Cyprus University of Technology

Faculty of Health Sciences

Doctoral Dissertation

Neuronavigated repetitive Transcranial Magnetic Stimulation (rTMS) in Chronic post-Stroke Aphasia Rehabilitation

Anastasios M. Georgiou

Limassol, February 2019

CYPRUS UNIVERSITY OF TECHNOLOGY
FACULTY OF HEALTH SCIENCES
DEPARTMENT OF REHABILITATION SCIENCES

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Approval Form

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Presented by

Anastasios M. Georgiou

Supervisor: Faculty of Health Sciences, Maria Kambanaros, Associate Professor

Signature _____

Member of the committee: Christakis Damianou, Professor

Signature _____

Member of the committee: Tali Bitan, Senior Lecturer

Signature _____

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The approval of the dissertation by the Department of Rehabilitation Sciences does not imply necessarily the approval by the Department of the views of the writer.

Acknowledgements

I am deeply thankful for the efforts of my supervisor Associate Prof. Maria Kambanaros in creating the Neurorehabilitation Lab at the University Rehabilitation Clinic of the Cyprus University of Technology as this is where this thesis was completed. It is really hard to put all her actions in one letter. I thank her for supervising me in the past three and a half years, as without her instrumental and generous guidance this thesis would not have been completed. I also thank her for her moral support as she was always there for me, even the most difficult, nerve racking and disappointing times, reassuring me that I would make it. Maria, thank you for your trust and belief in me.

Acknowledgements and thanks also go to Assistant Professor Nikos Konstantinou who helped me build my skills in neuronavigated rTMS. I also thank him for his time, interest, thoughts, detailed suggestions and comments along the way. My gratefulness also goes to my colleague Dr. Ioannis Phinikettos, statistician, who helped me with statistics and for being there 7/7. I also want to say a big “thank you” to Mr Michael Ktoris, the librarian of the Faculty of Health Sciences, for his devotion, meticulous occupation with my thesis and research skills that he helped me to develop. I express my profound gratitude to Ms Eleni Petrou for her continuous psychological support.

A huge thank goes to all eight participants who took part in this study. They are the bedrock of this thesis as without them this effort would not have come to an end. A big thank to all of them individually also for making me rethink life and feel blessed for being healthy and alive.

Finally, I want to thank my family for their unconditional support and love throughout my journey in life. This thesis is devoted to You. “Τὰ σὰ ἐκ τῶν σῶν Σοὶ προσφέρομεν κατὰ πάντα καὶ διὰ πάντα”.

ABSTRACT

Aphasia, a disorder of spoken and/or written language, is a significant aftermath of stroke affecting more than a third of all stroke survivors. Many stroke survivors continue to have language deficits greater than six months post-stroke. Numerous studies over the span of more than a decade have shown that transcranial magnetic stimulation (TMS) can facilitate language recovery for patients who suffer from aphasia due to stroke. Transcranial magnetic stimulation creates a fluxing magnetic field, which allows for the generation of weak currents in underlying cortical neurons, causing them to depolarize. Depending on the intensity, frequency and duration of stimulation, TMS can cause decreases or increases in cortical excitability beyond the period of stimulation aiming to facilitate language abilities.

The research reported in this thesis is the first of its kind in Cyprus. Specifically, the aim was to investigate the effectiveness of neuronavigated repetitive TMS (rTMS) as a standalone treatment for chronic aphasia post-stroke. A single subject experimental design (SSED) methodology preceded by a pilot study confirming the fidelity of trial procedures and patient acceptability of TMS was adopted.

Findings revealed that rTMS over the right pars triangularis (pTr) shows promise to promote neuroplasticity in patients suffering from chronic post-stroke aphasia. Behavioural changes included trends towards improvement in verbal comprehension, expressive language, naming and reading abilities. There was one case that showed significant improvement in spoken comprehension and reading performance. Regarding functional communication, the total number of narrative words increased in three participants and decreased in one participant post-treatment. Quality of life (QoL) did not significantly change as a result of the treatment. Further research exploring individualized TMS protocols for post-stroke aphasia rehabilitation is strongly recommended with the aspiration that TMS will be used as a standard treatment modality in clinical practice in the near future.

Keywords: stroke, aphasia, rTMS, cTBS, systematic review

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LIST OF ABBREVIATIONS

AC	alternating current
AHA.SOC	American Heart Association Stroke Outcome Classification
AMPARs	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors
GABA	γ-aminobutyric acid
AMT	Active Motor Threshold
BA	Brodmann area
BBB	Blood-Brain Barrier
BDAE	Boston Diagnostic Aphasia Examination
BDAE-SF	Boston Diagnostic Aphasia Examination Short Form
BDI-II	Beck Depression Inventory II
BDNF	Brain-derived neurotrophic factor
cAMP	cyclic adenosine monophosphate
CBF	Cerebral blood flow
Cc	circular coil
CILT	Constraint induced language therapy
CNS	Central Nervous System
COST	Cooperation in Science and Technology
CPM	Coloured Progressive Matrices
CSR	Cochrane Systematic Review
CT	Computerized Axial Tomography
cTBS	Continuous Theta Burst Stimulation
CUT	Cyprus University of Technology
CVAs	Cerebrovascular accidents
DBS	Deep Brain Stimulation
DC	direct current
DV	Dependent variable
EEG	Electroencephalogram
EOKA	Ethniki Organosi Kipriakou Agonos
f8c	figure-of-eight coil
FAST	Frenchay Aphasia Screening Test
FDI	First dorsal interosseous
fMRI	Functional Magnetic Resonance Imaging
GOAT	Greek Object and Action Test
H-coil	Hesed coil
IADL	Instrumental Activities of Daily Living
ICD	Implantable cardioverter defibrillator
ICH	Intracerebral hemorrhage
ID	Independent variable
ifs	Inferior frontal sulcus
imTBS	Intermediate Theta Burst Stimulation
iTBS	Intermittent Theta Burst Stimulation
IV	Independent variable
LTD	Long-term depression
LTP	Long-term potentiation
L-VGCCs	L-type voltage-gated calcium channels
M1	Primary motor cortex
MAIN	Multilingual Assessment Instrument for Narratives

MEP	Motor evoked potential
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NIBS	Non-invasive Brain Stimulation
NMDARs	N-methyl-D-aspartate receptors
ORLA	Oral Reading for Language in Aphasia
P(s)	Participant(s)
PD	Parkinson's Disease
POCS	Posterior circulatory syndrome
pOp	Pars opercularis
pOr	Pars orbitalis
PPVT-R	Peabody Picture Vocabulary Test-Revised
pTr	Pars triangularis
PWA	People with aphasia
QoL	Quality of life
QPA	Quantitative Production Analysis
RCPM	Raven's Coloured Progressive Matrices
RCT	Randomized Control Trial
RLC	resistor-inductor-capacitor
rTMS	repetitive Transcranial Magnetic Stimulation
SAQOL-39	Stroke and Aphasia Quality of Life Scale-39 item
SAQOL-39g	Stroke and Aphasia Quality of Life Scale-39 item generic
secs	seconds
SLT	Speech and language therapy
SLTs	Speech and language therapists
SSED	Single subject experimental design
TBS	Theta Burst Stimulation
tDCS	Transcranial direct current stimulation
TIA	Transient ischemic attack
TIDieR	Template for Intervention Description and Replication
TMS	Transcranial magnetic stimulation
VGSCs	Voltage-gated sodium channels
WEST	Weighted statistics
WHO	World Health Organization

CHAPTER 1: Introduction

The research presented in this thesis explores the effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) for improvement of language deficits in patients with chronic aphasia post-stroke. Stroke can occur at any point in a person's life and represents a clinically impactful disorder that affects every day functioning, quality of life (QoL) and often even survival. Moreover, the physical consequences of stroke are long-term and have a profound impact on the mental, emotional and physical status of the victim and his/her caregiver. Finally, stroke places a large burden on rehabilitation services and on society (Feigin et al., 2003).

Stroke is the second most prevalent cause of death and the third leading cause of disability (WHO, 2012). It is an evolving process and not a temporary event (Elkind, 2009). An in-depth understanding of the physical, biochemical and mechanical processes responsible for the instigation and development of stroke is of paramount importance for stroke prevention and treatment. In a recent review (Feigin et al., 2016) it was reported that above 90% of the stroke burden is attributed to modifiable risk factors and taking control of behavioural and metabolic risk factors may thwart more than 75% of the global stroke burden. Developments in stroke strategic planning regarding minimizing and managing the burden of stroke, raising stroke awareness and on the implementation of the best practices regarding blood pressure and atrial fibrillation screening in primary care, may all contribute to stroke prevention (Karnad, Pannelay, Boshnakova, Lovell & Cook, 2018).

In the context of the current research, the efficacy of therapy programmes for chronic post-stroke aphasia can be enhanced by non-invasive brain stimulation (NIBS) that targets specific brain areas. One such intervention is rTMS which influences cortical activity from outside of the skull and has the potential to improve language abilities of stroke survivors.

1.1 Stroke: Types, Classification, Epidemiology and Clinical Picture of Patients

Stroke is a heterogeneous medical condition including several types that differ in risk factor profiles, management and outcomes (Sudlow & Warlow, 1997). There are three main types of stroke; ischaemic, primary intracerebral hemorrhagic and, subarachnoid haemorrhagic (Tsai, Thomas & Sudlow, 2013; Feigin et al., 2006). Stroke may happen in cortical and/or subcortical brain areas and/or within the spinal cord (Donnan et al., 2002). Arteries but also the cerebral venous system may be affected (Ekici et al., 2013) and cause intracerebral hemorrhages (ICH) that are often linked to worse outcomes (Girot et al., 2007). Transient decrease in blood supply to the central nervous system (CNS) is associated with transient ischemic attack (TIA). Transient episodes of neurologic disturbance are not linked to persistent cerebral infarction (Albers et al., 2002).

Stroke classification gives information about the location of brain lesion, extent of damage, underlying causes and prognosis. This can inform decision making and enhance grouping and examination of stroke subtypes in epidemiological studies. So far, various stroke classification systems have been developed. The 'Bamford' or 'Oxford' stroke classification system relies on the combination of symptoms that are presented in each stroke episode. Limb weakness, visual disturbance and higher cortical dysfunction (e.g. aphasia) are the three main categories of stroke symptoms (Wardlaw et al., 1996). The American Heart Association Stroke Outcome Classification (AHA.SOC) is a reliable, valid and globally established classification system that precisely describes stroke related neurological impairments, disabilities, and handicaps (Kelly-Hayes et al., 1998).

Several epidemiological studies have explored incidence and prevalence rates, risk factors and causes of stroke in different populations (see Appendices 1 & 2). Around 80% of strokes are ischaemic in nature and 20% are due to primary haemorrhage (Markus, 2012; Warlow et al., 2001).

Differential diagnosis between ischemic and hemorrhagic stroke is difficult as both have similar clinical symptomatology (Ronning et al., 2008). The clinical manifestation of ischemic stroke involves motor (hemiparesis) and sensory (hemisensory loss) problems, aphasia, ophthalmoplegia and visual fields cuts (Runchey & McGee, 2010). Hemorrhagic stroke presents with severe headaches (Ronning et al., 2008), vomiting (Qureshi et al., 2001), neck stiffness, progressive deterioration, bilateral Babinski signs and coma (Runchey & McGee, 2010). People presenting with stroke symptoms should seek medical care immediately as prompt stroke treatment reduces brain damage and disability, prevents life-threatening complications, and helps patients regain functioning.

1.2 Stroke: Pathophysiological Processes

Stroke pathophysiology, both at the macro tissue level (cerebral blood flow, ischemic penumbra and, window of opportunity) and the microcellular level (development of microcirculatory disturbances) is intricate and its examination is done at the level of ischemia and hemorrhage as described below.

1.2.1 Ischemic Stroke

Ischemic stroke includes various subtypes, each subtype presenting with different pathophysiological mechanisms (Jerrard-Dune et al., 2003). Particularly, it involves atherothrombotic, embolic, lacunar, other determined and undetermined subtypes (Sudlow & Warlow, 1997); large vessel disease stroke, small vessel disease stroke and cardioembolic stroke being the commonest subtypes (Jerrard-Dune et al., 2003). Transient ischemic attack and ischemic stroke share the same pathophysiology (Elkind, 2009; Herderschee et al., 1992). Ischemic strokes result from embolism, thrombosis or systemic hypoperfusion (Tan & Martin, 2012). Unlike thrombosis, embolism is not linked to vascular problems inherent to the infarcted vessels (Tan & Martin, 2012) and may impact on various areas within different vascular sites (Ropper & Samuels, 2009). Systemic hypoperfusion drops cerebral perfusion pressures that in turn cause generalized brain ischemia (Tan & Martin, 2012).

Blood contains oxygen and glucose needed for normal brain function. Drop of cerebral blood flow (CBF) below 15 to 18mL/100g of brain/minute, causes the brain

to make efforts to preserve energy stores by reducing synaptic activity (Toole, 1999), leading to brain neurologic deficits (Tintinalli, Kelen & Stapczynski, 2004). Drop of CBF below 10mL/100g of brain/minute leads to a cascade of events that result in death (Toole, 1999). Donaghy (2009) outlines how neurophysiologic and functional changes caused by hypoperfusion can reversibly or irreversibly affect brain function. In the event of transient ischemia, brain can possibly recover its function. However, increasing ischemia causes progressive cell damage due to decreased energy consumption and blood supply. Protein synthesis is disturbed and ineffective anaerobic metabolism of glucose follows. As a result, lactate production increases, pH inside and outside of cells decreases, phosphocreatine and ATP synthesis become disturbed and production of energy fails. Then, all energy dependent cell membrane functions (e.g. cellular transport and neurotransmission) fail, causing cytotoxic and vasogenic edemas (occurring hours after stroke initiation). Those edemas cause cerebral swelling that may in turn cause brain herniation and possibly death. There is evidence that the mechanisms associated with ischemic cell death may differ between white and gray matter (Xing et al., 2012).

Furthermore, neurotoxic neurotransmitters, free oxygen radicals, lipid peroxides and nitric oxides are produced causing further cell damage (Donaghy, 2009). Glutamate, which is the major excitatory neurotransmitter in the brain, gathers in the extracellular space following ischemia, activating its receptors (Martin & Wang, 2010). Glutamate receptors encourage an inordinate calcium influx that stimulates i) catabolic processes (Xing et al., 2012), ii) sodium and water influx with accompanying cell swelling and edema and iii) shrinking of the extracellular space (Lipton, 1999). Also, in the affected hemisphere, the balance between excitatory and inhibitory synaptic activity is disturbed causing a shift towards excitation and activity reduction in local inhibitory circuits (Di Pino, 2014).

Ischemia is linked to several compensative processes (i.e. local vasodilatation, opening of cerebral collateral vessels and increase of the extraction of oxygen and glucose from blood) to provide protection to the affected brain areas (Tan & Martin, 2012). Apart from compensatory mechanisms, the brain also exhibits protective mechanisms that are as complex as the damage processes caused by ischemia

(Dirnagl, 2012). Brain immune cells (i.e. microglia and dendritic cells) and blood immune cells (i.e. neutrophils, macrophages, lymphocytes) are aroused to assist the injured brain (Iadecola & Anrather, 2011). A large body of research suggests that the activation of glial cells induces brain inflammation (e.g. Iadecola & Anrather, 2011; Woodruff et al., 2011) particularly in the ischemic penumbra (the viable ischemic tissue around the ischemic site that might be salvageable) (Gelderblom et al., 2009). Nevertheless, in ischemia, the pathophysiological significance of microglia (Xing et al., 2012) and lymphocyte brain infiltration (Woodruff et al., 2011) remains unclear.

The ischemic penumbra is maintained by blood supply from collateral vessels. It mounts up to almost half of the total lesion volume during the initial stages of ischemia (Ginsberg, 1997). It is pretty essential as it can encourage recovery or cause irreparable neuronal cell death (Fisher, 2004). Cellular integrity and function are preserved in the penumbra if CBF is restored quickly (McElveen & Macko, 2008). This may be linked to penumbra induced recovery (Donaghy, 2009). There is evidence that many neurons may stay vital for many hours or days post ischemia in the ischemic penumbra and hence, recovery may be doable for some time post-stroke onset (Woodruff et al., 2011). In addition to its protective role, restoration of CBF can also have detrimental effects to the brain. Particularly, free radicals may develop, the blood-brain barrier integrity may be compromised (Woodruff et al., 2011; del Zoppo & Hallenbeck, 2000) and programmed neural death and autophagy can still continue happening (Xing et al., 2012).

