunnstrom stage 3 for hand-fingers. modified AS showed an improvement in fingers flexors in 6 p., wrist flexors in 7 p., and elbow flexors in 8 patients; 3 p. did not show any improvement. Low-frequency rTMS combined with intensive occupational therapy improved motor function and attenuated spasticity of the affected upper limb.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Wataru Kakuda, Abo, Kobayashi, Momosaki, Yokoi, Fukuda, Ito, & Tominaga, 2011)	Pilot study	5 p.	(C) 70-mm figure-8, (A) Nonlesional hemisphere over motor cortex, (S) 22, (F) 1 Hz, (I) 90% of MT, (D) 1200 pulses (20 min), (SM) none	FMA, WMFT (time and functional ability scale), and modified AS	FMA increased in all patients, with the improvement being maintained 4 wk in 4 p. WMFT: total performance time showed a decrease in all patients. Functional ability scale of WMFT showed an increase in all p.; after discharge 2 p. revealed a decrease in score, nevertheless at 4-wk follow-up their scores were still higher than at baseline. modified AS: 3 p. showed a decrease. Low-frequency rTMS combined with occupational therapy and levodopa administration improved motor function of the affected upper limb.
(Wataru Kakuda, Abo, Kobayashi, Momosaki, Yokoi, Fukuda, Ito, Tominaga, et al., 2011)	N.A.	39 p.	(C) 70-mm figure-8, (A) nonlesional hemisphere, (S) 22, (F) 1 Hz, (I) 90% of MT, (D) 1200 pulses (20 min), (SM) none	Modified AS, FMA and WMFT	modified AS: 24 p. showed a decrease in score for finger and wrist flexors (MAS_D group), whereas 15 p. did not (MAS_{ND} group). FMA: both groups showed a significant increase; at 4-wk follow-up the increase was significantly greater in the MAS_D group. WMFT log performance time decreased significantly, except between baseline and 4-wk follow-up for the MAS_{ND} group; the improvement was significantly greater in the MAS_D group after treatment but not at 4-wk follow-up. Low-frequency rTMS combined with occupational therapy led to a significant decrease in spasticity that lasted at least 4 wk.
(Wataru Kakuda, Abo, Kobayashi, Momosaki, Yokoi, Fukuda, & Umemori, 2011)	Case series pilot study	11 p.	(C) 70-mm figure-8, (A) nonlesional hemisphere, (S) 22, (F) priming stimulation: 6 Hz, LF-rTMS: 1 Hz, (I) 90% of MT, (D) priming: 600 pulses (10 min: 5 s trains + 25 s intertrain int.), LF-rTMS: 1200 pulses (20 min), (SM) none	FMA, WMFT (log time and functional ability score)	FMA showed a significant increase from 42.2 ± 6.9 points to 45.6 ± 7.2 points. WMFT log performance time was significantly shortened from 3.26 ± 1.21 to 2.81 ± 1.26. Functional ability score of WMFT showed a significant increase from 41.9 ± 10.9 points to 45.7 ± 9.1 points. 6-Hz primed low-frequency rTMS combined with intensive occupational therapy has the potential to improve motor function in patients with upper limb hemiparesis.
(W Kakuda et al., 2012)	Preliminary study	14 p.	(C) 70-mm figure-8, (A) nonlesional hemisphere, (S) 22, (F) 1 Hz, (I) 90% of MT, (D) 1200 pulses (20 min), (SM) none	FMA, WMFT (log time and functional ability score), MAL (amount of use and how-well) and modified AS	FMA and functional ability score of WMFT increased significantly. WMFT log performance time did not decrease significantly. MAL: quality of movement showed a significant improvement that was maintained until 4-wk follow-up; the amount of use showed a significant increase only at 4-wk follow-up. modified AS: A significant reduction in score of all muscles examined at discharge and at follow-up was observed. rTMS combined with botulinum toxin type A and intensive occupational therapy significantly improved motor function of the affected upper limb and reduced spasticity.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(W. Kim et al., 2014)	Randomized, double-blind, sham-controlled pilot study	26 p. (20 rTMS, 6 sham)	(C) 75-mm figure-8, (A) cerebellar hemisphere ipsilateral to the ataxic side, (S) 5, (F) 1 Hz, (I) 100% of rMT, (D) 900 pulses (15 min), (SM) the coil held at 90º to the scalp	10MWT and BBS	10MWT and BBS showed significant improvements after real rTMS. After the last session, time in the 10MWT changed -16.7% ± 35.1% in rTMS group versus -8.4% ± 72.5% in sham group, steps in the 10MWT changed -8.5% ± 23.0% in rTMS group versus -0.3% ± 28.4% in sham group and BBS changed 46.4% ± 100.2% in rTMS group versus 36.6% ± 71.6% in sham group. Low-frequency rTMS over the cerebellum may be beneficial for ataxic patients with posterior circulation stroke.
(Koganemaru et al., 2010)	Crossover study	9 p.	(C) air-cooled 90-mm figure-8, (A) lesional hemisphere over M1, (S) 1 exercises+rTMS (EEx-TMS) + 1 exercises+sham (EEx) + 1 rest+rTMS (TMS) (each session on separate days), (F) 5 Hz, (I) 100% of aMT, (D) 15 cycles (15 min), each cycle: 50 s exercises/rest + 1 s rest + 8 s rTMS (40 pulses) /sham + 1 s rest, (SM) sham coil	Active and passive range of movements, pinch force, grip power, and modified AS	Active range of movement was significantly increased in extension for the wrist joint, thumb, index and middle finger metacarpophalangeal joint by 'EEx–TMS' session, whereas the results in flexion were not significantly changed. 'EEx' or 'TMS' alone did not change significantly results. Passive range of movement and pinch force did not change significantly after any session. Grip power was improved significantly by 'EEx–TMS' but not by 'EEx' or 'TMS' alone, as observed at 30 min follow-up. Modified AS was significantly decreased by 'EEx–TMS' but not by 'EEx' or 'TMS'. rTMS combined with focal extensor exercise improved upper-limb function; this improvement was not achieved with rTMS or motor training alone. The authors conducted another experiment with the same patients receiving 12 sessions of 'EEx–TMS' over 6 wk to study the long-lasting efficacy of the intervention and confirmed the long-term beneficial effects.
(Kwon, Kim, Chang, Bang, & Shin, 2014)	Single-blind, randomized crossover study	14 p.	(C) 70-mm figure-8, (A) lesional hemisphere over motor cortex, (S) 1 ICM + 1 PCM (minimum washout: 48 h), (F) 10 Hz, (I) 90% of rMT, (D) ICM: 1000 pulses (20 min: 20 times 5 s train + 55 s intertrain int. (20 s motor tasks + 35 s rest). PCM: 1000 pulses (10 min: 10 times 10 s train + 50 s intertrain int.) + 10 min motor practice (10 times 40 s task + 20 s rest), (SM) none	Movement accuracy and time, PPT, and NHPT	Both interventions (ICM and PCM) improved significantly motor performance. Movement accuracy increased and time decreased with both treatments but the improvements were significantly larger with PCM. PPT and NHPT were significantly improved after both interventions. The most effective method of combining rTMS and motor training to enhance motor skill acquisition was PCM (preconditioning combination method).

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Jitka Ludemann-Podubecka, Bosl, Theilig, Wiederer, & Nowak, 2015)	Prospective, randomized, double-blind, longitudinal, parallel- and factorial-design, sham-controlled trial	40 p. (20 rTMS, 20 sham)	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 15, (F) 1 Hz, (I) 100% of rMT, (D) 900 pulses (15 min), (SM) zero stimulation output intensity	WMFT, MESUPES, and velocity of index finger tapping	Stroke on the nondominant hemisphere: Both real and sham stimulation groups showed significant changes in motor function of the affected hand over the treatment period and at 6 mo follow-up. There were no significant differences between real stimulation and control group. Stroke on the dominant hemisphere: Only real stimulation group showed significant changes in motor function of the affected hand over the treatment period and at 6 mo follow-up. Significanlty greater changes in the affected hand function for real rTMS compared with sham stimulation were observed. The improvement of hand function was not significantly different between real rTMS in dominant-affected, real rTMS in nondominant-affected and sham rTMS in non-dominant affected. 1 Hz-rTMS improved dexterity significantly in patients who had the stroke on the dominant hemisphere, although it did not give additional improvements on patients with the non-dominant hemisphere affected.
(Málly & Dinya, 2008)	Controlled trial	64 p. (17 group A, 25 group B, 16 group C, 6 group D)	(C) 13-cm diameter circular, (A) Group A: both hemispheres, B: intact pathway to healthy extremities, C: lesional hemisphere, D: nonlesional hemisphere, (S) 14, (F) 1 Hz, (I) Sub-threshold intensity of MEP (30% of 2.3 T), (D) 100 pulses, (SM) N.A.	Score of spasticity at rest, score of movement, and behavior of the paretic extremities	Group A: significant decrease of spasticity; however, movement and behavior of paretic extremities did not change. Group B showed the most expressive improvements in spasticity, movement, and behavior. Group C: behavior did not change, but spasticity and movement were significantly altered. Group D: a mild change in spasticity and no change in movement or behavior was observed. 1 Hz-rTMS improved motor disability and spasticity in chronic patients; the best results were obtained for the groups in which the intact motor pathway or the reorganized contralateral pathway was stimulated together with nearby areas.
(Mansur et al., 2005)	Crossover, sham stimulation-controlled, double-blind study	8 p. and 6 healthy controls (without TMS)	(C) figure-8, (A) nonlesional hemisphere over M1 and over PMd, (S) 1 sham + 1 rTMS over M1 + 1 rTMS over PMd (separated by 1 h), (F) 1 Hz, (I) 100% of MT, (D) 600 pulses, (SM) sham coil	Simple RT, 4-choice RT, PPT and finger tapping	Simple and 4-choice RT: real rTMS led to a significant reduction in comparison with sham stimulation; real rTMS over premotor cortex revealed a tendency to be faster than sham, but it was not significant. PPT: similar results to those obtained for the reaction time tests. Finger-tapping test: there was a tendency to better improvement with real rTMS over M1 compared with sham, but this effect was small and variable. Control subjects showed no changes in any measure across repeated testing. rTMS over the motor cortex significantly decreased reaction times and improved performance of the affected hand in comparison with sham stimulation.
(Matsuura, Onoda, Oguro, & Yamaguchi, 2015)	Double-blind, randomized, placebo-controlled study	20 p. (10 rTMS, 10 sham)	(C) 70-mm figure-8, (A) nonlesional hemisphere over motor cortex, (S) 5, (F) 1 Hz, (I) 100% of MT, (D) 1200 pulses (20 min), (SM) the coil held at 90° to the scalp	FMA, PPT, and grip strength	FMA and PPT: the improvement was significantly more pronounced in the real stimulation group than in sham group. Grip strength was not affected in a significantly different manner from real and sham stimulation. Motor function of the upper limb was improved by 1 Hz-rTMS.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(N. Sasaki, Kakuda, & Abo, 2014)	Pilot study	58 p. (31 HF-rTMS, 27 BL-rTMS)	(C) 70-mm figure-8, (A) HF-rTMS: lesional over M1, BL-rTMS: both hemispheres over M1 (LF-rTMS to the nonlesional and HF-rTMS to the lesional), (S) 5, (F) HF-rTMS: 10 Hz, LF-rTMS: 1 Hz, (I) 90% of rMT, (D) HF-rTMS: 1000 pulses (10 min: 10 s trains + 50 s intertrain int). BL-rTMS: 1000 HF pulses + 1100 LF pulses (10 min LF, followed by 10 s HF + 50 s LF alternatively over 10 min), (SM) none	BRS (upper-limb and hand-fingers), grip strength, and tapping frequency	rTMS significantly improved all outcome measures. BRS for upper-limb and hand-fingers showed significantly greater improvements in the BL group, compared with the HF. Grip strength and tapping frequency also revealed a greater improvement with BL; however, the difference between groups was not statistically significant. Bilateral application of high-frequency and low-frequency rTMS improved the affected upper limb more than high-frequency rTMS.
(Naoyuki Takeuchi et al., 2008)	Double-blind study	20 p. (10 rTMS, 10 sham)	(C) 70-mm figure-8, (A) nonlesional hemisphere over motor cortex, (S) 1, (F) 1 Hz, (I) 90% of rMT, (D) 1500 pulses (25 min), (SM) the coil held at 90º to the scalp	Pinch force and acceleration	Acceleration: An improvement immediately after rTMS that lasted for 1 wk was observed. Although the acceleration showed a tendency to increase after motor training, it was not significant. Pinch force was not significantly improved immediately after rTMS but motor training following the rTMS intervention improved pinch force for 1 wk. Motor function was improved after motor training and sham stimulation, but this was not significant. rTMS strengthened the effect of motor training in improving motor function of the affected hand.
(Vaziri et al., 2014)	Clinical trial	12 p. (rTMS/ sham)	(C) 100-mm figure-8, (A) nonlesional hemisphere over M1, (S) 10, (F) 1 Hz, (I) 60-80% of MT, (D) 20 min, (SM) yes	FMA, grip strength and BI	FMA: rTMS increased score from 19 ± 2.45 to 26.5 ± 2.88, whereas sham showed an increase from 17 ± 3.95 to 23 ± 4.83. Grip strength: increased from 6.83 ± 4.88 to 10.5 ± 4.93 in the real stimulation group and from 3.17 ± 2.71 to 6.00 ± 4.10 after sham. BI: the score changed from 68.33 ± 14.02 to 78.33 ± 14.02 in the experimental group and from 73.33 ± 6.06 to 80 ± 4.48 in the control group. In the control group, there was a significant increase of FMA and BI but not of grip strength; in the experimental group there was a significant increase of FMA, BI and grip strength. 1 Hz-rTMS combined with routine rehabilitation led to greater improvements in functional motor performance compared with the routine rehabilitation, mainly in grip strength.
(R.-Y. Wang et al., 2012)	Double-blind, randomized controlled trial	24 p. (12 rTMS, 12 sham)	(C) figure-8 coil, (A) nonlesional hemisphere over motor cortex, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 600 pulses (10 min), (SM) the coil held at 90º to the scalp	Gait symmetry, FMA-LE, and spatial and temporal parameters of gait performance	Task-oriented training did not show significant effects, as observed in the control group. On the other hand, rTMS improved significantly motor control (as shown by FMA) and walking performance (i.e. walking speed, cadence, bilateral step length, affected single-leg support time, double-leg support time, and spatial asymmetry ratio). LF-rTMS improved significantly motor control and walking performance, enhancing the effect of task-oriented training.