1.2.2 Hemorrhagic Stroke

According to the anatomical area of the hematoma, intracranial hemorrhage is divided into four types: extradural, subdural, intracerebral and subarachnoid. The somewhat arbitrary distinction between intracranial bleeding (extradural and subdural) and hemorrhagic stroke (intracerebral and subarachnoid) may be unwarranted as all four entities may overlap (Liebeskind, 2010). In a hemorrhagic stroke, large or small arteries rupture and blood that outflows from them pushes against, and compresses adjacent tissues causing them ischemia, bloat and necrosis (Frizzell, 2005). During the initial stages, reflex mechanisms are stimulated to protect blood perfusion, but restoration of normal CBF ultimately fails due to secondary dysfunction of cerebral

flow autoregulation leading to ischemia, hypoxia and finally neuronal cell death (Liebeskind, 2010). After the initial injury of brain tissue due to mechanical compression from blood, a cascade of events is initiated.

In intracerebral hemorrhage, inflammation (Wang, 2010), red cell lysis and iron deposition (Hua, Keep, Hoff & Xi, 2007) and, local and distant ischemic lesions (Prabhakaran & Naidech, 2012) are all observed around the hematoma. Within 48 hours of hemorrhage onset, macrophages start phagocytize blood and necrotic tissue (Frizzell, 2005). Amongst other pathophysiological mechanisms, oxidative stress and neuronal cell apoptosis may disrupt the blood-brain barrier (BBB) and cause brain oedema and hydrocephalus leading to increased intracranial pressures (Ziai, 2013). Elevated pressures in local tissue increase pressures in the capillaries which in turn cause a decrease in regional cerebral flow and even if this occurs towards ischemic limits, such regional tissue is not completely deprived of oxygen or glucose due to metabolic autoregulation (Ronning et al., 2008).

Immediately after a subarachnoid hemorrhage, stimulated signaling cascades cause inflammation, oxidative stress, BBB disruption (through numerous pathophysiological mechanisms), disruption of homeostasis of ion gradients and channels, excitotoxicity, microcirculatory dysfunction, microthrombosis, and cortical spreading depolarization, all lasting up to 72 hours (Reis et al., 2017). Later events include i) cerebral vasospasm causing cerebral ischemia and infarction (Macdonald, Pluta & Zhang, 2007) and ii) vasospasm in deep cerebral veins (Dai et al., 2012). Rolling and adherent platelets and leukocytes that increase in number and size cause microthromboses and microvascular stases (Friedrich, Müller, Feiler, Schöller & Plesnila, 2012). Globalized brain oedema (Chen et al., 2014), hydrocephalus (Shah & Komotar, 2013) and subsequent cerebral hypoperfusion (Csokay, Pataki, Nagy & Belan, 2002) are also noticed.

1.3 Post-stroke Aphasia Epidemiology

Stroke is the second leading cause of mortality and the most frequent cause of disability with an incidence of approximately 200/100,000 internationally (Heiss &

Thiel, 2016). In addition to stroke induced physical impairments, many stroke survivors experience problems in cognition, swallowing and communication.

Aphasia is an acquired communication disorder resulting from damage to brain areas responsible for language. Aphasia can partially or totally affect the production or comprehension of speech and the ability to read and/or write. The severity of aphasia can range from mild to severe. That is, some people with aphasia (PWA) may have only occasional difficulties in finding the right words while speaking (i.e. mild anomia), whilst others may have trouble understanding and/or conveying basic messages.

In a recent systematic review of 248 papers and subsequent meta-analysis, it was found that reported post-stroke aphasia frequencies vary and depend on stroke type (ischemic vs hemorrhagic) and setting (e.g. emergency and rehabilitation centers) (Flowers et al., 2016). Aphasia, as a significant consequent of stroke affects more than a third of all stroke survivors (Heiss & Thiel, 2016; Dickey et al., 2010). There is extensive research showing that PWA engage poorly with their families, peers and community members, leading to social isolation and/or clinical depression (Davidson et al., 2008). Aphasia is associated with serious limitations in activities of daily living (e.g., reading information, shopping, using the phone, handling money), loss of independence (e.g., looking after households, paying bills and returning to work) and participation in social activities (Northcott, Marshall & Hilari, 2016). If aphasia does not improve over time and becomes chronic, it leads to long-term disability (Gialanella, Bertolinelli, Lissi, & Prometti, 2011), increased societal burden (Northcott et al., 2016), family carer strain (Kniepmann & Cupler, 2014) and poor quality of life (QoL) (Hilari, Needle & Harrison, 2012).

1.4 Aphasia Syndromes and Fluency of Speech

Aphasia is a broad term as there are many different presentations and severities of the disorder. Over 20 different aphasia classifications have been introduced since Broca's first report on language disturbance associated with brain damage in 1863 (Ardila, 2010). In Western countries, Luria's and the Neoassociationist classifications of the aphasias are generally accepted (Basso, 2003). According to the clinical classification

system aphasic syndromes are classified into two main groups; fluent and non-fluent aphasia with their subdivisions (table 1-1). This system is widely used in both research and clinical settings and underscores the critical value of fluency in the diagnostic classification of aphasias. However, judging fluency is a complex task that depends on the perceptions of listeners on fluency. Recovery from aphasia is a dynamic process and very often it is observed that one type of aphasia evolves to another (Klebic, Salihovic, Softic & Salihovic, 2011; McDermott, Horner & DeLong, 1996).

Table 1-1: Clinical Classification of Aphasias

Aphasia Syndrome	***Expressive Speech***	***Auditory Comprehension***	***Repetition***	***Naming***	***Reading***	***Neuroanatomical correlates***
Non fluent Aphasias						
Global	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	Extensive lesions that impact on anterior and posterior left hemispheric sites, including Broca's and Wernicke's areas.
Mixed Transcortical	↓↓↓	↓↓↓	Normal	↓↓↓	↓↓↓	Isolation of the perisylvian fissure area by extensive dominant hemispheric lesion - Large lesions affecting anterior and posterior left hemispheric regions, sparing the arcuate fasciculus. Most commonly the cause is ischemia.
Broca's	↓↓↓	↓ / Normal	↓↓↓	↓↓ / ↓↓↓	↓ / Normal	Anterior lesion in the dominant hemisphere - Left frontal and parietal lobes, insula and white matter below these cortical areas may be included as well. Lesion anterior to central sulcus causes milder (more transient) language difficulties and better language recovery. Posterior perisylvian fissure structures are spared. Most commonly caused by an infarct of the superior division of middle superior artery (MCA).
Transcortical Motor	↓↓ / ↓↓↓	↓ / Normal	Normal	↓ / ↓↓	Normal	Lesions observed in the dominant frontal lobe that can reflect dorsolateral damage anterior or superior to Broca's area. Lesions may include mesial left frontal areas associated with the anterior cingulate and supplementary motor area. Posterior perisylvian fissure structures are spared. Lesions may reflect damage of the dominant hemisphere, thalamus or basal ganglia. Usual etiology is infarct of left anterior cerebral artery (ACA) or anterior segment of the superior division of the middle superior artery (MCA).

Aphemia / pure word mutism	Mute – can only write	Normal	Normal	Mute – able to write	Normal	Distinct lesion of the dominant (left) frontal lobe affecting Broca's area.
Fluent Aphasias						
Wernicke's	Fluent but unintelligible	↓↓↓	↓↓↓	↓↓ / ↓↓↓	↓↓↓	Lesion of the dominant inferior perisylvian fissure (superior temporal lobe) that usually extends superiorly to the parietal region impacting on the supramarginal gyrus. Anterior perisylvian fissure structures are spared. Usual etiology is infarct of left inferior division of the middle cerebral artery (MCA).
Transcortical sensory	Fluent but unintelligible	↓↓↓	Normal	↓↓↓	↓↓↓	Lesion of the dominant temporoparietal-occipital region, or less frequently, the parieto-occipital area. The cerebral tissue affected is posterior (and often mesial) to Wernicke's area. Structures anterior to Wernicke's area are spared. Usual etiology is infarction of watershed zone between the inferior MCA territory and posterior cerebral artery (PCA) territory. Another usual lesion concerns damage to the basal ganglia or thalamus of the dominant hemisphere. Neurodegenerative conditions (e.g. Alzheimer's disease), may be associated with language impairment reflecting a transcortical sensory aphasia.
Conduction	Fluent but unintelligible	Normal	↓↓↓	↓ / ↓↓	Normal	Lesion of dominant temporoparietal regions, particularly the supramarginal gyrus and underlying white matter, such that the arcuate fasciculus is damaged. Wernicke's area and anterior structures are spared. Usual etiology is infarction of a limb of the inferior MCA territory.
Anomic	Intact with meaningful	Normal	Normal	↓↓↓	Normal	Apart from acute, isolated anomic aphasia, there is little localizing value. In acute isolated onset of anomic

	speech content					aphasia, lesion is usually in the dominant (left) hemisphere outside the perisylvian language area, in the inferior temporal area or angular gyrus of the parietal lobe area.
Key 1. ↓=minimal impairment; ↓↓=moderate impairment; ↓↓↓=severe impairment *Key 2*. Table adapted from Schoenberg, M. R., & Scott, J. G. (2011). Aphasia Syndromes. In M. R. Schoenberg, & J. G. Scott (Eds). *The Little Black Book of Neuropsychology: A Syndrome-Based Approach* (267-292). Boston, MA: Springer.						

Non-fluent aphasias include five aphasic syndromes that all share a common speech deficit; that is, non-fluent speech. Schoenberg and Scott (2011) outline language deficits of those syndromes as follows:

i) In global aphasia, speech is non-fluent and, oral and reading comprehension, repetition, naming and writing are all impaired. Memory problems, right hemiparesis, right visual field defect, Gerstmann's syndrome, hemianesthesia, visual agnosias and apraxias are all possible comorbid conditions. It typically evolves to Broca's aphasia.

ii) In mixed transcortical aphasia, oral and reading comprehension, naming and writing are impaired but, repetition is intact. Gersmann's syndrome, right hemiparesis, right visual field defect, right hemianesthesia, memory issues, visual agnosias and apraxias are all frequent comorbid conditions. Its prognosis is variable. Patients with vascular aetiology may evolve to either Broca's or anomic aphasia.

iii) In Broca's aphasia, fluency, repetition, naming and writing are all impaired. However, oral and reading comprehension is intact or mildly affected. Right hemiparesis, apraxias and/or verbal memory are frequent comorbid conditions. Its prognosis is also variable – patients with vascular aetiology frequently improve to anomic aphasia with mild fluency problems.

iv) Transcortical motor aphasia presents with impaired fluency, naming and writing. Oral and reading comprehension and repetition are preserved. Comorbid conditions may include apraxias, memory impairments, executive dysfunction, perseveration and behavioral apathy. Other comorbidities depend on the location of the lesion: right upper extremity weakness in left frontal dorsolateral lesions and right lower extremity weakness in medial frontal lesions. Patients with vascular aetiology may evolve to anomic aphasia or symptoms can almost resolve.

v) Aphemia/pure word mutism is characterized by an inability to articulate, leading to slow and very effortful speech. Severely affected patients are totally mute. In milder forms, aphemia can sound as if the patient is attempting to speak in an unusual accent. Comprehension, repetition, naming and writing are completely preserved. Paraphasias and mild dysnomia are occasionally observed.

Fluent aphasias reflect (almost) intact verbal fluency and include four aphasic syndromes (Schoenberg & Scott, 2011):

i) In Wernicke's aphasia, speech is fluent but unintelligible, writing is often fluent with identifiable letters but unintelligible content; oral and reading comprehension, repetition and naming are all impaired. Wernicke's aphasia can present without any other obvious neurological symptoms or with anosognosia, Gerstmann's syndrome, right homonymous visual field deficit, memory deficits and/or visuoconstructional apraxia. Its prognosis is variable. Wernicke's aphasia with vascular etiology often shows comprehension improvement and may evolve to either conduction- or transcortical sensory aphasia, and in patients with significant improvement it may evolve in anomic aphasia.

ii) Transcortical sensory aphasia presents with rapid and effortless speech fluency with unintelligible content due to paraphasias and neologisms. Compared to Wernicke's aphasia, oral and reading comprehension is less impaired. Repetition is intact, naming is impaired, and writing is usually fluent with identifiable letters but unintelligible content. Common comorbid conditions include right visual field loss, right hemianesthesia and constructional apraxia. The prognosis varies as with Wernicke's aphasia. In cases with vascular aetiology, comprehension improves and Wernicke's aphasia evolves to anomic aphasia and sometimes nearly resolves.

iii) In conduction aphasia, speech is rapid, fluent and difficult to understand (because of phonemic paraphasias and pauses resulting from naming errors), but is more meaningful and intelligible compared to speech of transcortical sensory- or Wernicke's aphasia. Verbal and written comprehension is intact for conversational speech. Repetition and naming are markedly impaired. Writing is fluent but sometimes difficult to understand due to paraphasias. Comorbid conditions include right hemianesthesia and apraxia, some right facial weakness, acalculia and rarely hemiparesis. The prognosis varies from evolution to anomic aphasia to complete recovery.

iv) Anomic aphasia presents with intact fluency with meaningful speech content and circumlocutions due to word finding difficulties. Comprehension, repetition, naming and writing are intact. Frequent comorbid conditions include Gerstmann's syndrome, limb apraxia and acalculia while its prognosis is variable. Anomic aphasia is the end phase of recovery from other, mild to moderate, aphasia types.

1.5 The Role of Broca's area in Language

The inferior frontal gyrus is delimited by the inferior frontal sulcus (ifs) dorsally, and the anterior part of the lateral (Sylvian) fissure ventrally. Three distinct parts of the inferior frontal gyrus can be recognized: the pars orbitalis (pOr), the pars triangularis (pTr) and the pars opercularis (pOp). In Brodmann's cytoarchitectonic map, Brodmann area (BA) 44 corresponds to pOp and BA45 to pTr. In the dominant (usually left) hemisphere, BA44 and BA45 constitute Broca's motor speech centre (Petrides, 2013; Jacobson & Marcus, 2008). However, some researchers suggest a more extended language production system. Ardila, Bernal and Rosselli (2016) suggest a "Broca's complex" that in addition to left BA44 and BA45, it includes left BA46, BA47, partially BA6 (mainly its mesial supplementary motor area) and extends subcortically towards basal ganglia and thalamus. Kadis et al. (2016) refer to an expressive language network; Bernal, Ardila and Rosselli (2015) to a Broca's network; Lemaire et al. (2013) to an extended Broca's area and; Hagoort (2006) to a "Broca's complex," involving BA44, BA45 and BA47. Figure 1-1 shows BAs in the Brodmann's Interactive Connectivity Map (Bernal, Broce & Ardila, n.d.). In addition to Broca's area itself, subcortical association fibers are considerably important for language production. In particular, Jacobson and Marcus (2008) cite that the arcuate fasciculus, an extension of the superior longitudinal fasciculus that interconnects the superior and lateral frontal, parietal, temporal, and occipital areas, passes through the subcortical white matter of supramarginal and angular gyri and connects Wernicke's with Broca's area. This connection must be made if a heard sentence is to be repeated.

There is a large body of literature on the role of Broca's area in language (e.g. verbal fluency, grammatical processing and lexical inflection, processing of metaphors, reasoning process, etc.) memory (e.g. working, non-verbal, declarative, etc.), motor functions (e.g. mirror neurons for expressive movements) and many other functions (e.g. music enjoyment, object manipulation, solving arithmetical tasks, etc.). What is well established so far is that anterior lesions cause non-fluent, Broca's-like aphasias and posterior lesions cause fluent, Wernicke's types of aphasias.

In the aphasia literature, it is assumed that a lesion in Broca's area is responsible for the clinical description of a Broca's aphasia (Jacobson & Marcus, 2008; Damasio & Geschwind, 1984; Goldstein, 1948). Also, stimulation of Broca's areas causes arrest of speech with occasional simple vocalizations (Jacobson & Marcus, 2008). Nonetheless, it has been suggested that lesions to Broca's area alone do not cause persisting Broca 's aphasia (e.g., Willmes & Poeck, 1993; Basso, Lecours, Moraschini & Vanier, 1985). Computerized axial tomography (CT) findings corroborate such findings. In particular, restricted damage to Broca's area is not enough to cause the "classical" Broca's aphasia and extension of the lesion to the lower motor cortex, insula, and subjacent subcortical and periventricular white matter is needed for Broca's aphasia symptomatology (Benson & Ardila, 1996; Alexander et al., 1990).

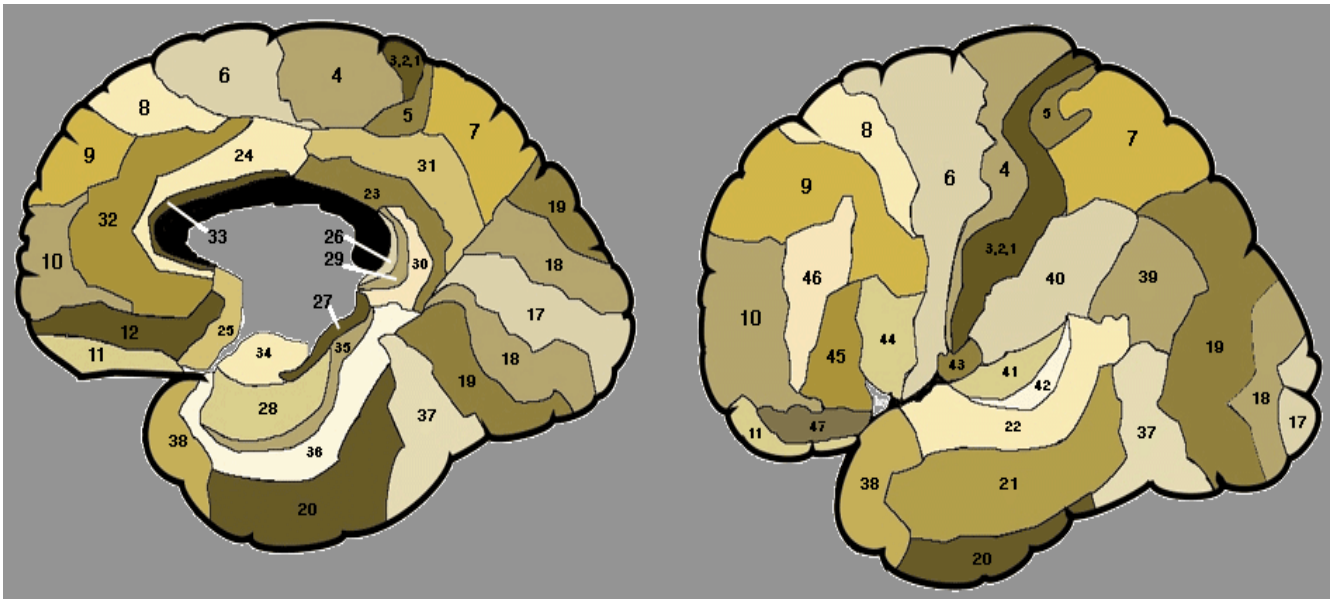

Figure 1-1: Brodmann's Interactive Connectivity Map (Bernal, Broce & Ardila, n.d.)

1.6 Spontaneous Recovery of Communication Deficits post-Stroke

After a stroke, the brain itself tries to compensate and/or repair its disrupted networks. Mechanisms of neuroplasticity become active within seconds or even months after the onset of the damage. The different mechanisms involved in neuroplasticity and the time course and characteristics of each are reported in table 1-2.

Table 1-2: Mechanisms of Neuroplasticity relating to Brain Recovery

Mechanism	Time course & Characteristics
Compensatory activation increase	• seconds to minutes • increased release of neurotransmitters
Disinhibition	• minutes to hours • recruitment of alternative neuronal networks ("silent synapses") normally not employed for the specific brain function represented by a damaged area
Denervation hypersensitivity	• hours • compensatory upregulation of postsynaptic neurotransmitter receptors
Stem cell migration	• days to weeks • existence and migration abilities of human stem cells have been demonstrated • functional relevance remains to be determined
Regeneration	• weeks to months • axonal sprouting and rerouting of dendrites from surviving neurons • regeneration of axons from damaged neurons remains to be demonstrated in the human brain
Note. Adapted from "The pathophysiology of post-stroke aphasia: A network approach" by A. Thiel and A. Zumbansen, 2016, *Restorative Neurology and Neuroscience, 34,* p. 510.	

The acute phase of stroke is usually defined as the first one to three weeks post stoke, the subacute phase is the period right after the acute phase and spans until the chronic phase that starts six months post-stroke (Lefaucheur et al., 2014). Even though the course of recovery is different for every patient, particular stages in the recovery process are common. Some degree of spontaneous recovery is usually observed in all patients in weeks to months post-stroke (Cramer, 2008). Nonetheless, even though the majority of language recovery takes place within the first 3 months post-stroke, a substantial number of patients continue to exhibit language gains for months or even years afterwards (Kertesz, 1988). Nevertheless, the chronic stage is characterized by a remarkable slowing in the rate of spontaneous (natural) functional recovery

(Lefaucheur et al., 2014). Aphasia types also play a significant role in the pattern of spontaneous recovery. Global aphasia often shows late recovery, transcortical aphasia has the fastest recovery rate and Broca's aphasia has the highest recovery rate (Cramer, 2008).

Three main theoretical models of language related brain reorganization post-stroke have been suggested so far. In the healthy brain, according to the "interhemispheric competition model", there exists a mutual and balanced inhibition between the two hemispheres (Di Pino et al., 2014). Stroke induced damage to one hemisphere disrupts this balance leading to reduced inhibition to the unaffected hemisphere. The unaffected hemisphere in turn causes increased inhibition to the affected hemisphere. Eventually, activity is decreased in the left hemisphere and increased in the right hemisphere. It has been reported that the observed activation in homologue areas is deleterious to recovery (e.g. Szaflarski et al., 2013; Postman-Caucheteux et al., 2010; Thiel et al., 2006). The second model is called "vicariation model". According to this model, activity in residual, unaffected homologue hemispheric areas may contribute to functional recovery for lost functions supported by damaged areas (Di Pino et al., 2014; Tillema et al., 2008; Musso et al., 1999; Thulborn, Carpenter & Just, 1999). However, it has been also suggested that the observed right hemispheric activation is a passive event reflecting stroke induced reduced interhemispheric inhibition (Murase, Duque, Mazzocchio & Cohen, 2004). More recently, it was reported that the exact function served by the observed increase in activity in homologous brain areas remains to be clarified (Xing et al., 2016). The third model suggests that perilesional regions of the left hemisphere are recruited to subserve the reorganization of language networks (Norise & Hamilton, 2017). Overall, a number of brain mapping stroke studies report that language related brain-reorganization is a dynamic process showing activation shifts over time. Specifically, in the early stages, cortical activity is initially reduced at the site of the lesion and as time passes it increases again (Nhan et al. 2003; Marshall et al., 2000). This suggests that the left hemisphere remains best equipped to sustain effective language functions (Thompson & den Ouden, 2008). Indeed, it has been reported that spontaneous recovery outcomes are correlated to the degree of activity in the brain area responsible for the expected behaviour (Cramer, 2008). Overall, shifts in representational brain maps (somatotopic shifts) are

postulated due to increased activation of i) proximate brain regions that surround the damaged area (perilesional regions activity) (Cornelissen et al., 2003; Warburton, Price, Swinburn & Wise, 1999) -it is believed that the volume of this periinfarct tissue is directly connected to final clinical behavioural outcomes (Furlan et al., 1996); ii) distributed networks that are connected to the damaged area (Tombari et al., 2004; Cao et al., 1999) and; iii) right hemispheric areas homologous to left damaged areas involved in language processes (Thompson & den Ouden, 2008).

Optimal recovery is also dependent on other parameters as well, such as the extent and location of the lesion, the type of language deficits and duration since stroke onset (Anglade, Thiel & Ansaldo, 2014). In addition to spontaneous recovery mechanisms relevant to brain activation shifts between the two hemispheres, speech and language therapy (SLT) also plays an important role in aphasia recovery.

1.7 Effectiveness of Speech and Language Therapy (SLT) for Aphasia post-Stroke

Currently, there are no available treatments that allow repair of damaged brain tissues (Di Pino et al., 2014). Although pharmacological approaches aiming at correction of neurotransmitter disruptions could enhance language skills and become even more efficacious, no medications are approved for aphasia treatment even though a fair number of agents have been tested for such purposes (Saxena & Hillis, 2017).

Thus, any attempts to restore functional ability comes from rehabilitation scientists (e.g. speech-language therapists and physiotherapists). What troubles speech-language therapists or other rehabilitation specialists is whether the afflicted PWA will be able to speak and/or understand language normally again. There are many theoretical SLT approaches that speech and language therapists can follow when treating aphasia. However, not all therapeutics schemas are equal as they differ in several therapy regimens as follows: i) timing (early vs delayed delivery), intensity, duration, frequency; ii) delivery approach (e.g. volunteer-facilitated SLT (Meinzer, Streiftau & Rockstroh, 2007), computer-facilitated SLT (Cherney, 2010), and group SLT (Pulvermuller et al., 2001)) and; iii) theoretical approach (e.g. constraint induced

language therapy (CILT) (Wilssens et al., 2015; Pulvermuller 2001), semantic and phonological therapy (Wilssens et al., 2015), melodic intonation therapy (der Meulen et al., 2016), verb versus preposition therapies (Crerar, Ellis & Dean, 1996)). Such huge variability troubles researchers regarding the exploration of the neuroplastic effects of language treatment as all the above factors may relate, to different extents, to the mechanisms engaged in the observed language changes. Also, there are additional factors that complicate the interpretation of the effectiveness of SLT even more. First, the aphasic population is heterogeneous in terms of language impairment profiles. Second, some patients receive social support interventions (e.g. creative interventions such as dance or music) in conjunction with SLT and this way they practice their language skills even more. Third, pharmacological interventions and/or other non-invasive neuromodulation therapies (e.g. Transcranial Magnetic Stimulation (TMS) or Transcranial Direct Current Stimulation (tDCS) that are often used as adjuncts to SLT, are probably influencing its (SLT) effectiveness. Also, the language outcome measures used for pre- and post-therapy evaluation vary across studies. The effectiveness of an intervention should reflect communication abilities in real world settings (i.e. functional communication). Discourse analysis is a key tool for such purposes, but it is rarely reported in the literature as a primary outcome measure. Given the lack of functional communication evaluation tools, most studies use secondary outcome measures as primary outcome measures. Secondary outcome measures include formal measures of receptive (oral, written and gestural) language, expressive (oral, written and gestural) language and overall aphasia severity level language batteries. Last but not least, many patients either withdraw from their allocated interventions or do not participate in follow-up examinations. This makes the analysis of the effectiveness of treatments problematic, given that the number of participants across studies is usually small. Nevertheless, even though current evidence is inconclusive with regards to the optimal time for initiation of SLT in PWA post-stroke (Nouwens et al., 2015); SLT remains the gold standard treatment for aphasia and the general consensus is that it improves language skills in all aphasia severities and stages post-stroke even if many patients are finally left with residual deficits (Saxena & Hillis, 2017). Crucially, intensive therapy over short periods is considered superior to less intensive therapy over a prolonged time (Cherney, 2012).

Speech and language therapy aims at either restoration of language functions or compensation. Compensation is usually necessary in chronic, severely affected PWA who appear resistant to therapy, or when language performance has reached a plateau and SLT does not seem to benefit the person with aphasia. This type of treatment focuses on new verbal, nonverbal or alternative methods of communication (Rose, 2012). Both approaches (restoration and compensation) have shown positive results in all aphasia stages post-stroke (Geranmayeh, Brownsett & Wise, 2014; Varley, 2011) while the efficacy of SLT has been mostly explored in chronic aphasia (Nouwens et al., 2015).

Brady et al. (2016) performed a Cochrane Systematic Review (CSR) to investigate the effectiveness of SLT for aphasia post-stroke. They analysed and synthesized data from 57 trials (3002 participants in total) and came to several conclusions reported below. Generally, comparisons were based on a small number of trials involving few participants (usually less than 20 PWA).

- Compared to PWA that did not receive any SLT, PWA that underwent SLT had better scores on functional communication, receptive and expressive language, reading and writing measures.
- Further research is needed to confirm that social support interventions can be advantageous for improvement of certain language skills (e.g. conversation).
- There was no evidence of a difference between direct SLT provided by professionals and SLT facilitated by volunteers or computers.
- There is some evidence that high intensity SLT is more beneficial than low intensity SLT. Similarly, there is some evidence that high therapy doses (between 60 and 208 hours of therapy) compared to lower SLT doses (ranging from five to 78 hours) is more beneficial but differences were significant based on results from one single trial with a small number of participants. However, high intensity and high dose interventions may not be acceptable to all PWA.
- There is no evidence that different theoretical approaches (e.g. CILT vs semantic therapy), yield different language outcomes. Therefore, additional data are needed to prove that popular SLT approaches (e.g. functional SLT or CILT) are superior to conventional SLT.

In conclusion, further research is required to establish the optimum approach, duration, frequency and format of SLT for PWA.

Aphasia spontaneously improves during the first four weeks post-stroke in one-third of patients and in almost half of afflicted individuals during the first six months (Heiss & Thiel, 2016). Even though aphasia rehabilitation leads to considerable improvement in communication (Brady et al., 2016; Brady, Kelly, Godwin, Enderby & Campbell, 2012), 43% of patients that undergo aphasia rehabilitation still present with aphasia 18 months post-stroke (Laska et al., 2001). Therefore, improved and additional treatment strategies are required to improve recovery of language functions.

1.8 Transcranial Magnetic Stimulation (TMS) in post-Stroke Aphasia Rehabilitation

The principle aim of aphasia rehabilitation is to enhance the recovery of speech and language functions after brain injury. Neuronal regeneration is limited in the adult nervous system and functional recovery is expected to occur via neuroplastic processes. Neuroplastic processes depict complex neuronal adaptations/modifications in neural pathways and synapses resulting from changes in behavior, intrinsic or extrinsic environment, or injury (Cramer et al. 2011). Such changes/adaptations are controlled by the synergic action of neurons and other brain cells (e.g. glial, immune, endothelial) (Lenz, Müller-Dahlhaus & Vlachos, 2016). Enduring changes in the efficiency of synaptic transmission, including both long-term depression (LTD) and long-term potentiation (LTP) constitute the basis of neuroplasticity (Huang & Rothwell, 2007).

Transcranial magnetic stimulation (TMS) is a NIBS technique that is used to enhance neuroplasticity. It has shown exploratory potential for post-stroke aphasia neurorehabilitation (Keser, & Francisco, 2016). In TMS, a coil is placed on the skull, right above discrete brain regions identified via various methods (e.g. neuronavigated TMS or 10-20 EEG (electroencephalogram) international system). Then, the coil passes magnetic pulses to the target area. Those pulses induce weak electrical currents, via electromagnetic conduction, in the target neural tissue. These electrical

currents in turn stimulate the targeted brain cells. Depending on the intensity, frequency and duration of stimulation, TMS can cause temporary decreases or increases in cortical excitability. When multiple TMS stimuli are delivered in trains, this is referred to as repetitive TMS (rTMS). Low frequencies of rTMS (below 5 Hz) may suppress excitability of the cortex, while higher rTMS frequencies (5-20 Hz) may increase cortical excitability (Kobayashi & Pascual-Leone 2003). Transcranial magnetic stimulation and other NIBS protocols can affect brain excitability beyond the period of stimulation and such effects may reflect basic synaptic mechanisms, such as LTP and/or LTD plasticity (Huang et al., 2017). Nonetheless, there is little consensus for their practicality in health service settings given the effects and benefits vary widely within and between individuals (Hamada, Murasel, Hasan, Balaratnam & Rothwell, 2013).

In rehabilitation of aphasia post-stroke, the standard protocol is inhibitory rTMS applied to specific brain regions of the right hemisphere to enhance language activity of the undamaged left hemispheric brain regions by suppressing competing homologue language activation, or simply by diminishing inhibitory processes in the right hemisphere. Most conservative studies have used rTMS of 1-4 Hz to inhibit increased activation of the homologous BA45 and other frontotemporal regions (Priyanka, Shah-Basak & Hamilton, 2016) and upper temporal areas (e.g. Abo et al., 2012; Kindler et al., 2012; Naeser et al., 2005). Over the last few years, positive effects of low frequency (1-Hz) rTMS over the right pTr of the IFG has been reported to improve language function in individuals with aphasia in the sub-acute (Rubi-Fessen et al., 2015; Weiduschat et al., 2011; Thiel et al., 2006) or chronic phase post-stroke (Martin et al., 2004).

Furthermore, other studies have demonstrated that excitatory rTMS over the damaged hemisphere induces improvements in aphasia post-stroke. Szaflarski et al. (2011) found that patients treated with excitatory rTMS applied to the affected Broca's area improved in semantic fluency and also, they were able to form more to-the-target words when prompted with a semantic category. The researchers also noticed that such improvements correlated with increased language lateralization in the left hemisphere. Significant improvement following rTMS treatment, either inhibitory or

excitatory, is reported in the literature for naming accuracy (Thiel et al., 2006); auditory comprehension (Kakuda, Abo, Momosaki & Morooka, 2011); spontaneous speech (Naeser et al., 2012) and fluency (Abo et al., 2012).