Ref.	Explicitly described study design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome measures *	Results
(Yamada et al., 2013)	Preliminary study	8 p.	(C) 70-mm figure-8, (A) both hemispheres, (S) 10, (F) nonlesional hemisphere: 1 Hz, lesional: 10 Hz, (I) 90% of MT, (D) 40 min (40 trains, each train consisted of 50 s 1 Hz-rTMS + 5 s int. + 5 s 10 Hz-rTMS), (SM) none	FMA, WMFT (log time and functional ability scale), and modified AS	FMA showed a significant increase from 41.1 ± 10.5 to 49.9 ± 9.4 points. WMFT log performance time decreased significantly from 3.5 ± 1.0 to 2.8 ± 1.0. WMFT functional ability scale increased in all patients. Modified AS: overall score showed a significant decrease in elbow, wrist, and finger flexors. Bihemispheric rTMS combined with occupational therapy led to improvements in upper limb function of hemiparetic poststroke patients.
(C.-J. Zheng, Liao, & Xia, 2015)	Double-blind, randomized controlled trial	112 p. (58 rTMS + VR, 54 sham + VR) (4 dropped out, 3 in real and 1 in sham group)	(C) 70-mm figure-8, (A) nonlesional hemisphere over M1, (S) 24, (F) 1 Hz, (I) 90% of rMT, (D) 1800 pulses (30 min), (SM) sham coil	FMA-UE, WMFT, and modified BI	FMA: after the first week of treatment there was no significant difference between groups; after the end of treatment, 1Hz-rTMS showed significantly higher scores than sham. WMFT: score increased from 32.4 ± 10.7 to 51.8 ± 11.3 after 1 Hz, and from 31.6 ± 11.6 to 44.7 ± 15.1 after sham. The increase was significantly larger after 4 wk of 1Hz compared with sham. Modified BI: for the 1 Hz group, the score increased from 52.6 ± 14.7 to 87.2 ± 12.1, whereas for the control score increased from 53.4 ± 15.3 to 71.6 ± 15.8. The increase was significantly larger after 4 wk of real stimulation compared with sham stimulation. The combination of 1Hz-rTMS with VR resulted in larger improvements on motor function when compared with control group.

Abbreviations: aMT, active motor threshold; BL, bilateral; CIMT, constraint-induced movement therapy; cTBS, continuous theta burst stimulation; HF, high-frequency; ICM, interleaved combination method; int., interval; iTBS, intermittent theta burst stimulation; LE, lower extremity; LF, low-frequency; M1, primary motor cortex; MT, motor threshold; N.A. not available/not applicable; NMES, neuromuscular electrical stimulation; OT, occupational therapy; p., patients; PCM, preconditioned combination method; PMd, dorsal premotor cortex; PT, physical therapy; rMT, resting motor threshold; RTG, reach-to-grasp; rTMS, repetitive transcranial magnetic stimulation; S1, primary sensory cortex; TBS, theta burst stimulation; UE, upper extremity; VR, virtual reality.

*2PD, 2-Point Discrimination; 3JC, 3-Jaw Chuck; 6MWT, 6-Minute Walk Test; 10MWT, 10 Meter Walk Test; AI, Activity Index Scale; ARAT, Action Research Arm Test; AS, Ashworth Scale; B&B, Box and Block Test; BBS, Berg Balance Scale; BI, Barthel Index; BRS, Brunnstrom Recovery Stage; FAC, Functional Ambulatory Category; FIM, Functional Independence Measure; FMA, Fugl-Meyer Assessment Score; FTT, Finger Tapping Test; JFT, Jebsen-Taylor Function Test; KT, Keyboard Tapping; LLFDI, Late-Life Functioning Disability Index; MAL, Motor Activity Log; MESUPES, Motor Evaluation Scale for Upper Extremity in Stroke Patients; MFT, Manual Function Test; MI, Motricity Index; MICARS, Modified International Cooperative Ataxia Rating Scale; MRC, Medical Research Council; NIHSS, National Institutes of Health Stroke Scale; NHPT, Nine-Hole Peg Test; PASS, Postural Assessment Scale for Stroke Patients; PCI, Physiological Cost Index; PD, Preload Duration; PF, Preload Force; POMA, Tinetti Performance-Oriented Mobility Assessment; PPT, Purdue Pegboard Test; RS, Rankin Scale; RT, Reaction Time; SIS, Stroke Impact Scale; SSS, Scandinavian Stroke Scale; STEF, Simple Test for Evaluating hand Function; STT, Serial Targeting Task; TIFT, Thumb-Index Finger Tapping Test; TUG, Timed Up and Go test; WMFT, Wolf Motor Function Test

Table A1.2 - Characterization data extracted from each reviewed study, including patients' age and gender, stroke subtype, time since stroke, and additional therapy

Ref.	Age (y)	Gender (% female/ % male)	Stroke subtype (% infarction/% hemorrhage)	Time since stroke	Additional therapy
(J Du et al., 2016)	HF-rTMS: 56.78 ± 8.47, LF-rTMS: 56.78 ± 12.4, sham: 53.61 ± 13.55	HF-rTMS: 35/65, LF-rTMS: 30/70, sham: 39/61	100/0	HF-rTMS: median 7 (4-16) d, LF-rTMS: median 6 (5-12) d, sham: median 8 (3-24) d	Physical and medical therapies
(Abo et al., 2014)	rTMS + OT: 57.7 ± 12.7, CIMT: 60.3 ± 10.6	rTMS + OT: 41/59, CIMT: 45/55	rTMS+OT: 41/59, CIMT: 50/50	rTMS+OT: 62.1 ± 47.7 mo, CIMT: 68.0 ± 53.1 mo	OT (one-to-one training + self exercise)
(Chieffo, De Prezzo, et al., 2014)	between 49 and 74; mean 62.2	N.A.	56/44	8-30 mo	No specific motor task involving lower limb associated to rTMS
(Galvão et al., 2014)	rTMS: 57.4 ± 12.0, sham: 64.6 ± 6.8	rTMS: 40/60, sham: 30/70	rTMS: 90/10, sham: 80/20	rTMS: 47.8 ± 43.2 mo, sham: 58.9 ± 27.2 mo	PT
(E M Khedr et al., 2009)	57.9 ± 11.0	47/53	100/0	17.1 ± 3.6 d	Passive limb movement + conventional therapy and medical treatment
(E. M. Khedr et al., 2010)	59.52 ± 13.10	50/50	100/0	6.5 ± 3.63 d	Passive limb movement + conventional therapy and medical treatment
(Nowak et al., 2008)	46 ± 8	27/73	100/0	1-4 mo	N.A.
(Sung et al., 2013)	35-85	24/76	1-Hz rTMS + iTBS: 67/33, sham 1-Hz rTMS + iTBS: 67/33,1-Hz rTMS+ sham iTBS: 62/38, sham 1-Hz rTMS +sham iTBS: 64/36	1-Hz rTMS + iTBS: 7.8 ± 1.7 mo, sham 1-Hz rTMS + iTBS: 8.1 ± 1.5 mo, 1-Hz rTMS+ sham iTBS: 7.9 ± 2.0 mo, sham 1-Hz rTMS +sham iTBS: 8.2 ± 1.6 mo	Conventional physical rehabilitation and OT
(Rastgoo et al., 2016)	rTMS+sham: 54.6 ± 11.75, sham+rTMS: 49.7 ± 11	rTMS+sham: 20/80, sham+rTMS: 20/80	rTMS+sham: 80/20, sham+rTMS: 70/30	rTMS+sham: 30.2 ± 18.3 mo, sham+rTMS: 27.4 ± 20.1 mo	N.A.
(Rose et al., 2014)	rTMS: 64.7 ± 7.0, sham: 64.6 ± 9	rTMS: 11/89, sham: 50/50	N.A.	rTMS: 60.4 ± 47.2 mo, sham: 62.8 ± 51.7 mo	Functional task practice
(N. Sasaki et al., 2013)	65 ± 10	31/69	sham: 44/56, HF: 44/56, LF: 45/55	17.4 ± 5.4 d	Conventional rehabilitation and medical treatment
(C. P. Wang et al., 2014)	mean 65	21/79	100/0	1Hz rTMS+iTBS: 4.6 +3.9 mo, iTBS+1Hz rTMS: 4.5+ 3.4 mo, sham: 4.4 + 3.1 mo	Conventional physiotherapy
(Avenanti et al., 2012)	rTMS-PT: 60.9 ± 8.8, PT-rTMS: 64.0 ± 7.7, sham: 64.0 ± 12.1	rTMS-PT: 50/50, PT-rTMS: 50/50, sham: 43/57	rTMS-PT: 75/25, PT-rTMS: 63/37, sham: 64/36	6-88 mo	PT (standard task-oriented upper-limb exercises)
(Higgins et al., 2013)	rTMS: 74 ± 8, sham: 60 ± 11	rTMS: 25/75, sham: 40/60	N.A.	rTMS: 134 ± 125 mo; sham: 95 ± 117 mo	Task-specific training for arm function
(Ameli et al., 2009)	56 ± 13	45/55	100/0	22 ± 26 wk	N.A.