Nonetheless, there are many inconsistencies between the above and other studies in several domains: (i) numbers of participants; (ii) different protocols have been applied (inhibitory vs excitatory rTMS, inhibitory together with excitatory rTMS); (iii) variability in the anatomic sites of stimulation, (iv) different methods of localization of stimulation sites (e.g. 10-20 international system vs frameless stereotactic neuronavigation systems); (v) outcome measures varied widely across studies making the results difficult to compare; (vi) type and intensity of SLT and; (vii) few studies included ecological language measures, making it unclear whether improved performance carried over into everyday communication abilities and consequently the individual's quality of life (QoL).

1.9 Theta Burst Stimulation (TBS): An alternative form of Brain Stimulation

Theta burst stimulation is a recent rTMS paradigm used for transient alteration of cortical excitability in the human brain. It was first introduced by Huang et al. in 2005 and was developed in animal experiments to mimic the normal pattern of neuronal firing in the hippocampus of the rodent (Huang & Rothwell, 2007). Rodent studies (slice and *in vivo*) have revealed that when pyramidal cells in the hippocampus are stimulated with bursts in the theta frequency range, LTP can be elicited (Staubli and Lynch, 1987; Larson, Wong & Lynch, 1986). Research in humans has revealed that TBS protocols appear to cause sustained changes in cortical activity that last over the duration of TMS conditioning and this has lead to the assumption that the underlying processes that support those changes are LTP and LTD (Oberman, Edwards, Eldaief & Pascual-Leone, 2011; Huang, Chen, Rothwell & Wen, 2007).

Theta burst stimulation protocols refer to repetitive application of short rTMS bursts at high frequency and low intensity interleaved by short pauses of no stimulation. In the basic TBS pattern of rTMS, a burst containing three pulses delivered at a

frequency of 50 Hz (i.e. 20 ms between each stimulus) is given every 200 ms (i.e. at 5 Hz) at 80% of individual active motor threshold (AMT) (Huang & Rothwell, 2007; Huang et al., 2005). The AMT represents membrane related cortical excitability of cortical axons; hence, it is considered an indicator of relative cortical excitability. It is defined as the minimum amount of machine output necessary to elicit a motor response in an individual in at least 50% of all attempts. Huang et al. (2005) investigated the effects of three different stimulation TBS paradigms on the human motor cortex. In particular, they assessed the time course of changes in motor evoked potential (MEP) size elicited from the contralateral first dorsal interosseous (FDI) muscle. In all three paradigms, a total of 600 pulses at an intensity of 80% AMT were given on different days to the primary motor cortex to the same people. The first paradigm, called "intermittent TBS" (iTBS), included the basic pattern delivered in a short train lasting for 2 seconds (secs) (i.e. 10 bursts in total), repeated every 10 secs for 20 cycles for a total of 600 pulses. The second paradigm, the so called "continuous TBS" (cTBS) delivers the basic TBS pattern in a continuous, uninterrupted train lasting for a total of 40 secs (i.e. 200 bursts with a total 600 pulses). In the third paradigm, intermediate TBS" (imTBS), a 5 secs train (i.e. 25 bursts) of the basic pattern is repeated every 15 secs for eight cycles (i.e. a total of 600 pulses). The researchers demonstrated that in the iTBS pattern, MEP size was facilitated for about 15 minutes; in the cTBS, an important reduction of MEP size was observed lasting for almost 60 minutes and; imTBS did not produce any changes in MEP size.

Compared to low frequency rTMS, TBS effects are observed after only secs or a few minutes of conditioning and this is a lot quicker than other rTMS paradigms in humans that require a) much longer periods of conditioning and b) higher stimulus intensities in order to elicit changes in cortical excitability similar to those observed in TBS (Huang & Rothwell, 2007).

Studies using TBS paradigms provide evidence that this quick NIBS protocol induces positive functional language changes (e.g. Griffis, Nenert, Allendorfer & Szaflarski, 2016; Vuksanovic et al., 2015; Szaflarski et al., 2011).

1.10 Repetitive TMS (rTMS) Safety Issues

Even if TMS is considered to be safe when applied within updated safety guidelines (Rossi et al., 2009), it can still cause adverse side effects. The most perilous acute risk is a seizure that can happen during conditioning and less dangerous but more common side effects of rTMS include headache and neck pain (Oberman et al., 2011). Reports of adverse events motivated researchers to update prior guidelines (Wassermann, 1998), producing a Consensus Statement reached at the Sienna Meeting (Rossi et al., 2009). This statement involves information about asynchronous trains, such as TBS, but does not include recommendations for parameters such as maximum duration or intensity of such type of conditioning. In 2011, Oberman and colleagues reviewed the adverse effects related to TBS and concluded that even though TBS's safety profile is similar to that of other rTMS paradigms, it has, theoretically, the potential to cause a higher risk of seizures as it delivers high frequency bursts. Since TBS is a relatively new method, it should be used with caution.

1.11 Repetitive TMS induced Neural Plasticity: Principles and Mechanisms of Action

In 1831, Michael Faraday established that a time-varying current produces a magnetic field, which in turn can induce an electric field and hence a secondary current within a nearby conducting medium (Lefaucheur et al., 2014). Transcranial magnetic stimulation was first introduced 150 years later (Barker, Jalinous & Freeston, 1985); and it is now used in many countries around the world for research and clinical purposes. The TMS circuit consists of several parts. A high voltage power supply with AC (alternating current) and DC (direct current)-AC transformer and amplifier is connected to, and charges, a capacitor or bank of capacitors. The capacitors rapidly produce a brief discharge current of several thousand amperes that flows, via an electronic switch, through the TMS coil (consisting of multiple wound copper wires) to create a brief time-varying magnetic pulse with field strengths up to several Teslas. During the discharge cycle, the TMS circuit behaves like a resistor-inductor-capacitor (RLC) circuit, where R, L and C are the total values of resistance, inductance and capacitance, respectively, in the circuit (Roth, Padberg & Zangen, 2007).

The TMS coil, through electromagnetic induction, induces weak and brief electric currents in the brain (figure 1-2) that are analogous to the rate of change of the current in the coil (Roth et al., 2007). Specifically, an electric field is generated in every point in space -*source for electric field A*- with the direction perpendicular to the magnetic field and the amplitude proportional to the time rate of change of the magnetic vector potential (Roth et al., 2007). The air and skull are almost complete insulators, whilst brain tissue has conducting properties and thence, the magnetic vector potential induces accumulation of electric charge at the brain surface -*source for electric field B*-. Sources for electric field A and B are opposed to each other and consequently reduce the total electric field (Roth et al., 2007). The amount of surface charge produced and thus the extent of action of the current in the brain tissue depends on many biological and physical parameters such as the magnetic pulse waveform, the intensity, frequency and pattern of stimulation, the type and orientation of coil, the distance between coil and brain and, the respective orientation of the current lines and excitable neuronal elements into the brain (Lefaucheur et al., 2014). Large ‘‘circular’’ coils (Cc) have a wide action radius, but for focal stimulation, the ‘‘figure-of-eight’’ coil (f8c), reduces the stimulation zone to a few square cm. The f8c (figure 1-3) was used in the current research and is described in further detail below.

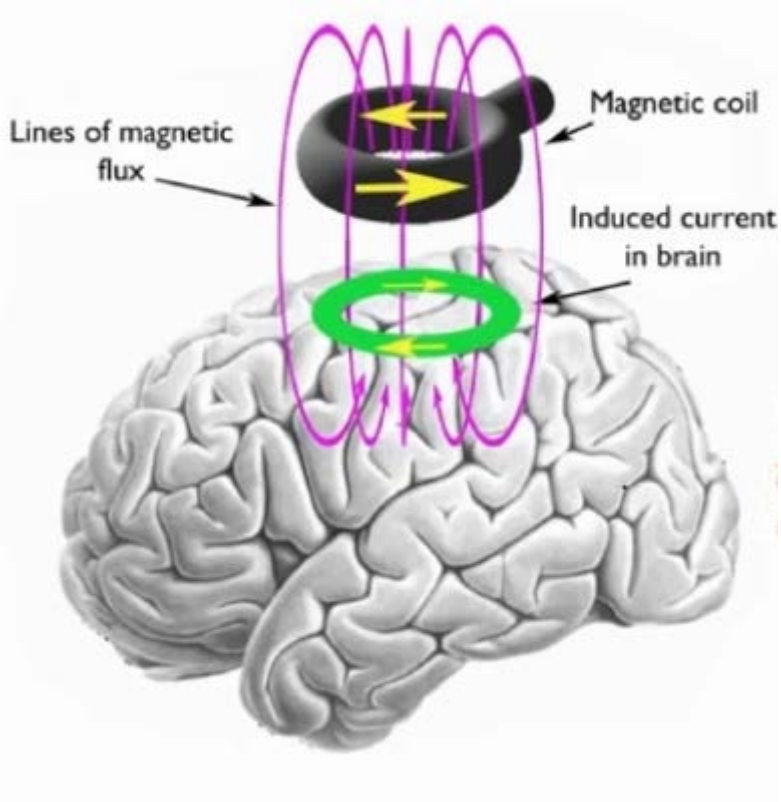

Figure 1-2: Transcranial Magnetic Stimulation Electromagnetic Induction
(Retrieved from: https://psychscenehub.com/psychinsights/transcranial-magnetic-stimulation-depression-case-study/)

Figure 1-3: Figure of 8 coil
(Retrieved from: http://www.icarelifemedical.com/products/magstim/)

The vast majority of TMS data is derived from studies in the primary motor cortex (M1). Single pulse TMS require monophasic (unidirectional) magnetic pulses, whilst rTMS usually requires a biphasic (bi-directional) stimulus waveform (Sommer et al., 2006). Monophasic rTMS activates a relatively uniform population of neurons compared to biphasic rTMS that generates a more complex pattern of neural activation (Arai et al., 2005). When the handle of f8c is oriented parallel to the interhemispheric midline (postero-anterior direction), motor cortex TMS activates the pyramidal tract only indirectly through interneurons (Sakai et al., 1997). When the handle of an f8c is oriented perpendicular to the interhemispheric midline (latero-medial direction) both interneurons and pyramidal neurons are activated (Di Lazzaro et al., 2003). The lowest intensity threshold to elicit MEPs in the M1 is achieved when the stimulus creates a postero-anterior current that is orthogonal to the central sulcus (i.e. the handle of the f8c oriented 45° posteriorly and laterally) (Di Lazzaro, Ziemann, Roger & Lemon, 2008), but the reverse orientation (antero-posterior) makes the latency time increase by several milliseconds (Lefaucheur et al., 2014) and is considered better for inducing motor cortex plasticity (Sommer et al., 2013). To optimize the effects of TMS it is suggested to maximise the strength of the electric field perpendicular to the targeted area (for all cortical surface areas) (Janssen, Oostendorp & Stegeman, 2015).

Results on MEP measurements in healthy people have led to the consensus that low frequency stimulation ($\leq$ 1 Hz) induces inhibition, whereas high frequencies ($\geq$ 5 Hz) induce excitation (Lefaucheur et al., 2014). Nonetheless, this dichotomy is not 100% correct as there is evidence that both conditions can have mixed excitatory and inhibitory results (Houdayer et al., 2008). For instance, doubling the duration of stimulation on the motor cortex can reverse excitation to inhibition and vice versa (Gamboa, Antal, Moliadze & Paulus, 2010).

It is assumed that rTMS after-effects (excitation and inhibition) represent changes in synaptic efficacy (LTP/LTD) (Lenz et al., 2016). However, as all of this evidence is indirect because it is obtained at the systems- and not cellular level, it cannot be definitely assumed that the underlying mechanisms of action of NIBS in humans are indeed LTP/LTD (Huang et al., 2017). Synaptic plasticity refers to activity-dependent

changes of synaptic efficiency, such as LTP or LTD, and the final effect –either LTD or LTP– is at least partly caused by the subsequent signaling cascades that take place after Ca^{2+} influx in post-synaptic neurons (Hamada & Rothwell, 2016). In addition to the activation of L-type voltage-gated calcium channels (L-VGCCs), voltage-gated sodium channels (VGSCs) and N-methyl-D-aspartate receptors (NMDARs), brain-derived neurotrophic factor (BDNF) and cyclic adenosine monophosphate (cAMP) dependent signalling pathways have been identified to play a crucial role in synaptic plasticity (Lenz et al., 2016). Brain-derived neurotrophic factor is highly expressed in the central nervous system (CNS), is the most abundant neurotrophic factor in the brain and has been reported to modulate NMDAR-dependent LTP and LTD related processes in animals (Uhm et al., 2015). An important role in neuroplasticity is also attributed to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), catecholamines, GABA, acetylcholine, cytokines and hormones, and metaplasticity (Abraham, 2008). Metaplasticity is a higher form of plasticity and manifests as a change in the ability to induce subsequent synaptic plasticity. There is evidence that metaplasticity induced by previous synaptic or cellular activity can modulate the capacity for subsequent neuroplastic changes (Turrigiano & Nelson, 2004). Also, molecular reorganization of dendritic spines and postsynaptic densities, presynaptic mechanisms, and remodelling of the cytoskeleton have been reported in the context of neuroplasticity related processes (Lenz et al., 2016). The after-effects of rTMS are consistent with the induction of a mixture of distinct modifications (either LTD or LTP) on many different synapses but, the origin of such neuroplastic changes is unknown and it is likely to be determined by a complex interaction of all the aforementioned factors (Hamada & Rothwell, 2016). Moreover, age, gender, genetics and epigenetics may also play a role in the biological and clinical effects of this neuromodulation modality (Lefaucheur et al., 2014).

However, as mentioned previously the effects of TMS on individual neurons are largely unknown (Dayan et al., 2013) and. On this basis, further research is needed to elucidate how structural and functional properties of individual neurons and local networks are related to the effects of single pulse and rTMS (Lenz et al., 2016). Also, there is evidence that the genetic profile can also give insight into effective rTMS protocols for specific groups of people. For instance, a recent study in healthy

participants reported that supra-threshold rTMS intensity could be the most effective rTMS protocol for people with the BDNF Val/Val genotype, and that rTMS intensity may not relate to cortical excitability for people with the BDNF Val66Met polymorphism (Hwang et al., 2015). To date, no study has investigated the possibility of developing personalized rTMS protocols in stroke patients according to their BDNF genotype (Uhm et al., 2015). Crucially, the effects of TMS on non-neuronal cells (i.e. endothelial cells, immune cells, astrocytes, microglia, oligodendrocytes) are not known either (Lenz et al., 2016). In clinical populations, the evidence on the cellular and molecular mechanisms that underpin rTMS based therapies is inconclusive (Muller-Dahlaus & Vlachos, 2013). What complicates the elucidation of such mechanisms in those populations even more is that in chronic patients, when prolonged therapeutic effects (i.e. up to several months) are observed, placebo effects should be taken into consideration (Lefaucheur et al., 2014). Placebo effect is related to a complex mixture of neurobiological effects, including the release of several neurotransmitters and also involves the activation of a wide neuronal network where the prefrontal brain areas seem to play an essential role (Krummenacher et al., 2010).

In clinical practice, the dose of rTMS stimulation is configured according to a percent of AMT/RMT. These measurements assess the excitability of the motor cortex, but thresholds for neural depolarization in other cortical areas is unknown (Keck, 2007). Also, the mixture of LTD and LTP effects on synapses measured by MEP behavioural changes is highly variable across individuals, showing that it would be an oversimplification to describe the rTMS after-effects as LTD or LTP-like plasticity solely based on MEP modifications (Hamada & Rothwell, 2016). However, MEP measurements provide an objective and useful way to measure cortical excitability (Hamada & Rothwell, 2016). It has been alleged that increases in MEP observed after excitatory rTMS might indirectly relate to a decrease of γ-aminobutyric acid (GABA) mediated inhibition (i.e. inhibition of inhibition), rather than direct enhancement of excitation (Ziemann, 2004). On the other hand, inhibitory rTMS may enhance inhibition probably via GABA-B transmission leading to lengthening of the duration of inhibition in healthy people (Daskalakis et al., 2006) and patients with movement problems (Borich, Arora & Kimberley, 2009).

Finally, there is some evidence that the rTMS after-effects may not be due to plasticity effects of cortical synapses. In particular, in a large sample of 56 healthy individuals it was shown that the concept of inhibitory effects of cTBS and excitatory effects of iTBS on MEP size is greatly variable and depends on differences in the interneuronal cortical networks that are recruited during TMS (Hamada et al., 2013).

Despite numerous clinical studies that have explored the therapeutic potential of rTMS in several neurological disorders, the cellular and molecular mechanisms responsible for the after-effects of rTMS are largely unknown. Therefore, more research is needed to allow a deeper understanding of rTMS induced neural plasticity. In addition, biomarkers of good and non-responders to brain stimulation treatments need to be investigated and established as previous trials (e.g. Seniow et al., 2013; Martin et al., 2009) have reported that not all patients with aphasia respond to rTMS. This will lead to individually tailored rTMS protocols and increased treatment efficacy (Kubis, 2016).