Ref.	Age (y)	Gender (% female/ % male)	Stroke subtype (% infarction/% hemorrhage)	Time since stroke	Additional therapy
(Lin et al., 2015)	rTMS: 58.3 ± 10.8, Sham: 62.3 ± 11.7	rTMS: 38/62, Sham: 31/69	rTMS: 75/25, sham: 62/38	rTMS: 40.6 ± 29.1 d, sham: 33.5 ± 23.8 d	PT session immediately after real rTMS/sham
(Naoyuki Takeuchi et al., 2009)	U-rTMS: 58.1 ± 12.3, A-rTMS: 59.0 ± 12.7, B-rTMS: 60.9 ± 12.4	27/73	N.A.	B-rTMS: 26.1 ± 28.0 mo, U-rTMS: 24.7 ± 28.9 mo, A-rTMS: 35.6 ± 38.7 mo	"Pinching" task as motor training after rTMS
(J Ludemann-Podubecka et al., 2016)	71.9 ± 7.9	40/60	90/10	1.0 ± 0.4 mo	N.A.
(Fregni et al., 2006)	56 ± 11.5	27/73	100/0	rTMS: 3.52 ± 2.93 y, sham: 3.97 ± 2.64 y	N.A.
(Liepert et al., 2007)	63 ± 11	33/67	N.A.	7.3 ± 4.5 d	N.A.
(Y.-H. Kim et al., 2006)	53.5 ± 4.5	13/87	80/20	mean 16.7 mo	Sequential finger motor tasks
(Emara et al., 2010)	HF-rTMS: 50.9 ± 10.3, LF-rTMS: 55 ± 7.0, sham: 55.9 ± 6.1	HF-rTMS: 30/70, LF-rTMS: 30/70, sham: 40/60	100/0	HF-rTMS: mean 2.5 mo, LF-rTMS: mean 6.5 mo, sham: mean 3.5 mo	Standard physical therapy and a custom rehabilitation protocol for fine hand movement
(W Kakuda et al., 2013)	52.1 ± 11.9	28/72	28/72	52.8 ± 30.7 mo	None
(Malcolm et al., 2007)	rTMS: 68.4 ± 8.4, sham: 65.7 ± 5.1	rTMS: 44/56, sham: 40/60	rTMS: 89/11, sham: 100/0	rTMS: 3.9 ± 3.1 y, sham: 3.8 ± 3.7 y	CIMT
(Naghdi et al., 2015)	56.7 ± 12.7	29/71	86/14	24.3 ± 16.1 mo	N.A.
(W H Chang et al., 2010)	56.6 ± 12.2	39/61	100/0	13.4 ± 5.4 d	Conventional, physical and occupational therapy
(H.-G. Cha et al., 2014)	HF-rTMS: 54.83 ± 6.32, LF-rTMS: 51.33 ± 8.71	HF-rTMS: 50/50, LF-rTMS: 33/67	HF: 42/58, LF: 33/67	HF-rTMS: 2.92 ± 1.31 mo, LF-rTMS: 3.58 ± 0.90 mo	Balance training
(Conforto et al., 2012)	rTMS: 54.8 ± 11.7, sham: 56.7 ± 14.8	rTMS: 33/67, sham: 47/53	100/0	rTMS: 27 ± 8.6 d, sham: 28.3 ± 10.5 d	Customary rehabilitative treatment
(C. Kim et al., 2014)	HF-rTMS: 65.1 ± 15.0, LF-rTMS: 62.0 ± 12.5	HF-rTMS: 55/45, LF-rTMS: 45/55	100/0	HF-rTMS: 14.8 ± 1.7 d, LF-rTMS: 14.7 ± 1.0 d	Conventional rehabilitation and conventional medical treatment
(Hosomi et al., 2016)	HF-rTMS: 62.4 ± 15.5, sham: 63.2 ± 12.5	HF-rTMS: 44/56, sham: 38/62	rTMS: 67/33, sham: 57/43	rTMS: 46.1 ± 8.7 d, sham: 45.1 ± 9.5 d	Conventional, physical and occupational therapy
(Ackerley et al., 2010)	60 ± 11	70/30	80/20	28 ± 25 mo	Standardized upper-limb training
(C.-C. Wang et al., 2014)	cM1 stimulation: 62.38 ± 12.09, cPMd stimulation: 63.07 ± 12.89, Sham stimulation: 68.00 ± 12.51	23/77	cM1: 63/37, cPMd: 57/43, sham:79/21	6.7 ± 3.2 mo	PT, OT and task-oriented training
(P. Talelli et al., 2007)	57.7 ± 14.9	33/67	100/0	31 ± 37.9 mo	N.A.
(Blesneag et al., 2015)	LF-rTMS: 69 ± 5.8, sham: 69.13 ± 7.2	LF-rTMS: 25/75, sham: 50/50	100/0	10 d	N.A.
(Tretriluxana et al., 2015)	59 ± 6.8	44/56	N.A.	mean 4.8 y (7 mo to 7 y)	N.A.

Ref.	Age (y)	Gender (% female/ % male)	Stroke subtype (% infarction/% hemorrhage)	Time since stroke	Additional therapy
(N Takeuchi et al., 2005)	59.0 ± 9.6	25/75	100/0	rTMS: 25.2 ± 18.4 mo, sham: 28.7 ± 16.7 mo	Motor training protocol and "pinching" task (before the rTMS study)
(Vongvaivanichakul et al., 2014)	57.8 ± 5.5	N.A.	N.A.	43 ± 42 mo	RTG training
(L J Volz et al., 2016)	67.2 ± 13.1	35/65	100/0	7.3 ± 3.6 d	PT and OT
(Wataru Kakuda et al., 2012)	58.5 ± 13.4	36/64	47/53	5.0 ± 4.5 y	OT (one-to-one training + self exercise)
(Penelope Talelli et al., 2012)	iTBS: 54.4 ± 15.8, iSham: 58.5 ± 12.0, cTBS: 55.8 ± 12.4, cSham: 59.4 ± 12.4	N.A.	100/0	cTBS: 29.8 ± 19.7 mo, cSham: 49.6 ± 76.9 mo, iTBS: 17.5 ± 5.1 mo, iSham: 38.5 ± 57.2 mo	PT
(Wataru Kakuda et al., 2016)	61.4 ± 13.0	34/66	51/49	58.7 ± 59.5 mo	Intensive OT (one-to-one training + self-exercise)
(Etoh et al., 2013)	59.7 ± 11.0	22/78	72/28	29.9 ± 18.8 mo	Repetitive facilitation exercises + voluntary training
(Wataru Kakuda et al., 2013)	56.2 ± 11.9	47/53	32/68	60.5 ± 25.6 mo	Mobility training
(Wataru Kakuda, Abo, Kobayashi, Takagishi, et al., 2011)	57 ± 13	27/73	42/58	50 ± 33 mo	OT (one-to-one training + self exercise)
(Koyama et al., 2014)	60.5 ± 10.3	47/53	N.A.	38.6 ± 28.8 mo	Intensive motor training and NMES (50 Hz, 250μs pulse width, cycle of 500 ms on and 500 ms off) with synchronous onset with rTMS
(J. Seniów et al., 2012)	PT+rTMS: 63.5 ± 8.9, PT+sham: 63.4 ± 9.2	35/65	PT+rTMS: 90/10, PT+sham: 85/15	PT+rTMS: 41.7 ± 21.3 d, PT+sham: 38.0 ± 26.6 d	Conventional physiotherapy
(Eman M. Khedr et al., 2005)	rTMS: 53.5 ± 9.5, sham: 52.2 ± 8.4	31/69	100/0	rTMS: 7.1 ± 1.4 d, sham: 7.3 ± 1.5 d	Standard physical and medical therapies
(Bonnì et al., 2014)	45.2 ± 2.8	17/83	50/50	9 mo to 7 y	Standard physical therapy
(Brodie et al., 2014)	mean 66.2	27/73	N.A.	16 to 248 mo	Skilled motor practice
(Won Hyuk Chang et al., 2012)	rTMS: mean 58.1, sham: mean 59.5	rTMS: 33/67, sham: 50/50	rTMS: 78/22, sham: 88/12	rTMS: mean 11.8 mo, sham: mean 8.1 mo	Sequential finger motor training of the paretic hand
(Dafotakis et al., 2008)	45 ± 9	33/67	100/0	1 to 4 mo	N.A.
(Wataru Kakuda, Abo, Kaito, et al., 2010)	58 to 74	40/60	80/20	15 to 17 mo (4 p.), 10 y (1 p.)	OT (one-to-one training + self exercise)
(Wataru Kakuda, Abo, Kobayashi, et al., 2010)	55 ± 17	33/67	40/60	57 ± 55 mo	OT (one-to-one training + self exercise)

Ref.	Age (y)	Gender (% female/ % male)	Stroke subtype (% infarction/% hemorrhage)	Time since stroke	Additional therapy
(Wataru Kakuda, Abo, Kobayashi, Momosaki, Yokoi, Fukuda, Ito, & Tominaga, 2011)	56 to 66	40/60	20/80	18 to 143 mo	OT (one-to-one training + self exercise) and levodopa administration
(Wataru Kakuda, Abo, Kobayashi, Momosaki, Yokoi, Fukuda, Ito, Tominaga, et al., 2011)	56.5 ± 16.0	23/77	41/59	50.3 ± 37.8 mo	OT (one-to-one training + self exercise)
(Wataru Kakuda, Abo, Kobayashi, Momosaki, Yokoi, Fukuda, & Umemori, 2011)	61.0 ± 13.7	45/55	36/64	70.2 ± 39.8 mo	OT (one-to-one training + self exercise)
(W Kakuda et al., 2012)	54.9 ± 9.2	29/71	36/64	87.1 ± 48.2 mo	Botulinum toxin type A injection and OT (one-to-one training + self-training)
(W. Kim et al., 2014)	rTMS: 66.7 ± 7.7, sham: 66.7 ± 11.4	rTMS: 50/50, sham: 50/50	100/0	rTMS: 16.8 ± 13.4 d, sham: 14.0 ± 4.9 d	Conventional rehabilitation service
(Koganemaru et al., 2010)	51.6 ± 11.6	56/44	78/22	24.0 ± 19.1 mo	Training of the paretic upper-limb aided by NMES
(Kwon et al., 2014)	53.3 ± 12.4	21/79	64/36	22.5 ± 24.5 mo	Motor training (sequential finger motor tasks)
(Jitka Ludemann-Podubecka et al., 2015)	rTMS: 65.7 ± 9.9, Sham: 68.3 ± 10.8	rTMS: 35/65, Sham: 40/60	rTMS: 50/50, sham: 85/15	rTMS: 1.7 ± 1.1 mo, sham: 1.6 ± 1.2 mo	Standard task-oriented upper-limb motor training
(Mály & Dinya, 2008)	57.6 ± 10.8	42/58	72/28	10.0 ± 6.4 y	N.A.
(Mansur et al., 2005)	35 to 63	70/30	100/0	Within 12 mo	N.A.
(Matsuura et al., 2015)	rTMS: 72.2 ± 6.0, sham: 74.7 ± 12.7	rTMS: 40/60, sham: 50/50	100/0	rTMS: 9.4 ± 5.3 d, sham: 9.8 ± 2.8 d	N.A.
(N. Sasaki et al., 2014)	64.5 ± 10.3	29/71	62/38	9.7 ± 3.3 d	Conventional rehabilitation and medical treatment
(Naoyuki Takeuchi et al., 2008)	62.3 ± 8.4	20/80	100/0	rTMS: 25.4 ± 20.8 mo, sham: 34.4 ± 38.6 mo	"Pinching" task as motor training after rTMS
(Vaziri et al., 2014)	rTMS: 55.17 ± 5.42, sham: 57.00 ± 8.67	N.A.	N.A.	rTMS: 24.00 ± 8.29 mo, sham: 23.00 ± 8.94 mo	Routine rehabilitation program
(R.-Y. Wang et al., 2012)	rTMS: 64.90 ± 12.37, sham: 62.98 ± 10.88	rTMS: 42/58, sham: 33/67	100/0	rTMS: 1.84 ± 1.16 y, sham: 2.00 ± 1.23 y	Task oriented training
(Yamada et al., 2013)	62.8 ± 4.9	N.A.	50/50	84.3 ± 87.2 mo	OT (one-to-one training + self-training)
(C.-J. Zheng et al., 2015)	rTMS+VR: 65.4 ± 13.5, Sham rTMS+VR: 66.2 ± 13.1	rTMS+VR: 40/60, Sham rTMS+VR: 39/61	rTMS: 59/41, sham: 65/35	rTMS: 19.3 ± 7.3 d, sham: 18.7 ± 8.1 d	Standard rehabilitation therapy (PT and OT) and VR training within 10 min after TMS (real or sham)

Abbreviations: CIMT, constraint-induced movement therapy; cTBS, continuous theta burst stimulation; HF, high-frequency; iTBS, intermittent theta burst stimulation; LF, low-frequency; M1, primary motor cortex; N.A., not available/not applicable; NMES, neuromuscular electrical stimulation; OT, occupational therapy; PMd, dorsal premotor cortex; PT, physical therapy; RTG, reach-to-grasp; rTMS, repetitive transcranial magnetic stimulation; VR, virtual reality.