1.12 Rationale for the Study, Aim and Objectives

The aim of this study was to measure the effectiveness of rTMS as a standalone treatment for chronic post-stroke induced aphasia. Aphasia is considered chronic when it lasts for over six months post aphasia onset and; there is a remarkable slowing in the rate of spontaneous functional recovery at this stage of recovery (Lefaucheur et al., 2014). Hence, it is assumed that if an individual with aphasia undergoes targeted language treatment after the 6-month period, then the possibilities for a change in language performance attributable to treatment per se are increased. That is the rationale for exploring changes in language performance only in chronic aphasia post-stroke in this study.

There are several reasons why TMS was used as a standalone treatment in this research. First, there is already research supporting that TMS in conjunction with SLT leads to language gains in post-stroke aphasia (e.g. Hu et al., 2018; Rubi-Fessen et al., 2015; Heiss et al., 2013). Nonetheless, there are significant inconsistencies between studies with regards to the type and intensity of SLT that is used as adjunct to TMS (see chapter 3). Even though, SLT improves language skills in all aphasia severities

and stages (Saxena & Hillis, 2017), the optimum time for SLT initiation (Nouwens et al., 2015) and the optimal approach, duration, frequency and format of SLT (Brady et al., 2016) are yet to be established. Also, it has been reported that the benefit offered by SLT declines over weeks to months and crucially, there is little convincing evidence that the addition of SLT is a significant determinant of response to TMS for aphasia rehabilitation (Coslett, 2016). So far, only two randomized control trials (RCTs) (i.e. Barwood et al., 2013; Medina et al., 2012) have investigated the effects of TMS as a standalone treatment for chronic aphasia post-stroke. Barwood et al. (2012) found improvements in naming, repetition, length of utterances and picture description tasks (i.e. picture description complexity and length of utterance) up to 12 months post-TMS. Medina et al. (2012) found an increase in the number of closed-class words of discourse productivity two months post-TMS. Those two studies provide evidence that TMS as a standalone treatment can lead to long-term language improvements in several language domains in people with chronic aphasia post-stroke.

The objectives of this thesis were:

- ✓ To explore whether continuous Theta Burst Stimulation (cTBS) (independent variable, IV) could modify performance on language tests (dependent variables, DV) one day (short-term) and/or two months (long-term) post treatment when administered for 10 consecutive days over the right pars triangularis (pTr) of individuals with chronic post-stroke aphasia;
- ✓ To explore whether 1 Hz (low frequency) rTMS (independent variable, IV) could modify performance on language tests (dependent variables, DV) one day (short-term) and/or two months (long-term) post treatment when administered for 10 consecutive days over the right pars triangularis (pTr) of individuals with chronic post-stroke aphasia;
- ✓ To explore whether the above protocols (i.e. cTBS & 1 Hz rTMS) could bring about similar changes in language performance in the sample under investigation.

The two protocols that were explored in this thesis exert the same effects on the brain (i.e. neuronal suppression). However, cTBS has a duration of only 40 secs, whereas 1 Hz rTMS has a 20 min duration. As both protocols exert the same effects on brain neurons, it would be wise to explore whether both protocols also bring about the same changes in language performance in post-stroke aphasia. If this is proved to be true, then the short in duration (40 secs) cTBS may outplace the long in duration (20 min) 1 Hz rTMS.

1.13 Chapter Summary

Aphasia is a serious stroke sequela that necessitates a deep understanding of the functional neuroanatomy of language. Interventions that target brain areas that are responsible for language functions may enhance recovery and facilitate rehabilitation. Transcranial magnetic stimulation is a non-invasive treatment modality that has the potential to bring about language changes in patients with induced aphasia post-stroke. However, its effectiveness as a standalone intervention for post-stroke aphasia rehabilitation has not been extensively investigated. The aim of the research presented in this thesis was to measure the effectiveness of rTMS as a standalone treatment for chronic post-stroke induced aphasia.

CHAPTER 2: Evaluating the quality of conduct of systematic reviews on the application of transcranial magnetic stimulation (TMS) for post-stroke aphasia rehabilitation [under review, *Aphasiology*]

Authors

Anastasios M. Georgiou, Eleni Lada and Maria Kambanaros

Affiliation for all authors:

Cyprus University of Technology

Department of Rehabilitation Sciences

Limassol, Cyprus

Introduction

Aphasia, an acquired communication disorder, afflicts more than one third of all stroke survivors (Heiss & Thiel, 2016). To date, there are no treatments enabling reparation of the brain damage (Di Pino et al., 2014). Pharmacological treatments for common aphasia symptoms (e.g. anomia) have been trialled, but no medication has yet been approved (see Saxena & Hillis, 2017 and references within). Traditional speech and language therapy (SLT) methods robustly remain the gold standard for aphasia rehabilitation (Breitenstein et al., 2017). Intensive and targeted SLT intervention improves language abilities for all aphasia types irrespective of time post-onset and aphasia severity (Saxena & Hillis, 2017). Nevertheless, there is an urgent need for further research to establish the best treatment approach or type of therapy, in relation to three key treatment components (Brady et al., 2016): frequency (how often), duration (how long for) and dosage (how much).

In recent years, brain stimulation techniques have also been applied to stroke patients with aphasia to facilitate language recovery. Transcranial magnetic stimulation (TMS) is one type of noninvasive brain stimulation (NIBS) technique used in the evolving field of neurostimulation protocols for stroke rehabilitation (Cappa, 2011). Variations in TMS methods with regards to intensity, frequency and duration of the stimulation,

can yield temporary decreases or increases in excitability of the affected brain area. For post-stroke aphasia rehabilitation, repetitive TMS (rTMS) protocols have been explored for their potential to induce changes in brain activity that last beyond the period of stimulation. Such effects could reflect basic synaptic mechanisms, such as long-term potentiation (LTP) (i.e. persistent strengthening of synapses) and/or long-term depression (LTD) (i.e. long-lasting decrease in synaptic strength) plasticity (Huang et al., 2017). In general terms, excitatory (high-frequency, 5-20 Hz) rTMS increases cortical excitability, whereas inhibitory (low-frequency, below 5 Hz) rTMS suppresses brain activity.

New research has revealed that applying excitatory rTMS over the lesioned left hemisphere improves language functions in individuals with post-stroke aphasia. Szaflarski et al. (2011) applied functional Magnetic Resonance Imaging (fMRI) guided excitatory theta burst stimulation[1] (TBS) to residual Broca's area of the left hemisphere in eight patients with chronic or moderate aphasia and found significant improvements in semantic fluency ($p=.028$), and an overall trend towards improvement in communication ($p=.075$) which were associated with stronger language lateralization to the left (dominant) hemisphere. This last finding was supported by another excitatory (to the left hemisphere) TBS study (Griffis, Nenert, Allendorfer & Szaflarski, 2016). Also, Vuksanovic et al. (2015) applied inhibitory TBS over the right Broca's homologue and immediately after excitatory TBS over the left Broca's area. The authors reported improvement in several linguistic domains, most notably in propositional speech, semantic fluency, and for cognitive skills such as short-term verbal memory, and verbal learning.

However, the rTMS protocol that has been examined the most and has demonstrated good potential for post-stroke aphasia recovery is inhibitory rTMS over the homologue frontal language areas in the right hemisphere (e.g. Rubi-Fessen et al., 2015; Abo et al., 2012; Naeser et al., 2012; Weiduschat et al., 2011). The reported language gains are diverse and concern auditory and reading comprehension,

[1] TBS refers to a rTMS protocol where pulses are applied in bursts of three, delivered at a frequency of 50 Hz and an inter-burst interval of 200 ms (5 Hz).

repetition, naming and spontaneous speech. In several studies, rTMS was combined also with SLT (e.g. Rubi-Fessen et al., 2015; Seniow et al., 2013) as an adjunct treatment to maximize therapy effects.

Prior to conceptualizing new rTMS studies in the area of post-stroke aphasia rehabilitation, it is important to critically appraise the existing literature on the topic. This will allow future researchers and rehabilitation practitioners to identify gaps that require further investigation. Systematic reviews aim to address these problems by identifying, critically evaluating and integrating the findings of all relevant, high-quality individual studies on the topic. In fact, systematic reviews are considered rigorous, transparent and comprehensive summaries of the best available evidence on what works (Hanley & Winter, 2013). Yet, conducting a systematic review is a resource-intensive process which involves a number of practical challenges. In particular, the way in which systematic reviews are planned and conducted can be subject to a range of biases that can compromise the quality of the systematic review and the reliability of the findings (Shea et al., 2017).

The aim of the present study was to analytically evaluate the quality of the evidence on the effects of TMS as a treatment method (standalone or adjunct) for stroke-induced aphasia in published systematic reviews on the topic. The AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) (Shea et al., 2017) instrument was used to evaluate the published research. The AMSTAR 2 is a critical appraisal tool used to evaluate the quality of conduct of systematic reviews for healthcare interventions with the primary goal to help researchers, clinicians and policy-makers to distinguish high quality reviews.

The research questions that further drove this study were three-fold:

1. What is the quality of conduct of systematic reviews on the application of TMS in post-stroke aphasia rehabilitation based on the AMSTAR 2?
2. Are the reported effects of rTMS on post-stroke aphasia recovery consistent across the systematic reviews?
3. Is there strong and reliable evidence regarding the positive effects of rTMS for post-stroke aphasia rehabilitation based on the results of the systematic reviews?

Below we report the process followed to identify and critically appraise published systematic reviews on the topic.

Methods

Requirements for inclusion

The present review was based on guidelines following the Cochrane Handbook on Overviews of Reviews (Becker & Oxman, 2008, pp. 607-631). Only published systematic reviews on RCTs focusing on the effectiveness of rTMS for post-stroke aphasia rehabilitation were included. Systematic review articles could also be published in languages beyond English known to the authors (e.g., Greek, French or Italian). For a systematic review to be eligible for evaluation, the trials reported in the review had to fulfil a number of predetermined criteria as reported below:

- participants of trials had to be stroke survivors defined within a post-stroke stage (acute/subacute/chronic);
- the interventions applied had to focus on TMS with and/or without SLT;
- the outcome measures used must have included standardised tests for the assessment of aphasia severity and/or assessment of receptive and expressive language skills with and/or without functional communication abilities;
- the control groups had to have been sham or placebo groups.

Reviews that reported case studies or case series and open label trials were excluded as were studies focussing on other types of NIBS other than TMS, (e.g., on transcranial direct current stimulation (tDCS)).

Search methods and selection of studies

The search was conducted on the 27th July 2017 for all articles published to that date and a three-step search process was followed. First, a search was performed in databases specific to systematic reviews recommended by internationally respected resources for the conduct of systematic reviews (Cochrane Handbook, Becker & Oxman, 2008):

- Campbell Library of Systematic Reviews
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effects

The search terms that were used were ("TMS" OR "brain stimulation") AND "aphasia". It was anticipated that only a small number of reviews would be identified and therefore broad terms were used in this first search. Second, articles published with the 27th of July 2017 as a cut-off date in Scopus, CINAHL and PubMed were reviewed. All identified records were screened, by two independent researchers, at title and abstract level using the pre-defined eligibility criteria. Third, all reference lists of the included articles were screened for eligibility. Full texts of all articles meeting the eligibility criteria were retrieved for evaluation by the authors.

Instrument for the assessment of the quality of conduct

To assess the quality of conduct of the included systematic reviews, the AMSTAR 2 instrument (Shea et al., 2017) reported in the appendix was used. The instrument encompasses ten domains with 16 items (questions) in total. The domains can be broadly grouped into 3 main areas: (i) quality of reporting; (ii) risk of bias and (iii) methodological quality. In general, the AMSTAR 2 is considered to have adequate content validity, inter-rater reliability and usability (Shea et al., 2017, p. 3) for measuring the quality of conduct of systematic reviews.

The overall confidence rating (high, moderate, low and critically low) applied to the conduct of a systematic review depend on the number of critical and non-critical weaknesses identified after addressing each question in the AMSTAR 2 instrument. A “yes” answer to a question/item from the instrument is a positive response to adherence to the standard (no weakness); a “no” answer means that no information is provided to rate an item (equals a weakness) and; a “partial yes” refers to instances where it is considered worthwhile to identify partial adherence to the standard, and this is not taken into account when rating overall confidence in the results of the review.

Critical weaknesses in the conduct of systematic reviews of RCTs have been identified by Shea et al. (2017, p. 5) as the following (AMSTAR 2 item in parenthesis):

- Not providing an explicit statement that the review methods (protocol) were established before commencement of the review (item 2)
- Not conducting an adequate literature search (item 4)
- Not providing a justification for excluding individual studies (item 7)
- Not using a satisfactory technique for assessing the risk of bias (ROB) from individual studies being included in the review (item 9)
- Not using appropriate methods for the meta-analysis (item 11)
- Not taking into consideration the risk of bias when interpreting the results of the review (item 13)
- Not carrying out an assessment for the presence of publication bias, and its potential impact on the results of the review (item 15)

For the purposes of our study we also considered the following items as critical weaknesses:

- Not reporting the components of PICO (population, intervention, comparison, outcome) (item1)
- Not performing study selection and data extraction in duplicate (items 5 & 6 respectively)
- Not describing in detail the included studies (item 8)
- Not assessing the potential impact of ROB of a meta-analysis (item 12)
- Not giving a satisfactory explanation for heterogeneity (item14)
- Not reporting any potential sources of conflict or interest, including any funding received for conducting the review (item 16).

We followed the AMSTAR recommendations and considered "not reporting the selection of study designs for inclusion" (item 3) and "source of funding" (item 10) as non critical weaknesses.

The overall confidence rating is *high* when none or one non-critical weakness is identified; *moderate* with more than one non-critical weaknesses; *low* with one critical weakness with/without non-critical weaknesses and; *critically low* with more than one critical weakness with/without non-critical weaknesses.

To our knowledge this is the first time the AMSTAR 2 has been used to measure the quality of conduct of systematic reviews on stimulation intervention in aphasia recovery, specifically the application of rTMS, the most extensively applied non-invasive brain stimulation method to date, in cognitive neuroscience (Parkin, Eichtiari & Walsh, 2015).

Results

Search results

Overall 274 entries (after duplicates were removed) were identified and screened at title and abstract level. Table 1 reports the search strategies followed for PubMed, CINAHL and Scopus.

Table 1. Search strategies used to access relevant systematic reviews from each database on the application of transcranial magnetic stimulation (TMS) for post-stroke aphasia rehabilitation.

PubMed	((aphasia[Title/Abstract] OR "Aphasia"[Majr])) AND ("Transcranial Magnetic Stimulation"[Majr] OR "transcranial magnetic stimulation"[Title/Abstract] OR TMS[Title/Abstract] OR "theta burst stimulation" OR TBS))) NOT ("transcranial direct current stimulation" OR TDCS)
CINAHL	(MM "Aphasia") OR TI aphasia OR AB aphasia) AND (MM "Transcranial Magnetic Stimulation") OR TI (transcranial magnetic stimulation OR TMS OR theta burst stimulation or TBS) OR AB (transcranial magnetic stimulation OR TMS OR theta burst stimulation or TBS) NOT (transcranial direct current stimulation OR TDCS)
Scopus	(TITLE-ABS-KEY (aphasia) AND TITLE-ABS-KEY ("transcranial magnetic stimulation") OR TMS OR "theta burst stimulation" OR TBS) AND NOT TITLE-ABS-KEY ("transcranial direct current stimulation" OR TDCS)

Fifteen (15) articles were selected for full-text analysis and, four articles were finally included in the review according to the eligibility criteria reported in figure 1. Studies that were excluded and a justification for their exclusion from the analysis is reported in Table 2.

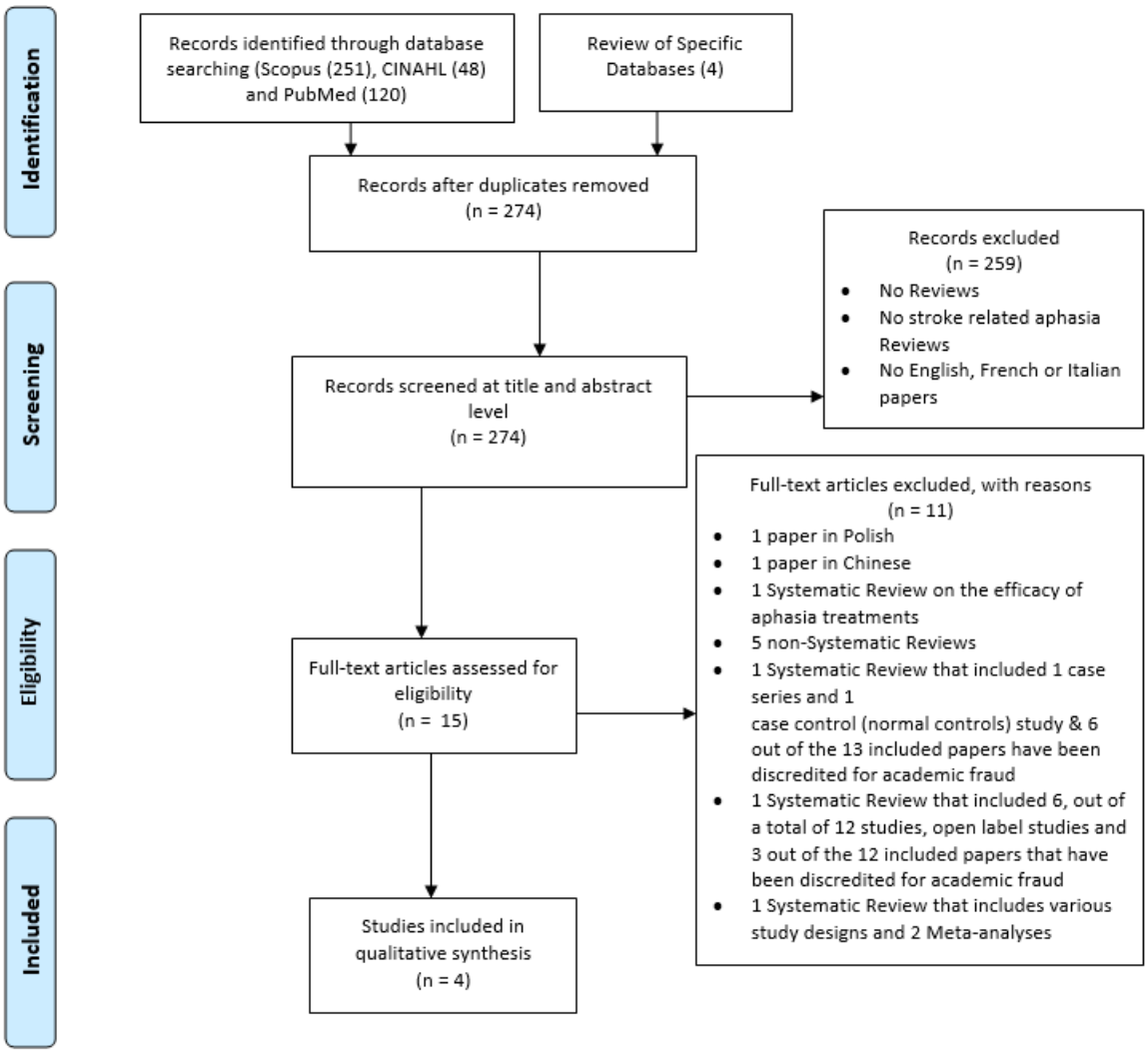

Figure 1. PRISMA flowchart used to identify studies to be included in the qualitative analysis

Table 2. A list of the research articles excluded from the analysis, and the justification for their exclusion.

List of excluded articles	Justification for exclusion
1. Allen, L., Mehta, S., Andrew McClure, J., & Teasell, R. (2012). Therapeutic Interventions for Aphasia Initiated More than Six Months Post-stroke: A Review of the Evidence. *Topics in Stroke Rehabilitation*, *19*(6), 523–535.	Systematic Review on the efficacy of general aphasia treatments
2. Gallletta, E. E., Rao, P. R., & Barrett, A. M. (2011). Transcranial Magnetic Stimulation (TMS): Potential Progress for Language Improvement in Aphasia. *Topics in Stroke Rehabilitation*, *18*(2), 87–91.	Not a Systematic Review
3. Heiss, W.-D., & Thiel, A. (2012). Is transcranial magnetic stimulation an effective therapy for aphasia? *Clinical Practice*, *9*(4), 473–482.	Not a Systematic Review
4. Kapoor, A. (2017). Repetitive transcranial magnetic stimulation therapy for post-stroke non-fluent aphasia: A critical review. *Topics in Stroke Rehabilitation*, *24*(7), 547-553.	Systematic Review that included 1 case series and 1 case control (normal controls) study & 6 out of the 13 included papers have been discredited for academic fraud
5. Lefaucheur, J. P. (2006). Stroke recovery can be enhanced by using repetitive transcranial magnetic stimulation (rTMS). *Neurophysiologie Clinique*, *36*(3), 105–115.	Not a Systematic Review
6. Martin, P. I., Naeser, M. A., Ho, M., Treglia, E., Kaplan, E., Baker, E. H., & Pascual-Leone, A. (2009). Research with transcranial magnetic stimulation in the treatment of aphasia. *Current Neurology and Neuroscience Reports*, *9*(6), 451–458.	Not a Systematic Review
7. Mendoza, J. A., Silva, F. A., Yovana, M., Rueda, L. C., Alberto, L., & Romero, L. (2016). Repetitive Transcranial Magnetic Stimulation in Aphasia and Communication Impairment in Post-Stroke : Systematic Review of Literature. *Journal of Neurology & Translational Neuroscience*, *4*(3), 1070.	Systematic Review including various study designs and 2 meta-analyses
8. Naeser, M. A., Martin, P. I., Treglia, E., Ho, M., Kaplan, E., Bashir, S., … Pascual-Leone, A. (2010). Research with rTMS in the treatment of aphasia. *Restorative Neurology and Neuroscience*, *28*(4), 511–529.	Not a Systematic Review
9. Waldowski, K., Seniów, J., Bilik, M., & Członkowska, A. (2009). Transcranial magnetic stimulation in the therapy of selected post-stroke cognitive deficits: aphasia and visuospatial hemineglect. *Neurologia i Neurochirurgia Polska, 43(5), 460-469.*	Paper written in Polish
10. Wang, P., Zhang, J., Yu, J., Zhang, B., Gu, S., Yang, L., … He, C. (2014). Elects of Repetitive Transcranial Magnetic Stimulation on Stroke Patients with Aphasia: A Systematic Review. *Chinese Journal of Evidence-Based Medicine*, *14*(12), 1497–1503.	Paper written in Chinese
11. Wong, I. S. Y., & Tsang, H. W. H. (2012). A review on the effectiveness of repetitive transcranial magnetic stimulation (rTMS) on post-stroke aphasia. *Reviews in the Neurosciences*, *24*(1), 105-114.	A systematic review that included 12 studies: 6 open label studies and 3 studies that have been discredited for academic fraud

Characteristics of the systematic reviews

Up until July 2017, four systematic reviews have explored the effects of low frequency rTMS for post-stroke aphasia rehabilitation. The research has come from three different countries: Brazil (Gadenz, Moreira, Capobianco & Cassol, 2015) China (Ren et al., 2014; Yi et al., 2015; Li, Qu, Yuan & Du, 2015) and Italy (Sebastianelli et al., 2017). Furthermore, meta-analyses was performed to explore the effects of rTMS on post-stroke aphasia in two systematic reviews (Li et al., 2015; Ren et al., 2014); while for the other two systematic reviews, one had a primary focus on communication and deglutition disorders (Gadenz et al., 2015) and one focussed on general stroke motor deficits (hand/arm/leg motor impairment, spasticity, aphasia, visuospatial neglect and dysphagia) (Sebastianelli et al., 2017). Nonetheless, the studies of Gadenz et al. (2015) and Sebastianelli et al. (2017) were included in the analysis as results on the effects of rTMS on post-stroke aphasia were individually described. The characteristics of each systematic review is described in detail in table 3.

Table 3. Detailed summary of the method and results of the research studies on the application of rTMS in post-stroke aphasia rehabilitation included in each systematic review.

Systematic review (references)	Type	Total number of studies & participants	Stroke timeline and aphasia type	Experimental groups	Intervention	Control groups	Outcome Measures	Major findings on recovery of language abilities	Side effects
Gadenz, et al. (2015)	RCTs	-4 studies -54 adult patients in total receiving real rTMS -52 adult patients in total receiving sham rTMS -All right-handed	-Subacute -Different aphasia-types -All with left H lesions stroke -Mainly ischemic	-Between 6-20 post-stroke individuals with aphasia -MA range: 61.8-69.8 years -Between 0-2 dropouts	-All applied -1 Hz rTMS, 90% RMT -20-30 min per day -8-15 sessions -Use of the figure-of-8 coil -Stimulation over Broca's homologue	-Between 4-20 individuals with post-stroke aphasia receiving sham rTMS -MA range: 59.7-71.2 years -Between 0-4 dropouts	-1 study used the BDAE -2 studies used the AAT -1 study used the CPNT & the ASRS of the BDAE	-1 study: improvement in *repetition* in severe aphasia 15 weeks post treatment, -1 study: overall *improvement in AAT scores* and *naming* -1 study: improvement in *naming reaction time* in patients with anterior lesions 15 weeks post treatment -1 study: *overall improvement in AAT scores* but not in subtests	None

Li, et al. (2015)	RCTs	-4 studies -74 adults in total receiving real rTMS -63 adults in total receiving sham rTMS -Most participants were right handed -MA range: 60.7-68.8 years	-Chronic -All aphasia types	-Between 6-33 post-stroke aphasic individuals	-All studies applied -1 Hz rTMS, 90% RMT -10-30 min per day -10-15 sessions, -Stimulation of the right pTr -With SLT (3) -Without SLT (1)	-Between 6-23 post-stroke aphasic individuals -Received sham rTMS -With SLT (3) -Without SLT (1)	-1 study used the BDAE -1 study used the AAT & the AVI -1 study used the PNT & the CCAT -1 study used the BDAE & the BNT	-Data synthesis showed that 1 Hz rTMS was beneficial for improvement in naming and changes in brain excitability	None
Ren et al. (2014)	RCTs	-7 studies -83 adults in total receiving real rTMS -77 adults receiving sham rTMS -All right-handed	-Acute, Subacute, Chronic -All with left H ischemic lesion	-Between 6-19 post-stroke aphasic individuals -MA range: 60.8-69.8 years	-All studies applied -1 Hz rTMS 90% RMT -Between 20-30 min per day -Between 10-15 sessions, -Stimulation of the right PTr, -Use of the figure-of-8 coil -With SLT (6) -Without SLT (1)	-Between 4-19 post-stroke individuals with aphasia -Received sham rTMS stimulation over the vertex	-3 studies used the AAT -1 study used the AAT subtest and total score -1 study used the CPNT -1 study used the BDAE -1 study used the BNT, the	-Data synthesis showed that 1 Hz rTMS was beneficial for post-stroke patients regarding severity of aphasia, naming, writing, repetition and receptive language. -Follow-up data reported from 3 of the studies (2 trials followed patients up at 15 weeks post-treatment &	None

							BDAE and a picture naming inventory	1 study followed up at 2, 8, & 12 months post-treatment) suggest long-term positive effects of rTMS on naming & repetition.	
Sebastianelli et al. (2017)	RCTs	-11 studies -155 adults -Received real rTMS -Most were right-handed	-Acute, Subacute, Chronic, -All aphasia types -Left H lesion	-Between 6-33 post-stroke aphasic individuals -MA range: 60.08-69.8 years -1 study did not report MA	-10 studies applied 1 Hz rTMS, 90% RMT for -20-30 min per day for -10-15 sessions -Over the right pTr / right Broca's homologue, -1 study applied 1 Hz rTMS at 110% RMT, 1000 pulses over the right IFG followed by 20 Hz 10 trains of 5 secs with 30 secs inter-train interval over the left IFG followed by SLT for 10 days	-Post-stroke aphasic individuals received sham rTMS	-2 studies used the AAT -1 study used the CCAT	-Improvement in global aphasia test scores, picture naming and naming accuracy, reaction time, functional communication & auditory comprehension	Not reported
Key: *RCTs: Randomized Control Trials; RMT: Resting Motor Threshold; LF: low frequency; pTr: pars triangularis; IFG: inferior frontal gyrus; BDAE: Boston Diagnostic Aphasia Examination; AAT: Aachen Aphasia Test; CPNT: Computerized Picture Naming Test; ASRS: Aphasia Severity Rating Scale; AVI: Activation Volume Indices; PNT: Picture Naming Test; CCAT: Concise Chinese Aphasia Test; BNT: Boston Naming Test; H: hemisphere; MA: mean age*									

In total, 26 RCT studies were reviewed in the 4 systematic reviews, but 14 of those studies were duplicates, leaving 12 original studies that included, in total, 174 participants with post-stroke aphasia who received rTMS for aphasia rehabilitation.

Procedure to evaluate the quality of the conduct of each systematic review

The criteria from the AMSTAR 2 instrument were considered for the evaluation of each systematic review, and the appraisal team (authors) recorded their judgements and rankings privately. The AMSTAR 2 guidance document was consulted for interpreting weaknesses detected in critical and non-critical items. The rankings were later aggregated and any differences of opinion during the whole process were discussed until a consensus was reached to derive the team judgement for each systematic review. The results are reported in table 4 and reveal that the studies of Gadenz et al., (2015), Sebastianelli et al. (2017) and Ren et al. (2014) include more than one critical weakness. On the other hand, Li et al., (2015) had one critical weakness.

Table 4. Results on the methodological quality of the four systematic reviews reporting the application of rTMS in aphasia recovery based on the AMSTAR 2 checklist.

	Systematic review															
AMSTAR 2 – Checklist 16 questions	**Gadenz, et al. (2015)**				**Li, et al. (2015)**				**Ren et al. (2014)**				**Sebastianelli et al. (2017)**			
	Yes	Partial Yes	No	No meta-analysis	Yes	Partial Yes	No	No meta-analysis	Yes	Partial Yes	No	No meta-analysis	Yes	Partial Yes	No	No meta-analysis
1. Did the research questions and inclusion criteria for the review include the components of PICO? (critical)	×				×				×						×	
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (critical)			×			×					×				×	
3. Did the review authors explain their selection of the study designs for inclusion in the review? (non-critical)			×				×				×		×			
4. Did the review authors use a comprehensive literature search strategy? (critical)		×				×				×				×		
5. Did the review authors perform study selection in duplicate? (critical)	×				×				×				×			
6. Did the review authors perform data extraction in duplicate? (critical)	×				×				×				×			
7. Did the review authors provide a list of excluded studies and justify the exclusions? (critical)			×		×						×				×	
8. Did the review authors describe the included studies in adequate detail? (critical)			x			×					x				x	

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (critical)		×			×				×						×	
10. Did the review authors report on the sources of funding for the studies included in the review? (non-critical)			×				×				×				×	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? (critical)				×	×				×							×
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? (critical)				×			×			×						×
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? (critical)	×				×				×						×	
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (critical)	×				×				×				×			
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (critical)				×	×				×							×
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? (critical)	×				×						×		×			
Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.																

The findings suggest that the overall confidence in the quality of the conduct of the systematic reviews as reported in table 5 is low for one (Li et al., 2015) and critically low for the remaining three (Gadenz et al., 2015; Ren et al., 2014; Sebastianelli et al., 2017).

Table 5. Overall confidence ratings based on the characteristics of each systematic review using the AMSTAR 2 checklist.

	High (none or one non-critical weakness)	**Moderate** (more than one non-critical weaknesses)	**Low** (one critical weakness with or without other non-critical weaknesses)	**Critically low** (more than one critical weakness with or without non-critical weaknesses)
Gadenz, et al. (2015)				×
Li, et al. (2015)			×	
Ren et al. (2014)				×
Sebastianelli et al. (2017)				×

Discussion

The aim of this study was to evaluate the quality of the conduct of four (4) systematic reviews on RCTs that assess the effects of rTMS for post-stroke aphasia rehabilitation. According to Shea et al. (2017, p.1) 'systematic reviews provide an opportunity to base decisions on accurate, succinct, credible and comprehensive summaries of the best available evidence on the topic'. Our goal was to determine if the systematic reviews regarding the application of rTMS to facilitate functional improvement in aphasia are of high quality based on the AMSTAR 2 criteria and whether the translational implications of rTMS on language recovery after stroke is consistent and reliable across the systematic reviews. We address our research questions below.