A2

Table A2.1.1 – Pertinent data extracted from the studies focusing aphasia rehabilitation, comprising study design, sample size, details of the TMS procedure, outcome measures and main behavioural findings

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(Kindler et al., 2012)	Randomized, sham-controlled, crossover study	18 p.	(C) figure-8 coil, (A) Nonlesional hemisphere over right Broca's homologue (BA 45), (S) 1 session cTBS + 1 session sham, (F) Each burst with 3 pulses at 30 Hz, repeated with an interburst int. of 100 msec, (I) 90% of rMT, (D) Continuous train of 801 pulses (267 bursts), (SM) sham coil	Naming Task and Alertness Test	Naming Task: The naming score increased from 23.1 ± 1.5 (SEM) at baseline to 24.2 ± 1.2 post-TBS and to 23.6 ± 1.6 post-sham stimulation. The naming latency decreased from 1240 ± 83 ms at baseline to 1214 ± 70 ms post-TBS and to 1235 ± 110 ms post-sham stimulation. Alertness Test showed no differences between groups for reaction times and errors (anticipations and omissions). TBS improved significantly naming performance and naming latency in aphasic patients.
(Szaflarski et al., 2011)	Exploratory study	8 p.	(C) 70-mm figure-8 coil, (A) Lesional hemisphere over left Broca's area, (S) 10, (F) Short bursts of 3 stimuli at 50 Hz, repeating at 5 Hz, (I) 80% of aMT, (D) 600 pulses (2-sec. train repeated every 10 sec. for 200 sec.), (SM) none	BNT, COWAT, SFT, BDAE (complex ideation subtest), PPVT IV and mini-CAL	iTBS demonstrated a trend to improve aphasia in all tests but COWAT. The improvements observed in semantic fluency showed significance while mini-CAL showed a tendency towards improvements in communication. iTBS led to improvements in language skills in aphasic patients.
(Joanna Seniów et al., 2013)	Randomized, double-blind, sham-controlled pilot study	40 p. (20 rTMS, 20 sham)	(C) air-cooled 70-mm figure-8 coil, (A) Anterior portion of the right Broca's area homologue (PTr), (S) 15, (F) 1 Hz, (I) 90% of rMT, (D) 1800 pulses (30 min.: single train with 1 sec interstimulus int.), (SM) sham coil	BDAE (Polish version) and 6-point ASRS	All patients showed improvements in language abilities and further recovery during the follow-up. Mean language test scores did not demonstrate significant differences between real and sham stimulation groups. Nevertheless, at the end of the follow-up, real rTMS group showed better improvements (minimal regarding naming and statistically significant regarding repetition), compared to sham group. Although low-frequency rTMS was not effective for aphasia recovery in all patients, it might be minimally effective for severely impaired aphasics and for patients with a lesion including the frontal part of the language area.
(Rubi-Fessen et al., 2015)	Randomized controlled study	30 p. (15 rTMS, 15 sham)	(C) double 70-mm coil, (A) Nonlesional hemisphere over right triangular part of IFG (BA 45), (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 20 min, (SM) coil over the vertex	AAT (auditory and written comprehension, token test, naming, writing, and repetition), SV picture naming inventory, ANELT and FIM	Both real and sham stimulation groups showed improvements in language and communication. AAT: real stimulation led to significantly greater improvements regarding AAT profile score, written language, naming and comprehension. For AAT Token Test there was just an insignificant trend for improvement after stimulation and for AAT repetition there was no significant effect. Naming screening: there was just an insignificant trend for improvement after stimulation. ANELT: active intervention showed significant improvements. FIM: it was not detected a significant improvement after stimulation. 1 Hz-rTMS combined with SLT showed significantly greater improvements in basic linguistic skills and functional communication comparing to sham with SLT.

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(Chieffo, Ferrari, et al., 2014)	Double-blind, placebo-controlled, crossover study	5 p.	(C) H-coil, (A) Right IFG, (S) 1 session LF-rTMS + 1 session HF-rTMS + 1 session sham (washout period: 6 days), (F) HF-rTMS: 10 Hz, LF-rTMS: 1 Hz, (I) 100% of rMT, (D) HF-rTMS: 800 pulses (15 min: 40 trains with 20 sec intertrain int.). LF-rTMS: 900 pulses, (SM) sham coil	SV picture naming inventory	10-Hz rTMS significantly improved the percentage of correct answers, compared to 1-Hz stimulation. In fact, 1 Hz-rTMS led to similar or even smaller improvements than sham stimulation. High-frequency rTMS significantly improved naming performance, while 1 Hz-rTMS and sham stimulation did not.
(Weiduschat et al., 2011)	Randomized, controlled, blinded pilot study	10 p. (6 rTMS, 4 sham)	(C) double 70-mm coil, (A) Right triangular part of IFG, (S) 10, (F) 1 Hz, (I) 90% of MT, (D) 20 min, (SM) coil over the vertex	AAT	AAT total score: patients that received real stimulation showed significant improvements by 19.8 points, while those who received sham improved by 8.5 points, and the improvement was not significant. Although only rTMS intervention led to significant improvements in the subtest naming, the difference between groups in single subtests was not significant. rTMS combined with speech and language therapy led to significant clinical improvements in aphasia while sham stimulation did not.
(Heiss et al., 2013)	Controlled, randomized protocol	31 p. (15 right-handed rTMS, 14 right-handed sham, 2 left-handed rTMS)	(C) double 70-mm coil, (A) RH: Triangular part of right IFG; LH: over the left (non-dominant) IFG, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 20 min, (SM) coil over the vertex	AAT	RH patients: rTMS group showed a significantly higher change in global AAT score, compared to the sham group. The largest difference was identified in picture naming. LH patients: The two patients improved; nevertheless, while 1 p. improved within confidence limits of RH treated with rTMS, the other p. performed within the limits of RH p. that received sham stimulation. Low-frequency rTMS was effective in improving language performance of right-handed poststroke aphasics; in left-handed aphasic patients the treatment efficiency was less obvious.
(Naeser et al., 2011)	N.A.	8 p., 8 healthy subjects	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over right PTr, POp, motor cortex mouth area and posterior-STG, (S) 1 session for each area (maximum 2 sessions per day with a minimum washout period of 30 min.), (F) 1 Hz, (I) 90% of MT, (D) 600 pulses (single train, 10 min.), (SM) none	SV picture naming inventory	Poststroke patients with aphasia: Suppression of right PTr with 1 Hz-rTMS was the only intervention that significantly increased the number of pictures named and, at the same time, significantly reduced response time. On the other hand, suppression of right POp did not change the number of pictures named and was the only intervention that significantly increased RT. Suppression of right pars triangularis with low-frequency rTMS improved naming in aphasia, while suppression of pars opercularis did not.

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(Medina et al., 2012)	Exploratory study	10 p. (5 rTMS, 5 sham (after 2 months follow-up, p. from the sham group also received rTMS treatment))	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over right PTr (9 patients) and over right pars orbitalis (1 patient), (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses, (SM) coil held at 90° to the scalp	BDAE, QPA (discourse and sentence productivity, grammatical accuracy and lexical selection) and CIU	rTMS significantly increased discourse productivity and showed a tendency to increase the number of generated CIUs. However, the other three fluency categories (i.e. sentence productivity, grammatical accuracy and lexical selection) did not change significantly. Sham stimulation did not produce significant improvements in any of the four categories of fluency. rTMS improved fluency by increasing discourse productivity; nevertheless, sentence productivity, grammatical accuracy and lexical selection did not change significantly.
(C. Barwood, Murdoch, Whelan, Lloyd, Riek, O' Sullivan, et al., 2011)	Double-blind study	12 p. (6 rTMS, 6 sham)	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over anterior portion of right PTr (BA 45), in the homologue to Broca's area, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses (20 min.), (SM) sham coil	BNT, BDAE and SV picture naming inventory (picture naming latency and accuracy)	Two months after treatment, significant differences were observed between real and sham stimulation groups for a number of language subtests. rTMS increased significantly BDAE naming actions, tools and instruments, Cookie Theft picture description complexity index, BDAE overall score and picture-naming accuracy, compared to sham. Real stimulation also decreased significantly picture-naming latency, in comparison to sham. rTMS group showed significant differences across time, whereas sham did not. Low-frequency rTMS improved language behaviour, particularly picture naming, spontaneous speech and auditory comprehension.
(C. H. S. Barwood et al., 2012)	Open-label study	7 p.	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over anterior portion of right PTr (BA 45), in the homologue to Broca's area, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses (20 min.), (SM) none	BNT, BDAE and SV picture naming inventory (picture naming latency and accuracy)	BNT and BDAE: significant differences in performance for a number of subtests, after the intervention. SV picture naming inventory: accuracy improved significantly and latency decreased significantly. The improvements in language function were sustained up to 8 months post-stimulation. rTMS had a significant effect on picture naming, spontaneous speech and auditory comprehension, with long-term duration, up to 8 months follow-up.
(Thiel et al., 2013)	Randomized, blinded, sham-controlled, proof-of-principle study	24 p. (13 rTMS, 11 sham)	(C) double 70-mm coil, (A) Nonlesional hemisphere over right triangular part of posterior IFG, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 20 min, (SM) coil over the vertex	AAT (language comprehension, token test, picture naming, writing, and repetition)	Global AAT score improved significantly in rTMS group (mean change: 23.6 ± 12.15) compared to sham group (mean change: 7.55 ± 11.00). A larger treatment effect was also observed in the subtest analysis, such that the mean increases in all subtests' scores were higher in the rTMS group. The subtest that showed the largest improvement induced by rTMS was picture naming. Low-frequency rTMS combined with speech and language therapy improves language recovery significantly, enhancing the efficacy of conventional SLT.

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(Eman M Khedr et al., 2014)	Randomized, double-blind clinical trial	29 p. (19 rTMS, 10 sham)	(C) 90-mm figure-8 coil, (A) Sequential stimulation of each hemisphere over right (nonlesional) and left (lesional) Broca's area (PTr and POp), (S) 10, (F) Nonlesional: 1 Hz; Lesional: 20 Hz, (I) 1 Hz-rTMS: 110% of rMT; 20 Hz-rTMS: 80% of rMT, (D) 1Hz-rTMS: 1000 pulses (1 train); 20 Hz-rTMS: 1000 pulses (10 trains, each train 5 sec + 30 sec intertrain int.). 500 pulses over PTr + 500 pulses over POp in each hemisphere, (SM) coil held at 90° to the scalp	ASRS, Hand strength, HSS (language assessment section), SADQ (hospital version) and NIHSS	ASRS was significantly improved by rTMS (mean increase: 1.8 ± 1.2 points), compared to sham stimulation (mean increase: 0.9 ± 0.3 points). HSS: real rTMS group showed significant improvements in all 4 main items (comprehension, naming, repetition and fluency) in comparison to sham group, at post-stimulation and at 1 month and 2 month follow-up. SADQ: rTMS significantly decreased SADQ compared to sham. NIHSS: no differences. Hand strength: there was a similar increase in both groups. Dual-hemisphere rTMS combined with language training showed good results on treating nonfluent aphasia.
(Tsai et al., 2014)	Sham-controlled, double-blind parallel study	56 p. (33 rTMS, 23 sham)	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over PTr, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 600 pulses (10 min.), (SM) sham coil	Picture Naming Test, CCAT (conversation, description, expression and repetition)	Picture Naming Test: real stimulation led to higher object and action naming accuracy and shorter reaction time in action and object naming compared to sham stimulation. CCAT: patients receiving real rTMS showed significant improvements in overall score and all sub-tests compared to sham stimulation. At 3 months follow-up, differences in overall score, description, expression and repetition were significant compared to baseline. 1 Hz-rTMS led to improvements in language function that were maintained 3 months after intervention.
(T. Hara et al., 2017)	Single-group intervention study	8 p. (4 LF-rTMS, 4 HF-rTMS)	(C) 70-mm figure-8 coil, (A) Right hemisphere over IFG (F8), (S) 10, (F) LF-rTMS: 1 Hz; HF-rTMS: 10 Hz, (I) 90% of MT, (D) LF-rTMS: 2400 pulses (40 min.); HF-rTMS: 2400 pulses (12 min.), (SM) none	SLTA (listening, speaking, reading, writing)	SLTA: total score increased significantly from a median of 125.5 (112.3) to 134.0 (116.5) after LF-rTMS and from 73.0 (51.5) to 86.5 (49.5) on the HF stimulation group. Patients also improved in the subscales of listening, speaking, reading and writing, although the improvement was not statistically significant. Also, the difference between groups was not significant. Both LF-rTMS applied over the right hemisphere of patients with left hemisphere activation for language and HF-rTMS over the right hemisphere of patients with right hemisphere activated for language, combined with intensive ST, were effective in improving language.