With regards to our first question on the quality of each systematic review (how they were planned and conducted) as evaluated using the AMSTAR 2 instrument, the results are very discouraging. The finding based on our aggregated confidence ratings was that the overall quality of the conduct of the systematic reviews was in the low

range. The systematic review by Li et al. (2015), in which a meta-analysis was performed, was of low quality because the authors failed to assess the potential impact of risk-of-bias (ROB) in the individual studies on their results given they had included RCTs of variable quality. The systematic reviews by Gadenz et al. (2015), Ren et al. (2014) and Sebastianelli et al. (2017) were of critically low quality because of several flaws in critical domains that significantly weaken the confidence that can be placed in this body of work. For example, none reported the methods for the review before the review commenced, and nor did they provide a list of excluded studies and justify the exclusions. Furthermore, Gadenz et al. (2015) and Ren et al. (2014) failed to describe the included studies in adequate detail and only provided brief summaries on the description of participants, interventions, controls, outcomes, design and analysis across the primary studies. For example, regarding PWA, there was no information on education, employment, socioeconomic status, ethnicity and any co-morbidities, all variables that could have influenced the results of the treatment. Also, Ren et al. (2014) and Sebastianelli et al. (2017) failed to account for risk of bias in individual studies when interpreting and discussing the results.

With regards to the second question on the consistency of the reported evidence concerning the effects of rTMS on post-stroke aphasia across the systematic reviews, the results are most discouraging given the irregularities in the reporting of the data across the same studies. To highlight this critical issue, we take the study of Seniow et al. (2013) reported in all 4 systematic reviews as our comparison study, and note the following in relation to, for example, the PWA descriptors:

- Gadenz et al. (2015) report that all participants were right handed, whereas no data for handedness for the same study are reported by Li et al. (2015);
- Sebastianelli et al. (2017) and Li et al. (2015) report no data on the type of stroke;
- Ren et al. (2014) did not report aphasia type;
- Li et al. (2015) provided inaccurate mean age and mean time post-stroke data
- Li et al. (2015) and Ren et al. (2014) did not report the sex of participants;
- The number of drop-outs in the Seniow et al. (2013) study were not reported in the systematic review by Sebastianelli et al. (2017) nor by Li et al. (2015).

In the same way, there were differences between the systematic reviews in relation to reports from the primary studies on the exact timeline of the rTMS treatment. Within the systematic reviews, there were studies for which treatment was over a period of two to three weeks (weekends excluded), whereas for other studies, treatment was conducted over consecutive days. Only Ren et al. (2014) report treatment timing details accurately.

Moreover, information on stimulation parameters across the systematic reviews was missing. For example, the type of coil used for rTMS was not reported by Sebastianelli et al. (2017) and Li et al. (2015) for the studies included in their respective systematic reviews. Likewise, there were inaccuracies in the reported site of stimulation for studies across all four systematic reviews. For example, Sebastianelli et al. (2017) mention that in the study of Tsai et al. (2014), the site of stimulation was the dorsal anterior pTr, whereas for the same study, Li et al. (2015) cite that the stimulation site was pTr generally. Also, Gadenz et al. (2015) and Sebastianelli et al. (2017) cite that in the Waldowski study (2012) the stimulation site was Broca's homologue (this includes pTr and pOp). This was indeed the site of stimulation, but Ren et al. (2014) report that the site of stimulation for this study was the pTr only. There were also discrepancies in the reports on outcome measures used in the primary studies. For example, Sebastianelli et al. (2017) cite outcome measures for only 3 out of their 11 included studies. Finally, no systematic review reported data from their included studies on first, the methods used to localize the region of interest (RoI) for brain stimulation and second, on the definition of resting motor threshold (RMT).

Our third question on the subject of strong and reliable evidence regarding the positive effects of rTMS for rehabilitation of aphasia post-stroke, based on the quality of conduct of the systematic reviews, the findings are inconclusive. Gadenz et al. (2015) report controversial results from their included studies. Some PWA improved and in different linguistics domains but others did not (see table 3). Li et al. (2015) who performed an additional meta-analysis found that performance in naming improved with changes in brain excitability, but not repetition and auditory comprehension. The researchers contend that low-frequency rTMS in the right

hemisphere is effective in terms of naming and reorganization of the left-hemisphere language network. Ren et al. (2014) who also performed a meta-analysis, support the efficacy of low-frequency rTMS in the right hemisphere with regards to severity of aphasia, receptive language, naming, repetition and writing. Also, Sebastianelli et al. (2017) observed a considerable variability between studies. They found that low-frequency rTMS improves global aphasia test scores, picture naming and naming accuracy, reaction time, functional communication, and auditory comprehension. But the shift of activation to the damaged hemisphere, and response to low frequency (LF)-rTMS may vary with respect to optimal site within the pTr.

Overall, it seems that the evidence from the quality of conduct of the systematic reviews regarding the positive effects of rTMS on improving post-stroke aphasia is inconclusive for two reasons. First, not all PWA reported in the primary studies included and analysed in the four systematic reviews had shown improvement in language performance post-treatment. Second, language gains for PWA who did show improvement seemed to correlate with other (non-linguistic) parameters, such as the severity and type of aphasia at baseline, the site of the lesion and the elapsed time between treatment and assessment.

Summing up the results of the four published systematic reviews on the topic leaves us with more questions than answers. For example, why do some PWA respond positively to brain stimulation and others do not? Amongst those who benefit, who benefits the most and why? How important is the neural location and extent of the lesion?

There is a crucial need for rigorous research to verify rTMS induced behavioural-language change in PWA with different types and severity of aphasia. In particular, the distinctive types of neuromodulation (excitatory/inhibitory), the potentially effective stimulation sites and optimal parameters, the effect of the duration, and the long-term impact remain challenges to the field. With regards to the latter, only a few RCTs reported follow-up times, something that does not allow for the evaluation of long-term, if any, effects of rTMS on post-stroke aphasia rehabilitation. From our reading of literature, there is evidence that functional changes induced by inhibitory

rTMS may occur over a period of many months (Seniow et al. 2013; Waldowski et al., 2012; Martin et al., 2009), therefore post-treatment follow-up assessments should be carried out to measure progress over time. Also, the four systematic reviews included RCTs that applied only low-frequency rTMS. There was one exception, a review of one out of eleven studies (Khedr et al., 2014), that used dual hemispheric rTMS. Such TBS paradigms are currently being explored and appear a most promising innovative approach as positive results in aphasia recovery are surfacing (e.g. Griffis et al., 2016; Vuksanovic et al., 2015). For this reason, RCTs applying high frequency rTMS, bihemispheric stimulation (inhibition and excitation), and TBS paradigms need to be explored further to determine whether such protocols are superior, equally or less effective than low-frequency rTMS.

Likewise, the possible contribution of rTMS to pharmacological treatments or whether rTMS could serve as a standalone treatment or should only be given as an adjunct to SLT are areas requiring further investigation. Future studies should compare PWA receiving rTMS with SLT with PWA receiving rTMS without SLT. Providing SLT to rTMS as an adjunct treatment to rTMS may have a truly synergic action but it can also mask the actual therapeutic effects of rTMS.

As most RCTs have included right handed patients with first-time ischemic stroke, the evidence may not applicable to left handed stroke patients or those with hemorrhagic stroke. Furthermore, results from the systematic reviews were not subgrouped by aphasic severity and syndrome and there is a need to see whether severity and type of aphasia is a determining factor for the effectiveness of rTMS applications on language recovery (Boyd et al., 2017). Future studies should apply accurate methods of localization of regions of interest. Neuronavigation systems are incorporated in most rTMS equipments and allow for precise localization. It is also suggested that studies use the same outcome measures, as different outcome measures do not allow, or make comparison of outcomes between studies challenging (Walker et al., 2017). Currently, the fact that various scales are used across studies shows that there is lack of consensus with regards to which aphasia scale is the most appropriate. The Boston Diagnostic Aphasia Examination (BDAE: Goodglass, Kaplan & Barresi, 2001) is widely used in clinical trials (Berthier, 2005). It is therefore suggested that amongst

other scales, researchers also administer the BDAE to decrease outcome measure heterogeneity.

Finally, specific functional markers and biomarkers of good responders to brain stimulation treatments need to be explored and established as previous studies (e.g. Seniow et al., 2013; Martin et al., 2009) have demonstrated that not all patients with aphasia respond to inhibitory rTMS over the right hemisphere. Combining rTMS with methodologically advanced fMRI techniques in large-scale RCTs may elucidate biomarkers of brain pathology or treatment induced neurophysiological changes (see Calhoun, Kiehl & Pearlson, 2008). This will lead to individually tailored rTMS protocols and increased treatment efficacy (Kubis, 2016).

Conclusions

In the field of stroke rehabilitation, systematic reviews on the use of noninvasive brain stimulation (NIBS) methods for treatment of aphasia are based on very small numbers, and well-conducted clinical trials are scarce, suggesting that currently there is not sufficient evidence to draw solid conclusions on the positive effects of NIBS on language recovery after stroke.

The present overview of systematic reviews on the application of rTMS for language recovery post-stroke identifies the serious need for more research with methodological rigor. Without high quality published descriptions of rTMS interventions researchers cannot replicate and build on research findings, and clinicians cannot reliably implement interventions that may have potential benefit for people with post-stroke aphasia.

"Disclosure of interest"

The authors report no conflict of interest.

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CHAPTER 3: Transcranial Magnetic Stimulation in post-Stroke Aphasia Rehabilitation: A Systematic Review of the Literature (to be submitted to journal after viva)

Chapter 2 provided an overview of existing reviews on the use of rTMS for post-stroke chronic aphasia rehabilitation. Critical appraisal of the reviews identified four reviews that had used a systematic approach to assess the overall level of evidence. The analysis revealed that the overall quality of conduct of the four published systematic reviews of RCTs on the application of rTMS for post-stroke aphasia rehabilitation is exceptionally poor. The overview of reviews therefore identified a need to conduct an up-to-date systematic review of the literature on rTMS for post-stroke chronic aphasia rehabilitation. Hence, a systematic review was conducted. This chapter describes the process of the systematic review and discusses findings regarding rTMS for the rehabilitation of post-stroke chronic aphasia.

Introduction

Aphasia is the most common language disorder caused by stroke and afflicts more than a third of all stroke survivors (Brady, Kelly, Godwin, Enderby & Campbell, 2012). Several patient related factors (age, gender, handedness, intelligence, education and socioeconomic status) and stroke related features (lesion site and size, and initial severity) have been identified as potentially influential indices in poststroke aphasia rehabilitation (Yu, Jiang, Jia, Xiao & Zhou, 2017). People with aphasia receive speech and language therapy (SLT) to improve their language deficits as SLT is considered the mainstream and mainstay treatment for aphasia. Even though aphasia therapy leads to substantial communication improvement (Brady et al., 2012); 43% of patients that undergo aphasia rehabilitation still present with aphasia 18 months post-stroke (Laska et al., 2001).

The advent of non-invasive brain stimulation (NIBS) techniques has opened new windows in post-stroke language rehabilitation. Transcranial magnetic stimulation (TMS) is one such technique that has been used to facilitate neuroplasticity in post-stroke aphasia. Through electromagnetic induction, the TMS coil induces weak and

brief electric currents in the brain that are analogous to the rate of change of the current in the coil (Roth, Padberg & Zangen, 2007). Depending on the frequency, intensity, and duration of the stimulation, TMS can lead to transient increases or decreases in excitability of the stimulated cerebral area. Repetitive TMS (rTMS) is the term used to describe the delivery of TMS pulses in trains. Low rTMS frequencies (below 5 Hz) can suppress brain excitability and higher frequencies (5-20 Hz) lead to an increase in cortical excitability (Kobayashi & Pascual-Leone 2003).

Currently, we lack evidence on the neurophysiological rTMS related mechanisms that are involved in speech and language gains. Suppression and increase in cortical excitability that are induced by rTMS may reflect basic synaptic mechanisms, such as long-term potentiation (LTP) (i.e. persistent strengthening of synapses) and/or long-term depression (LTD) (i.e. long-lasting decrease in synaptic strength) plasticity (Huang et al., 2017). Currently, those synaptic mechanisms are believed to be related to speech and language gains in rTMS research and the network approach (Thiel & Zumbansen, 2016) gives a possible explanation for this claim. According to this model, speech and language are organised in distributed networks across the two brain hemispheres. Transcallosal inhibition and activation allow the two hemispheres to cooperate to support speech and language processes. In the event of a left hemispheric stroke that affects speech and language areas (e.g. Broca's area), transcallosal inhibition, that normally takes place in the unaffected brain, is decreased and causes the contralateral (homologous) speech and language areas to overactivate. This is considered maladaptive as it blocks the reactivation of brain areas of the dominant hemisphere that support speech and language processes. Thus, applying low-frequency rTMS on homotopic speech and language areas may reduce the overactivation of contralateral brain areas and this way allow speech and language areas of the dominant hemisphere to increase their neuronal activity to support speech and language processes.

Even if rTMS is believed to be safe when applied within updated safety guidelines (Rossi et al., 2009), it can still cause adverse side effects. The most perilous acute rTMS related risk is a seizure that can happen during rTMS conditioning and less dangerous but more common side effects include headache and neck pain (Oberman,

Edwards, Eldaief & Pascual-Leone, 2011). Reports of adverse events have urged researchers to update prior guidelines (Wassermann, 1998), producing a Consensus Statement reached at the Sienna Meeting (Rossi et al., 2009). This Statement involves information about asynchronous trains, such as TBS, but does not include recommendations for parameters such as maximum duration or intensity of such type of conditioning. In 2011, Oberman et al. reviewed adverse effects related to TBS and concluded that theoretically, TBS has the potential of causing a higher risk of seizures compared to other rTMS protocols because it delivers high frequency bursts. Nonetheless, its safety profile is similar to that of other rTMS paradigms. Since TBS is a relatively new method, it should be used with caution and more studies are needed to associate adverse effects with TBS parameters (e.g. intensity, frequency and location).

The growth rate of scientific publications on the potential effectiveness of rTMS for post-stroke aphasia rehabilitation has increased over the last decade. Nonetheless, findings are controversial. The aim of this review was to examine systematically all the published randomised controlled trials (RCTs) of rTMS on post-stroke aphasia rehabilitation to provide rigorous, transparent and comprehensive summaries of the best available evidence on this topic. The objective of this study was to assess the efficacy of rTMS in the field of post-stroke aphasia rehabilitation. We used AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) (Shea et al., 2017) as our guide for planning and conducting our review. AMSTAR 2 is a published critical appraisal tool that evaluates the quality of conduct of systematic reviews for healthcare interventions.

Methods

Predetermined written criteria for considering studies for this systematic review

We included only published RCTs in which rTMS treatment was compared to sham rTMS for post-stroke aphasia rehabilitation. Only studies that applied unilateral stimulation of any rTMS protocol (i.e. excitatory, inhibitory, TBS) were considered for evaluation. One-real-rTMS-session-cross-over studies and studies that applied bilateral stimulation were excluded. This was done to maximise the comparability of studies and to minimize confounding stimulation effects introduced by the application

of multiple rTMS paradigms in one intervention. We evaluated the following comparisons:

1. rTMS as a standalone treatment compared to sham rTMS alone
2. rTMS as an add-on treatment compared to sham rTMS as an add-on treatment

For a study to be eligible for evaluation, the trials reported in this review had to fulfil a number of predetermined criteria as reported below. Studies should have recruited:

- at least four participants of any age and sex;
- participants that had suffered a left hemispheric stroke;
- participants that were in the acute, subacute or chronic stage;
- participants who exhibited post-stroke aphasia of any type and severity

Standardized aphasia scales (e.g. Boston Diagnostic Aphasia Examination; Aachen Aphasia Test) and discourse productivity analysis were considered primary outcome measures. Quality of life measurements (e.g. Stroke and Aphasia Quality of Life scale-39 item (SAQOL-39g)) and adverse outcomes (e.g. fatigue, headache, dizziness, nausea, seizure, etc.) were considered secondary outcome measures. Studies had to be published in English, French or Italian language.

Search Methods and Selection of Studies

We reviewed articles published with the 27th of July 2017 as a cut-off date in Scopus, CINAHL and PubMed. Also, all reference lists of the included articles were screened for eligibility. In stage one, all identified records were screened, by two independent researchers, at title and abstract level using the pre-defined eligibility criteria and in stage two; full texts of all articles meeting the eligibility criteria were retrieved for evaluation by the same researchers that have subject and methodological knowledge. Differences of opinion during the whole process were discussed until a consensus was reached.

Assessment of risk of bias in included studies

To assess the methodological quality of the included papers, the guidelines as described in the Cochrane Handbook for Systematic Reviews of Interventions

(Higgins, Altman & Sterne, 2011) were followed. The Cochrane's tool for assessment of risk of bias evaluates the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias, and for each individual domain, classifies studies into low, unclear, or high risk of bias. Two independent researchers assessed the methodological quality of the included studies. Unanimous agreement was required for quality appraisal for all studies. Where differences of opinion occurred, the papers of conflict were discussed until a consensus was reached.

Key themes

We organized reporting of findings in seven key themes: (1) demographic information; (2) stimulation parameters (method of determination of RMT, % RMT, frequency, duration of stimulation, number of sessions, timeline of treatment); (3) stimulation site; (4) method of localization of stimulation site; (5) characteristics/approach of adjuvant SLT; (6) outcome measures and durations of follow-ups and; (7) risk of bias.