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(Waldowski et al., 2012)	Prospective, randomized, double-blind, sham-controlled study	26 p. (13 rTMS, 13 sham)	(C) air-cooled 70-mm figure-8 coil, (A) Nonlesional hemisphere over PTr and POp (Broca's area homologues), (S) 15, (F) 1 Hz, (I) 90% of rMT, (D) 30 min. (15 min. over PTr and 15 min. over POp), (SM) sham coil	CPNT (naming accuracy and RT), BDAE and ASRS	It was not observed a significant difference between groups; both rTMS and sham groups showed significant improvements in naming abilities during treatment and also demonstrated improvement in the follow-up. The real intervention tended to improve average RT minimally better than sham. Patients with a lesion including the anterior part of language area that received real stimulation demonstrated significantly greater improvements in naming RT and in functional communication abilities at follow-up. This protocol of low-frequency rTMS cannot be assumed as being effective for all aphasic post-stroke patients; nevertheless, it may be useful for patients with a lesion including the anterior part of language area.
(Abo et al., 2012)	Pilot study	24 p. (14 with nonfluent aphasia, 10 with fluent aphasia)	(C) 70-mm figure-8 coil, (A) nonfluent aphasics: right/left IFG of the frontal lobe; Fluent aphasics: right/left STG of the temporal lobe. (The position for rTMS application was based on individual fMRI and aphasia type), (S) 10, (F) 1 Hz, (I) 90% of MT, (D) 2400 pulses (40 min.), (SM) none	SLTA (spontaneous speech, auditory comprehension, reading comprehension and writing), SLTA-ST (naming) and WAB (Japanese version)	rTMS showed significant improvements in some categories of language function. Patients with nonfluent aphasia improved significantly in auditory and reading comprehension as well as in repetition. On the other hand, individuals with fluent aphasia improved significantly only in spontaneous speech. The intervention led to larger improvements in language function in nonfluent aphasics, compared to patients with fluent aphasia. rTMS combined with intensive speech therapy improved language function in aphasic poststroke patients.
(C. Barwood, Murdoch, Whelan, Lloyd, Riek, O'Sullivan, et al., 2011)	Double-blind study	12 p. (6 rTMS, 6 sham)	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over anterior portion of right PTr (BA 45), in the homologue to Broca's area, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses (20 min.), (SM) sham coil	BNT, BDAE and SV picture naming inventory (picture naming latency and accuracy)	Significant differences were observed one week after treatment in the real stimulation group on: BDAE naming tools and instruments, BDAE overall score, BDAE repetition of sentences, Commands and SV picture naming latency and accuracy. rTMS and sham groups differed significantly for some subtests at 1 week post-stimulation; real stimulation but not sham showed significant improvements in performance on picture naming and repetition subtests of BDAE and naming accuracy and latency. Patients that received low-frequency rTMS showed improvements on behavioural language function at 1 week post-treatment.
(C. H. S. Barwood et al., 2013)	Longitudinal, follow-up, placebo-controlled, double-blind study	12 p. (6 rTMS, 6 sham)	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over anterior portion of right PTr (BA 45), in the homologue to Broca's area, (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses (20 min.), (SM) sham coil	BNT, BDAE and SV picture naming inventory (picture naming latency and accuracy)	rTMS group showed improvements in a range of language expressive and receptive behaviours, over the 5 assessment points (baseline, 1 week, 2 months, 8 months and 12 months post-stimulation), in comparison to the sham group. The improvements were significantly larger at 8 months and at 12 months after stimulation, compared with those observed at 1 week and at 2 months. The largest improvements in language performance, provided by rTMS, were observed between 2 and 8 months post-stimulation and were sustained until 12 months follow-up.

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(C.-P. Wang et al., 2014)	Sham-controlled, double-blind parallel study	45 p. (15 rTMSsyn, 15 rTMSsub, 15 sham)	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over PTr (Broca's area homologous), (S) 10, (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses (20 min.) rTMSsyn and sham: rTMS/sham coupled with synchronous picture-naming task; rTMSsub: rTMS followed by picture-naming task, (SM) sham coil	CCAT (conversation, description and expression) and Picture-Naming test (action naming accuracy and object-naming accuracy)	CCAT: after the end of the intervention, it was observed an improvement on total score of 30.3% for TMSsyn, 9.5% for TMSsub and 1.0% for sham; the improvement between baseline and 3 months follow-up was 33.4% for TMSsyn, 17.8% for TMSsub and 4.6% for sham. The improvement was significantly superior for TMSsyn in CCAT score, expression and description subtests compared to TMSsub and sham. Picture-Naming test: there was a significantly greater effect for action naming and object naming accuracy in the TMSsyn group compared to TMSsub and sham. Synchronous verbal training during repetitive transcranial magnetic stimulation proved to be more effective for treating aphasia than rTMS followed by verbal training.
(Yoon, Han, Yoon, Kim, & Yi, 2015)	N.A.	20 p. (10 rTMS, 10 Control that did not receive rTMS, just SLT)	(C) air-cooled figure-8 coil, (A) Nonlesional hemisphere over right frontal lobe (IFG), (S) 20, (F) 1 Hz, (I) 90% of MT, (D) 1200 pulses (20 min.), (SM) none	WAB - Korean version (oral language subtests: spontaneous speech, comprehension, repetition and naming)	WAB spontaneous speech: rTMS increased score from 10.50 ± 3.31 at baseline to 12.30 ± 4.32 after treatment, whereas the control group scored 11.70 ± 3.23 before and 13.00 ± 2.73 after treatment. The improvement was not significantly different between groups. WAB comprehension: In the rTMS group, the score changed from 92.40 ± 26.94 at baseline to 99.80 ± 27.53 after treatment, while the controls scored 99.40 ± 34.60 before and 111.20 ± 36.05 after treatment. The improvement was significantly different between groups. WAB repetition: The score increased significantly with rTMS from 56.60 ± 22.82 at baseline to 68.80 ± 20.47 after treatment, whereas the control group scored 54.00 ± 25.88 before and 59.60 ± 23.43 after treatment. WAB naming: In the stimulation group, the score increased significantly from 48.00 ± 12.28 at baseline to 65.00 ± 12.38 after treatment, whereas the control group scored 43.00 ± 18.56 before and 51.40 ± 17.52 after treatment. 1 Hz-rTMS combined with SLT led to significant improvements in aphasia, compared to SLT alone.

Abbreviations: aMT - active motor threshold; BA - Brodmann area; cTBS - continuous theta burst stimulation; fMRI – functional magnetic resonance imaging; HF - high-frequency; IFG - inferior frontal gyrus; int. - interval; iTBS - intermittent theta burst stimulation; LF - low-frequency; LH - left-handed; MT - motor threshold; N.A. - not available/not applicable; p. - patients; POp - pars opercularis; PTr - pars triangularis; RH - right-handed; rMT - resting motor threshold; rTMS - repetitive transcranial magnetic stimulation; SLT - speech and language therapy; ST - speech therapy; STG - superior temporal gyrus; sub - subsequent; syn – synchronous

* AAT - Aachen Aphasia Test; ANELT - Amsterdam-Nijmegen Everyday Language Test; ASRS - Aphasia Severity Rating Scale; BDAE - Boston Diagnostic Aphasia Examination; BNT - Boston Naming Test; CAL - Communicative Abilities Log; CCAT - Concise Chinese Aphasia Test; CIU - Correct Information Units; COWAT - Controlled Oral Word Association Test; CPNT - Computerized Picture Naming Test; FIM - Functional Independence Measure; HSS - Hemispheric Stroke Scale; NIHSS - National Institutes of Health Stroke Scale; PPVT IV - Peabody Picture Vocabulary Test IV; QPA - Quantitative Production Analysis; RT - Response Time; SADQ - Stroke Aphasic Depression Questionnaire; SFT - Semantic Fluency Test; SLTA - Standard Language Test of Aphasia; SV - Snodgrass and Vanderwart; WAB - Western Aphasia Battery

Table A2.1.2 – Pertinent data extracted from the studies focusing dysphagia rehabilitation, comprising study design, sample size, details of the TMS procedure, outcome measures and main behavioural findings

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(E. M. Khedr et al., 2009)	N.A.	26 p., 14 rTMS, 12 sham	(C) 90-mm figure-8 coil, (A) Lesional hemisphere over oesophageal cortical area, (S) 5, (F) 3 Hz, (I) 120% of rMT, (D) 10 min.: 10 trains each lasting 10 sec. and then repeated every min., (SM) coil held at 90º to the scalp	DOSS, BI and grip strength (MRC scale)	Dysphagia score: patients receiving real rTMS showed a significantly larger improvement compared to patients receiving sham stimulation, that lasted at least 2 months. Hand grip strength: the difference between groups was not significant. BI increased in both groups; nevertheless, the effect was larger after real rTMS. 3 Hz-rTMS improved significantly dysphagia, in comparison to sham stimulation, and the improvement lasted at least 2 months.
(Lee et al., 2015)	Comparative study	24 p., 12 rTMS of suprahyoid muscle (group A), 12 rTMS of APB (group B)	(C) figure-8 coil, (A) Group A: Lesional hemisphere over suprahyoid muscle cortical area; Group B: Lesional hemisphere over APB cortical area, (S) 10, (F) 10 Hz, (I) 110% of MT, (D) 1000 pulses (10 min.: 10 trains each lasting 10 sec. and then repeated every min.), (SM) none	FDS, PAS and DOSS	Group A: there was an improvement of all outcome measures until 4 weeks after treatment; Group B: an improvement was observed only for FDS. Comparing both groups, there were no significant differences immediately after intervention and 4 weeks after rTMS in FDS or PAS improvement, but there was a statistically significant improvement in DOSS for group A. The stimulation of the cortex representing the suprahyoid muscle of the affected side proved to be more effective in treating dysphagia when comparing to the stimulation of the cortical area representing APB of the affected side.
(Cheng et al., 2017)	Double-blind, randomized, controlled study	15 p. (11 rTMS, 4 Sham)	(C) 70-mm double air film coil, (A) Lesional hemisphere over tongue cortical area (For p. with bilateral lesion, left hemisphere was stimulated), (S) 10, (F) 5 Hz, (I) 90% of rMT, (D) 3000 pulses (30 trains of 100 pulses, 15 sec. intertrain int.), (SM) sham coil	VFSS, SAPP and maximum tongue strength	VFSS: oral, stage and pharyngeal transit times increased after both real and sham stimulation, while the amount of post-swallow residue in piriform sinus decreased after stimulation. SAPP: decreased from 111.1 ± 61.9 at baseline to 83.1 ± 52.4 at the first follow-up (2 months) in the real group and from 57.8 ± 24.2 to 51.0 ± 32.6 in the sham group. Maximum tongue strength: increased from 32.0 ± 17.4 kPa at baseline to 32.1 ± 14.9 kPa at 2 months follow-up in the real rTMS group and from 34.0 ± 19.3 kPa to 41.3 ± 27.3 kPa in the sham group. Significant effects for group or interaction between group and time were not found for any outcome measure. 5 Hz-rTMS was not effective on improving swallowing function in chronic post-stroke patients.
(Juan Du et al., 2016)	Prospective, randomized, sham rTMS-controlled, double-blinded clinical trial	40 p. (15 HF-rTMS, 13 p. LF-rTMS, 12 sham)	(C) 90-mm figure-8 coil, (A) HF-rTMS: lesional hemisphere ; LF-rTMS: nonlesional hemisphere (over mylohyoid cortical area), (S) 5, (F) HF-rTMS: 3 Hz; LF-rTMS: 1 Hz, (I) HF-rTMS: 90% of rMT; LF-rTMS: 100% of rMT, (D) HF-rTMS: 1200 pulses (40 trains of 10 sec., 10 sec. intertrain int.); LF-rTMS: 1200 pulses (40 trains of 30 sec., 2 sec. intertrain int.), (SM) coil held at 90º to the scalp	SSA, water swallow test, degree of dysphagia	SSA improved significantly both with LF and with HF-rTMS comparing to sham stimulation. Water swallow test and degree of dysphagia improved both after sham and real stimulation. The swallowing function and functional disability improved significantly after active comparing to sham stimulation. 1 Hz- and 3 Hz-rTMS enhanced recovery from dysphagia and the effects were maintained for at least 3 months.

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(J. W. Park et al., 2013)	Double-blind, randomized, controlled study	18 p., 9 rTMS, 9 sham	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over pharyngeal motor cortex, (S) 10, (F) 5 Hz, (I) 90% of MT, (D) 10 min.: 10 trains, each lasting 10 sec. and then repeated every min., (SM) coil held at 90º to the scalp	VDS and PAS	VDS: rTMS decreased mean VDS from 33.6 ± 12.1 at baseline to 25.3 ± 9.8 after intervention; the results were maintained until 2 weeks follow-up. The improvement was significant just in the pharyngeal phase, not in the oral phase. Sham stimulation did not change significantly VDS. PAS: rTMS decreased mean PAS from 3.41 ± 2.32 at baseline to 1.93 ± 1.52 after intervention and to 1.37 ± 0.87 at follow-up. Sham stimulation did not change significantly PAS. 5 Hz-rTMS applied to the intact hemisphere over pharyngeal motor cortex improved dysphagia and the effect lasted up to 2-week follow-up.
(Eman M Khedr & Abo-Elfetoh, 2010)	N.A.	22 p., LMI group: 6 rTMS, 5 sham; Other brainstem infarction group: 5 rTMS, 6 sham	(C) 90-mm figure-8 coil, (A) Both hemispheres over the provisional oesophageal cortical area, (S) 5, (F) 3 Hz, (I) 130% of rMT, (D) 10 min.: 10 trains each lasting 10 sec. and then repeated every min., (SM) coil held at 90º to the scalp	Dysphagia rating scale, grip strength (HSS), NIHSS and BI	LMI: real rTMS led to a significantly larger improvement compared to sham stimulation, which lasted at least 2 months. BI improved in all patients but the improvement was significantly greater in those receiving real rTMS. For hand grip strength and NIHSS, the observed improvements did not differ significantly between real and sham stimulation. Other brainstem infarction: patients receiving real TMS showed a significantly larger improvement in dysphagia compared to those receiving sham, that lasted at least 2 months. For hand grip strength, NIHSS and BI, the results did not differ significantly between real or sham stimulation. rTMS applied over the oesophageal motor cortex of both hemispheres can be beneficial as an adjuvant strategy for dysphagia rehabilitation.
(Verin & Leroi, 2009)	Noncontrolled pilot study	7 p.	(C) 70-mm, air-cooled figure-8 coil, (A) Nonlesional hemisphere over mylohyoid cortical area, (S) 5, (F) 1 Hz, (I) 120% of MT, (D) 20 min., (SM) none	VDS and dysphagia handicap index	Dysphagia handicap index: after stimulation, total score decreased indicating a tendency for less swallowing impairment and less nutritional and respiratory consequences. VDS: After rTMS intervention, it was observed an improvement in swallowing coordination; the swallow response time was reduced for liquids and paste. In addition, aspiration score for liquids and residue score for paste decreased significantly. Oral and pharyngeal transit times as well as laryngeal closure duration were not significantly altered. rTMS improved dysphagia in poststroke patients; the improvement appears to be related to specific dysphagia symptoms.

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(E. Park et al., 2017)	Single-blind, randomized controlled design	33 p., 11 BL-rTMS, 11 UN-rTMS, 11 sham	(C) 70-mm figure-8 coil, (A) BL-rTMS: lesional hemisphere followed by nonlesional; UN-rTMS: rTMS on lesional hemisphere followed by sham rTMS on nonlesional (over mylohyoid cortical area), (S) 10, (F) 10 Hz, (I) 90% of rMT, (D) 500 pulses in each hemisphere (10 min.: 5 sec. with 55 sec. intertrain int.), (SM) coil held at 90º to the scalp	CDS, DOSS and VFSS (PAS and VDS)	CDS, DOSS, PAS and VDS: improved significantly in patients that received active stimulation, either bilateral (BL-rTMS) or unilaterally (UN-rTMS). BL-rTMS induced an improvement on CDS at T1 (post-intervention) and T2 (3 week follow-up) that was significantly greater comparing to the UN-rTMS and sham stimulation. The remaining measures also showed a more profound effect of bilateral stimulation at T1, with a statistically significant difference between groups. UN-rTMS and sham rTMS did not produce significantly different results. Bilateral stimulation of the mylohyoid cortical representation with 10 Hz led to significant improvements on the swallowing function that were superior to those obtained with unilateral or with sham stimulation.

Abbreviations: APB - abductor pollicis brevis; BL - bilateral; HF - high-frequency; int. - interval; LF - low-frequency; LMI - lateral medullary infarction; MT - motor threshold; N.A. - not available/not applicable; p. - patients; rMT - resting motor threshold; rTMS - repetitive transcranial magnetic stimulation; UN – unilateral

* BI - Barthel Index; CDS - Clinical Dysphagia Scale; DOSS - Dysphagia Outcome and Severity Scale; FDS - Functional Dysphagia Scale; HSS - Hemispheric Stroke Scale; MRC - Medical Research Council; NIHSS - National Institutes of Health Stroke Scale; PAS - Penetration-Aspiration Scale; SAPP - Swallowing Activity and Participation Profile; SSA - Standardized Swallowing Assessment; VDS - Videofluoroscopic Dysphagia Scale; VFSS - Videofluoroscopic Swallowing Study

Table A2.1.3 – Pertinent data extracted from the studies focusing neglect and visual extinction rehabilitation, comprising study design, sample size, details of the TMS procedure, outcome measures and main behavioural findings

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(Cazzoli et al., 2012)	Randomized, double-blind, sham-controlled study	24 p., Groups: cTBS+sham, sham+cTBS and control (no stimulation)	(C) Round coil with 60 mm outer radius, (A) Nonlesional hemisphere over PPC (P3), (S) 8 trains of cTBS over 2 days, (F) Each burst with 3 pulses at 30 Hz repeated at 6 Hz, (I) 100% of rMT, (D) Continuous train of 801 pulses (267 bursts), (SM) sham coil	VTS, paper-pencil assessment (random shape cancellation test, two-part picture test and Munich reading texts) and CBS	CBS: cTBS application, both before and after sham stimulation, reduced significantly spatial neglect's severity, compared to the control condition. VTS: cTBS led to better and faster detection of left-sided visual targets. Paper-pencil assessment: left-sided omissions in the random shape cancellation test and in the two-part picture test were significantly reduced by cTBS, in comparison to control group. cTBS improved spontaneous everyday behaviour by 37% in neglect patients; this improvement lasted at least 3 weeks.
(Yang et al., 2015)	N.A.	38 p., 9 LF-rTMS, 10 HF-rTMS, 9 cTBS, 10 sham	(C) figure-8 coil, (A) Nonlesional hemisphere over PPC (P3), (S) 28, (F) LF-rTMS: 1 Hz, HF-rTMS: 10 Hz; cTBS: Each burst with 3 pulses at 30 Hz repeated at 5 Hz, (I) 80% of rMT, (D) LF-rTMS: 656 pulses (82 sequences of 8 sec.); HF-rTMS: 1000 pulses (int. of 55 sec.); cTBS: continuous train of 801 pulses, (SM) back of the coil facing patients head	Line bisection and star cancellation tests	Line bisection test: decreased significantly after real stimulation; 1 Hz changed score from 61.27 ± 8.97 to 30.02 ± 7.49 at the end of treatment, while 10 Hz decreased it from 62.35 ± 8.45 to 32.20 ± 6.38 and cTBS from 59.28 ± 7.22 to 28.75 ± 6.86. Sham stimulation, in turn, showed a non-statistically significant decrease from 62.59 ± 8.75 to 53.09 ± 7.69. Star cancellation test: decreased significantly after 1 Hz (from 51.60 ± 6.09 to 27.49 ± 5.76), 10 Hz (from 52.79 ± 5.47 to 29.01 ± 5.57) and cTBS (from 54.02 ± 7.85 to 16.54 ± 5.15). Sham stimulation decreased score from 50.50 ± 5.51 to 49.28 ± 5.41, which was not statistically significant. Comparing the efficacy of the real stimulation protocols, the most effective was cTBS, the second was 1 Hz and the last 10 Hz.
(B. R. Kim et al., 2013)	Prospective, double-blind, sham-controlled trial	27 p., 9 LF-rTMS, 9 HF-rTMS, 9 sham	(C) 70-mm, air-cooled figure-8 coil, (A) LF-rTMS: nonlesional hemispere over PPC (P3). HF-rTMS: lesional hemisphere over PPC (P4), (S) 10, (F) LF-rTMS: 1 Hz, HF-rTMS: 10 Hz, (I) 90% of MT, (D) LF-rTMS: 1200 pulses (20 min.: 4 trains of 5 min., separated by 1 min.). HF-rTMS: 1000 pulses (20 min.: 20 trains of 5 sec., separated by 55 sec.), (SM) coil held at 90º to the scalp	MVPT, line bisection test, star cancellation test, CBS and the Korean-Modified BI	Line bisection test: the change in score was -30.0 ± 9.2 for LF group, -36.9 ± 11.2 for HF and -8.3 ± 4.2 for patients that received sham stimulation; HF-rTMS led to a significantly larger improvement, compared to sham. Korean-Modified BI: the improvements in both real stimulation groups (change in score: 27.6 ± 10.0 in LF and 30.6 ± 9.9 in HF) showed statistical significance in comparison to sham group (change in score: 15.1 ± 5.7). MVPT, star cancellation test and CBS did not show significant differences. 10 Hz-rTMS improved significantly visuospatial neglect.
(Lim et al., 2010)	Open-label pilot study	14 p., 7 rTMS+BT, 7 p. BT	(C) figure-8 coil, (A) Nonlesional hemisphere over parietal area, (S) 10, (F) 1 Hz , (I) 90% of rMT, (D) 900 pulses (15 min.), (SM) none	Line bisection test and Albert test	Line bisection test: rTMS combined with BT resulted in greater improvements in % deviation of the left-sided line-set compared to BT alone; but not in the centred line-set or right-sided line-set. Albert test: the improvements were not significantly different between groups. Low-frequency rTMS combined with behavioural therapy resulted in improvements in line bisection test, potentially enhancing recovery in patients with neglect. Further studies are needed to evaluate the efficacy of stimulation on hemispatial neglect.

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(W. Fu et al., 2015)	Prospective study	20 p., 10 cTBS, 10 Sham	(C) 87 mm figure-8 coil, (A) Nonlesional hemisphere over PPC (P5), (S) 14, (F) Each burst with 3 pulses at 30 Hz, repeated every 200 msec, (I) 80% of rMT, (D) Each session with 4 trains of 40 sec separated by 15 min., (SM) coil held at 90º to the scalp	Star cancellation test and line bisection test	Star cancellation test: cTBS changed score from 53.47 ± 7.07% to 16.43 ± 7.03% after treatment and to 6.25 ± 5.94% at 4-week follow-up; sham stimulation changed it from 52.14 ± 7.07% to 50.00 ± 7.03% after treatment and to 45.29 ± 5.94% at follow-up. cTBS showed a significant improvement compared to sham, both after treatment and at follow-up. Line bisection test: score was changed from 47.16 ± 23.65% to 25.79 ± 27.32% post-intervention and to 11.17 ± 14.27% at follow-up, following cTBS and from 46.03 ± 22.82% to 32.79 ± 13.12% post-intervention and to 35.79 ± 18.65% at follow-up, following sham. The difference between groups was statistically significant only in the follow-up. cTBS in combination with conventional rehabilitation led to a significant improvement in visuospatial neglect that was maintained at least for 4 weeks after the end of treatment.
(Y. Kim et al., 2015)	N.A.	34 p., 19 Group 1, 15 Group 2	(C) 50-mm figure-8 coil, (A) Nonlesional hemisphere over PPC (P3), (S) Group 1: 1; Group 2: 10, (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses (20 min.), (SM) none	Line bisection test, letter cancellation test and Ota's task	Line bisection test: in Group 1, there was a significant improvement with a decrease from 45.05 ± 7.83 to 39.26 ± 8.48 mm; in Group 2 the decrease was also significant (from 38.47 ± 16.9 to 14.45 ± 7.34 mm). The improvement was significantly superior in Group 2. Letter cancellation test: score significantly increased from 14.42 ± 3.73 to 16.63 ± 3.24, in Group 1, and from 11.87 ± 3.76 to 17.00 ± 2.85, in Group 2. The improvement was significantly superior for Group 2. Ota's task: Group 2 revealed a significant improvement of responses and correct response to reverse C in left side as well as correct responses to O in the left side, compared to Group 1. Ten sessions of 1 Hz-rTMS were more effective on improving hemispatial neglect than one session; ten sessions improved both egocentric and allocentric neglect.
(Song et al., 2009)	Pilot study	14 p., 7 rTMS, 7 control (without stimulation, just conventional rehabilitation)	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over PPC (P3), (S) Twice a day over 2 weeks, (F) 0.5 Hz, (I) 90% of MT, (D) 15 min., (SM) none	Line bisection and cancellation tests	Line bisection and cancellation performance: rTMS intervention improved significantly neglect; the performance did not differ significantly between the end of the treatment and at 2 weeks follow-up. Control group did not show improvements between the beginning and the end of treatment. The difference between groups was significant for cancellation but not for line bisection test. Patients that received low-frequency rTMS showed significant improvements on visual spatial neglect that were maintained at least for 2 weeks.

Ref.	Explicitly Described Study Design	Participants	TMS parameters: (C) coil, (A) area, (S) number of sessions, (F) frequency, (I) intensity, (D) duration, (SM) sham method	Outcome Measures *	Results
(H. G. Cha & Kim, 2016)	Randomized, controlled trial	30 p., 15 rTMS, 15 Sham	(C) 80 mm figure-8 coil, (A) over P3, (S) 20, (F) 1 Hz, (I) 90% of rMT, (D) 1200 pulses, (SM) sham coil	Line bisection test and Albert test	Line bisection test: 1 Hz-rTMS changed score from 35.87 ± 8.08 cm at baseline to 19.33 ± 6.87 cm after treatment; sham stimulation changed score from 38.20 ± 4.72 cm at baseline to 34.60 ± 4.00 cm after treatment. The differences in improvement between real and sham groups were significant. Albert test: 1 Hz-rTMS changed score from 21.40 ± 3.98% to 35.33 ± 2.90% after treatment, while sham stimulation changed it from 24.07 ± 4.11% to 27.33 ± 4.55%. The differences between groups were significant. 1 Hz-rTMS significantly improved unilateral spatial neglect more than sham stimulation.
(Agosta et al., 2014)	N.A.	6 p.	(C) 70-mm figure-8 coil, (A) Nonlesional hemisphere over PPC (P3), (S) 1 session rTMS + 1 session sham (minimum washout period: 24h), (F) 1 Hz, (I) 90% of rMT, (D) 10 min., (SM) coil held at 90º to the scalp	Multiple object tracking task (accuracy)	Real rTMS, but not sham stimulation, led to significant improvements in sustained attention; the improvement was larger in the unilateral task than in the bilateral task after rTMS compared to sham. In addition, the effect was observed only in the left visual field. 1 Hz-rTMS led to improvements in sustained attention in the left visual field, contralateral to the lesion.

Abbreviations: BT - behavioural therapy; cTBS - continuous theta burst stimulation; HF - high-frequency; int. - interval; LF - low-frequency; MT - motor threshold; N.A. - not available/not applicable; p. - patients; PPC - posterior parietal cortex; rMT - resting motor threshold; rTMS - repetitive transcranial magnetic stimulation
* BI - Barthel Index; CBS - Catherine Bergego Scale; MVPT - Motor-Free Visual Perception Test; VTS - Vienna Test System.

Table A2.2.1 – Clinical data from the patients that participated on the reviewed studies focusing aphasia recovery and comprising demographic data such as age and gender and stroke characteristics, including sub-type, time since stroke, and additional therapy

Ref.	Age (years)	Gender (% female/ % male)	Stroke Sub-Type (% infarction/ % hemorrhage)	Time Since Stroke	Additional Therapy
(Kindler et al., 2012)	55.0 ± 8.6	56/44	72/28	0.5 to 57 months	Ongoing or already completed standard language therapy
(Szaflarski et al., 2011)	54.4 ± 12.7	50/50	100/0	5.3 ± 3.6 years	None
(Joanna Seniów et al., 2013)	60.7 ± 11.2	55/45	100/0	11 to 106 days	Speech and language training
(Rubi-Fessen et al., 2015)	rTMS: 67.9 ± 8.12, sham: 69.6 ± 6.67	rTMS: 67/33, sham: 40/60	N.A.	rTMS: 41.47 ± 21.51 days, sham: 48.73 ± 21.57 days	Speech and language therapy
(Chieffo, Ferrari, et al., 2014)	46 to 66	40/60	80/20	1.6 to 5 years	Naming task before rTMS to preactivate the linguistic circuits involved in naming
(Weiduschat et al., 2011)	Mean 65	rTMS: 83/17, sham: 0/100	N.A.	sham: mean 57.5 days, rTMS: mean 45.2 days	Speech and language therapy
(Heiss et al., 2013)	RH rTMS: 68.5 ± 8.19, RH sham: 69.0 ± 6.33, LH rTMS: 64 and 72	N.A.	100/0	RH rTMS: 39.7 ± 18.43 days, RH sham: 50.1 ± 23.96 days, LH rTMS: 25 and 93 days	Speech and language therapy
(Naeser et al., 2011)	44 to 76	25/75	87.5/12.5	1.5 to 30 years	N.A.
(Medina et al., 2012)	61.60 ± 8.32	30/70	100/0	rTMS: 49.8 ± 29.6 months, sham: 58.6 ± 34.8 months	N.A.
(C. Barwood, Murdoch, Whelan, Lloyd, Riek, O' Sullivan, et al., 2011)	rTMS: 60.8 ± 5.98, sham: 67 ± 13.11	25/75	100/0	rTMS: 3.49 ± 1.27 years, sham: 3.46 ± 1.53 years	None
(C. H. S. Barwood et al., 2012)	59 ± 7.3	29/71	100/0	2 to 6 years	None
(Thiel et al., 2013)	rTMS: 69.8 ± 7.96, sham: 71.2 ± 7.78	N.A.	100/0	rTMS: 37.5 ± 18.52 days, sham: 50.6 ± 22.63 days	Speech and language therapy (deficit-specific aphasia therapy)
(Eman M Khedr et al., 2014)	57.3 ± 12.5	53/47	100/0	5 ± 3.2 weeks	Speech and language training
(Tsai et al., 2014)	rTMS: 62.3 ± 12.1, sham: 62.8 ± 14.5	rTMS: 27/73, sham: 26/74	100/0	rTMS: 17.8 ± 7.2 months, sham: 18.3 ± 8.2 months	Conventional speech rehabilitation program and other medical treatments
(T. Hara et al., 2017)	LF-rTMS: 42 to 73, HF-rTMS: 53 to 75	LF-rTMS: 25/75, HF-rTMS: 25/75	LF-rTMS: 75/25, HF-rTMS: 75/25	LF-rTMS: 358 to 1046 days, sham: 444 to 3174 days	Intensive ST
(Waldowski et al., 2012)	61.2 ± 10.8	50/50	100/0	rTMS: 28.92 ± 19.39 days, sham: 48.54 ± 32.33 days	Specific speech and language therapy

Ref.	Age (years)	Gender (% female/ % male)	Stroke Sub-Type (% infarction/ % hemorrhage)	Time Since Stroke	Additional Therapy
(Abo et al., 2012)	55.9 ± 8.8	8/92	46/54	34.7 ± 20.5 months	Intensive ST
(C. Barwood, Murdoch, Whelan, Lloyd, Riek, O'Sullivan, et al., 2011)	rTMS: 60.8 ± 5.98, sham: 66.6 ± 9.09	25/75	100/0	rTMS: 3.49 ± 1.27 years, sham: 3.46 ± 1.53 years	None
(C. H. S. Barwood et al., 2013)	rTMS: 60.8 ± 5.98, sham: 67 ± 13.11	25/75	100/0	rTMS: 3.49 ± 1.27 years, sham: 3.46 ± 1.53 years	None
(C.-P. Wang et al., 2014)	rTMSsyn: 61.3 ± 13.2, rTMSsub: 62.1 ± 12.7, sham: 60.4 ± 11.9	rTMSsyn: 7/93, rTMSsub: 13/87, sham: 13/87	100/0	rTMSsyn: 16.8 ± 6.4 months, rTMSsub: 15.7 ± 8.5 months, sham: 16.1 ± 7.3 months	Speech training program shortly after intervention
(Yoon et al., 2015)	rTMS: 60.46 ± 9.63, Control: 61.13 ± 8.72	rTMS: 20/80, control: 30/70	rTMS: 60/40, control: 50/50	rTMS: 6.8 ± 2.39 months, control: 5.20 ± 2.67 months	Speech and language therapy

Abbreviations: HF - high-frequency; LF - low-frequency; LH - left-handed; N.A. - not available/not applicable; RH - right-handed; rTMS - repetitive transcranial magnetic stimulation; ST - speech therapy; sub - subsequent; syn - synchronous

Table A2.2.2 – Clinical data from the patients that participated on the reviewed studies focusing dysphagia recovery and comprising demographic data such as age and gender and stroke characteristics, including sub-type, time since stroke, and additional therapy

Ref.	Age (years)	Gender (% female/ % male)	Stroke Sub-Type (% infarction/ % hemorrhage)	Time Since Stroke	Additional Therapy
(E. M. Khedr et al., 2009)	57.3 ± 12.5	62/38	100/0	5 to 10 days	Standard physical and medical therapies
(Lee et al., 2015)	group A: 66.1 ± 11.2, group B: 60.9 ± 11.4	Group A: 42/58, group B: 17/83	100/0	Group A: 34.3 ± 17.4 days, group B: 30.9 ± 17.2 days	Swallowing training (oral and facial sensory training, oral and pharyngeal muscle training, compensatory techniques, neuromuscular electrical stimulation on pharyngeal muscles during TMS, PT and OT)
(Cheng et al., 2017)	rTMS: 65.1 ± 8.3, Sham: 63.3 ± 7.8	rTMS: 36/64, sham: 0/100	N.A.	rTMS: 42.4 ± 19.9 months, sham: 39.8 ± 25.4 months	N.A.
(Juan Du et al., 2016)	HF-rTMS: 58.2 ± 2.78, LF-rTMS: 57.92 ± 2.47, sham: 58.83 ± 3.35	HF-rTMS: 13/87, LF-rTMS: 46/54, sham: 50/50	100/0	HF-rTMS: median 8 (4-15) days, LF-rTMS: median 6 (5-28.5) days, sham: median 9 (7-26.25) days	Physical and medical therapies
(J. W. Park et al., 2013)	71.3 ± 7.3	44/56	rTMS: 78/22, sham: 89/11	rTMS: 59.9 ± 16.3 days, sham: 63.9 ± 26.8 days	N.A.
(Eman M Khedr & Abo-Elfetoh, 2010)	LMI group: 56.4 ± 15, Other brainstem infarction group: 58.2 ± 10.4	27/73	100/0	LMI group - rTMS: 6 ± 4.15 weeks, sham: 5.5 ± 0.2 weeks. Other brainstem - rTMS: 3.2 ± 0.8 weeks, sham: 3.7 ± 0.8 weeks	Conventional therapy and medical treatment
(Verin & Leroi, 2009)	65 ± 10	43/57	N.A.	56 ± 50 months	N.A.
(E. Park et al., 2017)	BL-rTMS: 60.2 ± 13.8, UN-rTMS: 67.5 ± 13.4, sham: 69.6 ± 8.6	BL-rTMS: 27/73, UN-rTMS: 27/73, sham: 36/64	BL-rTMS: 64/36, UN-rTMS: 82/18, sham: 64/36	BL-rTMS: 4.1 ± 2.4 weeks, UN-rTMS: 4.2 ± 1.7 weeks, sham: 6.6 ± 7.8 weeks	Conventional therapy (oral sensory training, oral and pharyngeal muscle exercise training and compensatory techniques)

Abbreviations: BL - bilateral; HF - high-frequency; LF - low-frequency; LMI - lateral medullary infarction; N.A. - not available/not applicable; OT - occupational therapy; PT - physical therapy; rTMS - repetitive transcranial magnetic stimulation; UN - unilateral

Table A2.2.3 – Clinical data from the patients that participated on the reviewed studies focusing neglect and visual extinction recovery and comprising demographic data such as age and gender and stroke characteristics, including sub-type, time since stroke, and additional therapy

Ref.	Age (years)	Gender (% female/ % male)	Stroke Sub-Type (% infarction/ % hemorrhage)	Time Since Stroke	Additional Therapy
(Cazzoli et al., 2012)	58 ± 2.25	29/71	58/42	26.63 ± 4.44 days	Neuropsychological training + occupational therapy + physiotherapy
(Yang et al., 2015)	LF-rTMS: 46.72 ± 13.11, HF-rTMS: 48.01 ± 12.25, 9 p. cTBS: 49.45 ± 10.78, sham: 47.70 ± 11.81	LF-rTMS: 33/67, HF-rTMS: 60/40, cTBS: 56/44, sham: 70/30	LF-rTMS: 56/44, HF-rTMS: 70/30, cTBS: 67/33, sham: 60/40	LF: 100.96 ± 38.52 days, HF: 107.52 ± 39.24 days, cTBS: 104.85 ± 36.38 days, sham: 105.91 ± 37.59 days	Routine rehabilitation
(B. R. Kim et al., 2013)	mean 67	44/56	LF-rTMS: 89/11, HF: 100/0, sham: 67/33	LF: 14.2 ± 4.7 days, HF: 14.3 ± 3.6 days, sham 16.4 ± 8.5 days	Conventional rehabilitation and rehabilitation programs for visuospatial neglect
(Lim et al., 2010)	68.8 ± 11.4	71/29	rTMS+BT: 57/43, BT: 71/29	rTMS+BT: 61.9 ± 111.1 days, BT: 139.0 ± 194.8 days	BT
(W. Fu et al., 2015)	33 to 78 years	20/80	cTBS: 50/50, sham: 40/60	17 to 114 days	Conventional rehabilitation training (visuospatial scanning)
(Y. Kim et al., 2015)	Group 1: 62.3 ± 11.2, Group 2: 66.7 ± 6.9	Group 1: 47/53, Group 2: 67/33	Group 1: 63/37, Group 2: 62/38	Group 1: 19.1 ± 12.4 months, Group 2: 15.7 ± 12.3 months	Conventional visuospatial rehabilitation (visual scanning training + systemic training of visual organization skill)
(Song et al., 2009)	rTMS: 56.14 ± 8.99, control: 64.43 ± 12.57	rTMS: 71/29, control: 14/86	rTMS: 43/57, control: 43/57	rTMS: 38.43 ± 15.20 days, control: 31.57 ± 11.47 days	Conventional rehabilitation
(H. G. Cha & Kim, 2016)	rTMS: 64.07 ± 12.1, sham: 63.33 ± 12.16	rTMS: 53/47, sham: 40/60	rTMS: 53/47, sham: 67/33	rTMS: 4.13 ± 1.13 months, sham 3.86 ± 0.83 months	Conventional rehabilitation (neurodevelopment-al facilitation techniques)
(Agosta et al., 2014)	Between 51 and 79	33/67	Ischemic (4 p.), hemorrhagic (1 p.), massive ischemic lesion + signs of hemorrhagic stroke (1 p.)	8 to 33 months	N.A.

Abbreviations: BT - behavioural therapy; cTBS - continuous theta burst stimulation; HF - high-frequency; LF - low-frequency; N.A. - not available/not applicable; rTMS - repetitive transcranial magnetic stimulation

A3

Table A3.1 – Individual clinical and demographic data from patients.

Participant code	Age	Gender	Handedness (points)	Days since-stroke	NIHSS	WMFT log performance time	Lesion side	Stimulated hemisphere	Group
Patient 1	67	male	36	7	6	3.0075	right	left	real
Patient 2	59	male	36	7	8	3.0872	left	right	real
Patient 3	67	male	36	10	3	1.6351	left	right	sham
Patient 4	77	female	36	10	9	3.0407	right	left	sham
Patient 5	68	male	36	10	5	1.7750	right	left	real
Patient 6	75	male	36	7	2	1.6972	right	left	real
Patient 7	44	male	36	10	15	2.2310	left	right	sham
Patient 8	48	female	36	7	5	1.4856	left	right	sham
Patient 9	82	female	36	10	7	1.6822	left	right	real
Patient 10	84	female	36	7	4	1.7928	left	right	sham

Table A3.2 – Individual demographic data from healthy participants.

Participant code	Age	Gender	Handedness (points)	Stimulated hemisphere
CTRL1	61	female	36	right
CTRL2	68	male	36	left
CTRL3	74	male	36	right
CTRL4	75	male	35	right
CTRL5	65	female	36	left
CTRL6	73	female	36	right
CTRL7	68	female	36	left
CTRL8	67	female	36	right
CTRL9	68	female	35	left
CTRL10	67	female	36	left
CTRL11	66	male	35	left
CTRL12	68	female	36	right
CTRL13	57	female	36	right
CTRL14	44	female	36	left
CTRL15	53	female	36	right
CTRL16	49	male	36	left
CTRL17	42	male	36	right
CTRL18	53	male	34	left
CTRL19	45	male	36	right
CTRL20	41	male	36	left

A4

Table A4.1 – Wolf Motor Function Test data extraction sheet. On the first column it is possible to note the tasks we asked patients to perform, according to Wolf et al.(Wolf *et al.* 2001).

Wolf Motor Function Test

Patient ID: ___

Task	BEFORE cTBS Time (sec)	BEFORE cTBS FAS (points)	AFTER cTBS Time (sec)	AFTER cTBS FAS (points)	3 Months Follow-up Time (sec)	3 Months Follow-up FAS (points)
Forearm to table (side)						
Forearm to box (side)						
Extend elbow (side)						
Extend elbow (weight)						
Hand to table (front)						
Hand to box (front)						
Reach and retrieve						
Lift can						
Lift pencil						
Lift paper clip						
Stack checkers						
Flip cards						
Turn key in lock						
Fold towel						
Lift basket						
TOTAL						

5

Arm does participate

•Movement appears to be normal

For the determination of normal, the uninvolved limb can be used as an available index for comparison, with premorbid limb dominance taken into consideration

4

Arm does participate

•Movement is close to normal, but slightly slower
•May lack precision, fine coordination or fluidity

For the determination of normal, the uninvolved limb can be used as an available index for comparison, with premorbid limb dominance taken into consideration

3

Arm does participate

•Movement is influenced to some degree by synergy or is performed slowly and/or with effort

2

Arm does participate

•Requires assistance of uninvolved extremity for minor readjustments or change of position or
•Requires more than 2 attempts to complete or
•Accomplishes very slowly

In bilateral tasks the involved extremity may serve only as a helper or stabilizer

1

Involved arm does not participate functionally

•An attempt is made to use the arm

In unilateral tasks the uninvolved extremity may be used to move the involved extremity

0

Does not attempt with involved arm

Figure A4.1 – Wolf Motor Function Test Functional Ability Scale score guidelines. Adapted from (Morris *et al.* 2001).

A5

Table A5.1 – Individual data from healthy participants: *beta* power with bimanual thumb opposition.

Participant code	*Beta* Power (dB)	
	Motor planning	**Movement execution**
CTRL1	-1.57178	-1.18734
CTRL2	-2.86274	-4.51405
CTRL3	-1.28838	-2.72813
CTRL4	-1.48910	-2.54155
CTRL5	-1.66521	-4.30262
CTRL6	-1.89863	-3.80909
CTRL7	-1.84629	-3.11909
CTRL8	-2.98704	-3.95831
CTRL9	-1.48116	-2.35957
CTRL10	-3.32687	-4.10616
CTRL11	-0.57785	-3.55179
CTRL12	-2.10714	-3.59247
CTRL13	0.12133	-1.88288
CTRL14	-0.65483	-2.58570
CTRL15	-0.32219	-1.74831
CTRL16	-1.27216	-0.73634
CTRL17	-0.93590	-1.08195
CTRL18	0.30172	-1.91361
CTRL19	0.09012	-1.60487
CTRL20	-0.02840	0.01342

Table A5.2 – Individual data from stroke patients: *beta* power with bimanual thumb opposition.

Participant code	*Beta* Power (dB)	
	Motor planning	**Movement execution**
Patient 1	0.70566	0.42136
Patient 2	-0.95917	-0.85551
Patient 3	-0.31081	-2.25745
Patient 4	N.A	N.A.
Patient 5	-0.71391	-0.50556
Patient 6	-0.81381	-0.19357
Patient 7	1.03205	-0.59961
Patient 8	-0.01892	-1.86396
Patient 9	-1.05733	-1.99272
Patient 10	0.61798	-1.24609

A6

Table A6.1 – Individual data from healthy participants: contralateral *mu* and *beta* power with arm elevation, before and after the continuous theta burst protocol.

Participant code	*Mu* Power (dB)		*Beta* Power (dB)	
	Pre-cTBS	Post-cTBS	Pre-cTBS	Post-cTBS
CTRL1	-4.23004	-0.63258	-2.35890	0.10648
CTRL2	-3.48157	-1.41618	-2.21474	0.31077
CTRL3	-1.23145	-2.18735	-1.18234	-2.03180
CTRL4	-3.30643	-1.00999	-1.32386	-0.94987
CTRL5	-0.67972	0.12751	-3.84500	-2.82446
CTRL6	-5.09999	-0.03499	-6.23302	-0.35221
CTRL7	-1.73977	-0.84316	0.42390	-0.42676
CTRL8	-3.02992	-0.69272	-5.03716	-1.14840
CTRL9	-3.53343	-1.00419	-2.57607	-0.43130
CTRL10	-0.60284	-0.17025	-3.08331	-1.66999
CTRL11	-1.33691	0.29625	-1.25268	2.17350
CTRL12	-2.79818	-1.61537	-0.47604	2.10574
CTRL13	-0.97096	-1.70229	-1.00477	-0.22926
CTRL14	-0.63862	-2.28177	0.77283	-0.38825
CTRL15	0.69545	0.14622	-2.03499	-0.29593
CTRL16	1.35215	0.20613	4.82594	1.94480
CTRL17	-0.93448	-0.94047	-1.28856	0.15385
CTRL18	-3.66451	-3.05665	-2.37630	-1.08249
CTRL19	-1.18648	3.56191	0.69031	3.29311
CTRL20	1.17661	0.70080	-0.50368	-0.28912

A7

Table A7.1 – Individual data from stroke patients: contralateral *beta* power with motor preparation for the affected thumb opposition, before and after the continuous theta burst protocol, and at 3-months follow-up.

Participant code	Stimulation group	*Beta* Power (dB)		
		Pre-cTBS	Post-cTBS	Follow-up
Patient 1	real	0.18023	-1.67170	-0.09488
Patient 2	real	0.05042	-0.06277	-1.39302
Patient 3	sham	-0.84320	-1.10324	-0.41661
Patient 4	sham	N.A.	N.A.	N.A.
Patient 5	real	-0.21969	-0.77296	-0.30423
Patient 6	real	-1.09357	-1.46901	-0.82843
Patient 7	sham	-1.66161	0.31578	-1.28206
Patient 8	sham	1.00616	1.89434	-1.58281
Patient 9	real	0.02095	-0.71716	-0.12294
Patient 10	sham	-1.05414	1.71764	N.A.