Results

Results of the Search

Overall, 270 entries (after duplicates removal) were identified and screened at title and abstract level, 35 articles were selected for full-text analysis and, 11 articles were finally included in the review according to the eligibility criteria (figure 1). Table 1 shows the search strategies in PubMed, CINAHL and Scopus. Table 2 involves the list of the excluded studies and justifications for their exclusion from analysis.

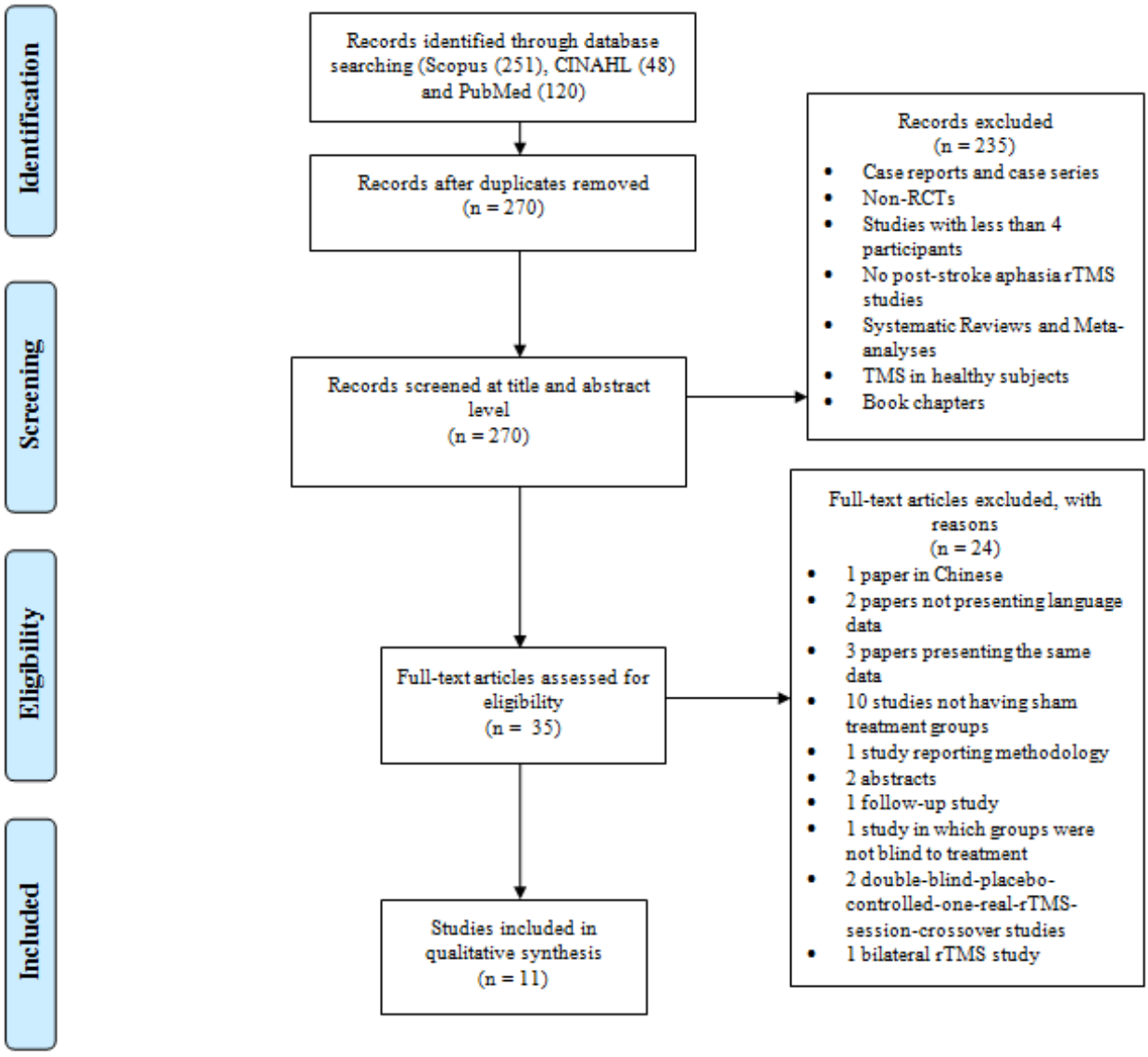


Figure 1. PRISMA flowchart used to identify studies to be included in the qualitative analysis

Table 1: Search strategies used to access relevant RCTs from each database on the application of transcranial magnetic stimulation (TMS) for post-stroke aphasia rehabilitation.

PubMed	((((aphasia[Title/Abstract] OR "Aphasia"[Majr])) AND ("Transcranial Magnetic Stimulation"[Majr] OR "transcranial magnetic stimulation"[Title/Abstract] OR TMS[Title/Abstract] OR "theta burst stimulation" OR TBS))) NOT ("transcranial direct current stimulation" OR TDCS)
CINAHL	((MM "Aphasia") OR TI aphasia OR AB aphasia) AND ((MM "Transcranial Magnetic Stimulation") OR TI (transcranial magnetic stimulation OR tms OR theta burst stimulation or TBS) OR AB (transcranial magnetic stimulation OR tms OR theta burst stimulation or TBS)) NOT (transcranial direct current stimulation OR TDCS)
Scopus	(TITLE-ABS-KEY (aphasia) AND TITLE-ABS-KEY ("transcranial magnetic stimulation" OR TMS OR "theta burst stimulation" OR TBS) AND NOT TITLE-ABS-KEY ("transcranial direct current stimulation" OR TDCS)

Table 2: A list of the research articles excluded from the analysis, and the justification for their exclusion.

List of excluded articles	Justification for exclusion
1. Abo, M., Kakuda, W., Watanabe, M., Morooka, A., Kawakami, K., & 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.	No sham treatment group
2. Barwood, C. H. S., Murdoch, B. E., Whelan, B. M., Lloyd, D., Riek, S., O'Sullivan, J. D., … 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*, 935-943.	Same data as in Barwood et al. (2013)
3. Barwood, C. H. S., Murdoch, B. E., Whelan, B. M., Lloyd, D., Riek, S., O'Sullivan, J. D., … Wong, A. (2011). Modulation of N400 in chronic non-fluent aphasia using low frequency Repetitive Transcranial Magnetic Stimulation (rTMS). *Brain and Language, 116*(3), 125-135.	No language data – same sample as in Barwood et al. (2013)
4. Barwood, C. H. S., Murdoch, B. E., Whelan, B. M., Lloyd, D., Riek, S., O'Sullivan, J., … 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.	Same data as in Barwood et al. (2013)
5. Barwood, C. H. S., Murdoch, B. E., Whelan, B. M., O'Sullivan, J. D., Wong, A., Lloyd, D., … Coulthard, A. (2012). Longitudinal modulation of N400 in chronic non-fluent aphasia using low-frequency rTMS: A randomised placebo controlled trial. *Aphasiology, 26*(1), 103-124.	No language data – same sample as in Barwood et al. (2013)
6. Barwood, C., Murdoch, B., Whelan, B. M., Lloyd, D., Riek, S., & O'Sullivan, J. D. (2010). Repetitive Transcranial Magnetic Stimulation (rTMS) and Sham Modulation of Language Function in Non-fluent Aphasia 2 Months Post Stimulation. *Procedia Social and Behavioral Sciences, 6*, 233-234.	Not a full paper
7. Garcia, G., Norise, C., Faseyitan, O., Naeser, M. A., & Hamilton, R. H. (2013). Utilizing Repetitive Transcranial Magnetic Stimulation to Improve Language Function in Stroke Patients with Chronic Non-fluent Aphasia. *Journal of Visualized Experiments*, (77), 1-7.	Detailed steps for identifying a responsive target site in the right hemisphere in patients with chronic non-fluent aphasia
8. Cheng, Y., N., Wang, J., & Song, W. Q. (2014). Effects of low-frequency repetitive transcranial magnetic stimulation on picture naming of non-fluent aphasia in patients with stroke. *Chinese Journal of Cerebrovascular Diseases, 11*(3), 148-151.	paper in Chinese
9. Chieffo, R., Ferrari, F., Battista, P., Houdayer, E., Nuara, A., Alemanno, F., … 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*	double-blind-placebo-controlled-one-real-rTMS-session-crossover study

Repair, *28*(3), 291-298.	
10. Griffis, J. C., Nenert, R., Allendorfer, J. B., & Szaflarski, J. P. (2016). Interhemispheric Plasticity following Intermittent Theta Burst Stimulation in Chronic Poststroke Aphasia. *Neural Plasticity, 2016*, 20-23.	No sham treatment group
11. Hara, T., Abo, M., Kakita, K., Mori, Y., Yoshida, M., & 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.	No sham treatment group
12. Hara, T., Abo, M., Kobayashi, K., Watanabe, M., Kakuda, W., & Senoo, A. (2015). Effects of Low-Frequency Repetitive Transcranial Magnetic Stimulation Combined with Intensive Speech Therapy on Cerebral Blood Flow in Post-Stroke Aphasia. *Translational Stroke Research*, *6*, 365-374.	No sham treatment group
13. Harvey, D. Y., Podell, J., Tukeltaub, P. E., Faseyitan, O., Coslett, B., & Hamilton, R. H. (2017). Functional Reorgranization of Right Prefrontal Cortex Underlies Sustained Naming Improvements in Chronic Aphasia via Repetitive Transcranial Magnetic Stimulation. *Cognitive and Behavioral Neurology, 30*, 133-144.	No sham treatment group
14. Ilkhani, M., Baghini, H. S., Kiamarzi, G., Meysamie, A., & Ebrahimi, P. (2017). The effect of low-frequency repetitive transcranial magnetic stimulation (rTMS) on the treatment of aphasia caused by cerebrovascular accident (CVA). *Medical Journal of The Islamic Republic of Iran (MJIRI)*, *31*, 1-5.	No sham treatment group
15. Kakuda, W., Abo, M., Momosaki, R., & Morooka, A. (2011). Therapeutic application of 6-Hz-primed low-frequency rTMS combined with intensive speech therapy for post-stroke aphasia. *Brain Injury*, *25*(12), 1242-1248.	No sham treatment group
16. Khedr, E. M., Abo El-Fetoh, N., Ali, A. M., El-Hammady, D. H., Khalifa, H., Atta, H., & 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.	Bilateral rTMS
17. Kindler, J., Schumacher, R., Cazzoli, D., Gutbrod, K., Koenig, M., Nyffeler, T., … 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.	double-blind-placebo-controlled-one-real-rTMS-session-crossover study

18. Lin, W. S., & Tsai, P. Y. (2018). Inhibitory RTMS in post-stroke non-fluent aphasia facilitates functional brain changes and language recovery: An FMRI study. *Annals of Physical and Rehabilitation Medicine*, *61*, e47-e48.	Abstract
19. Martin, P. I., Naeser, M. A., Theoret, H., Tormos, J. M., Nicholas, M., Kurland, J., … Pascual-Leone, A. (2004). Transcranial magnetic stimulation as a complementary treatment for aphasia. *Seminars in Speech and Language*, *25*(2), 181-191.	No sham treatment group
20. Medina, J., Hamilton, R. H., Norise, C., Turkeltaub, P. E., & Coslett, H. B. (2011). Transcranial magnetic stimulation improves discourse productivity in individuals with non-fluent aphasia. *Procedia - Social and Behavioral Sciences*, *23*, 167-168.	Abstract
21. Szaflarski, J. P., Griffis, J., Vannest, J., Allendorfer, J. B., Nenert, R., Amara, A. W., … Zhou, X. (2018). A feasibility study of combined intermittent theta burst stimulation and modified constraint-induced aphasia therapy in chronic post-stroke aphasia. *Restorative Neurology and Neuroscience*, *36*, 503-518.	No sham treatment group
22. Winhuisen, L., Thiel, A., Schumacher, B., Kessler, J., Rudolf, J., Haupt, W. F., & Heiss, W. D. (2007). The right inferior frontal gyrus and poststroke aphasia: A follow-up investigation. *Stroke*, *38*(4), 1286-1292.	Follow-up study
23. Winhuisen, L., Thiel, A., Schumacher, B., Kessler, J., Rudolf, J., Haupt, W. F., & Heiss, W. D. (2005). Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: A combined repetitive transcranial magnetic stimulation and positron emission tomography study. *Stroke*, *36*(8), 1759-1763.	No sham treatment group
24. Yoon, T. H., Han, S. J., Yoon, T. S., Kim, J. S., & Yi, T. I. (2015). Therapeutic effect of repetitive magnetic stimulation combined with speech and language therapy in post-stroke non-fluent aphasia. *NeuroRehabilitation*, *36*(1), 107-114.	Groups not blind to treatment

Summary of included studies

In summary, the 11 included studies, published from 2011 to 2018, included 130 adult controls and 149 adults assigned to experimental groups for the investigation of the efficacy of rTMS for aphasia rehabilitation post-stroke. Details of all studies' characteristics are provided in table 3.

Table 3: Detailed summary of the method and results of the research studies on the application of rTMS in post-stroke aphasia rehabilitation included in the present systematic review.

First author and year of publication	Experimental group(s)	Intervention	Control group(s)	Outcome Measures & Assessment Timeline	Major findings	Side effects and number of dropouts
Haghighi et al. (2018)	Group 1: 6 participants (3 males + 3 females); mean age (years): 61.67 ± 7.06; number of strokes in the past 12 months: 0.67 ± 0.52; stroke type: no data; localization: left hemisphere (6); Broca's aphasia (6); severity: no data; time since onset of stroke (weeks): 4-8; right-handed (6); education: no data	Group 1 (LF-rTMS + SLT): f8c coil; 1 Hz rTMS to the right homologue of Broca's area; 100% RMT; 20 min per day (session); 10 sessions in total, 5 days per week, 2 weeks in total with SLT SLT: 45 min, 5 days per week, 2 weeks in total	Group 2 (sham rTMS + SLT): 6 participants (2 males + 4 females); mean age (years): 60.5 ± 11.85; number of strokes in the past 12 months: 0.5 ± 0.56; stroke type: no data; localization: left hemisphere (6); Broca's aphasia (6); severity: no data; time since onset of stroke (weeks): 4-8; right-handed (6); education: no data SLT: 45 min, 5 days per week, 2 weeks in total	Farsi version of the WAB-R before and after treatment	Immediately post-rTMS: experimental vs control: significant improvements in content, fluency, command comprehension, repetition and severity of aphasia;	No data regarding side effects 0 dropouts
Hu et al. (2018)	Group 1: 10 participants (7 males + 3 females); mean age (years): 46.5 ± 12.1; first ever stroke (10); stroke type: hemorrhagic (5), ischemic (5); localization: Broca's area (10); non-fluent aphasia (10); severity: no data; mean time since onset of stroke (months): 7.1 ± 2.7; right-handed (10);	Group 1 (HF-rTMS + SLT): f8c coil; 10 Hz rTMS to the right homologue of Broca's area; 80% RMT; 10 min per day (session); 10 sessions in total, with SLT	Group 3 (sham rTMS + SLT): 10 participants (5 males + 5 females); mean age (years): 50.7 ± 10.4; first ever stroke (10); stroke type: hemorrhagic (5), ischemic (5); localization: Broca's area (10); non-fluent aphasia (10); severity: no data; mean time since onset of stroke (months): 6.8 ± 2.3;	Chinese version of the WAB before treatment, after treatment and 2 months post treatment	Immediately post-rTMS: LF-rTMS vs all 3 groups: improvement in spontaneous speech, comprehension, and severity of aphasia. Naming abilities were also improved in the LF group vs	1 patient reported dizziness during the first treatment 0 dropouts

	education: primary school (1), secondary school (8), University (1) Group 2: 10 participants (6 male + 4 female); mean age (years): 48.5 ± 11.2; first ever stroke (10); stroke type: hemorrhagic (4), ischemic (6); localization: Broca's area (10); non-fluent aphasia (10); severity: no data; mean time since onset of stroke (months): 7.5 ± 3.2; right-handed (10); education: primary school (1), secondary school (7), University (1)	Group 2 (LF-rTMS + SLT): f8c coil; 1 Hz rTMS to the right homologue of Broca's area; 80% RMT; 10 min per day (session); 10 sessions in total, with SLT SLT: once a day for 30 min, 10 days in total	right-handed (10); education: primary school (1), secondary school (6), University (3) Group 4 (control: SLT): 10 participants (6 male + 4 female); mean age (years): 47.3 ± 9.8; first ever stroke (10); stroke type: hemorrhagic (4), ischemic (6); localization: Broca's area (10); non-fluent aphasia (10); severity: no data; mean time since onset of stroke (months): 7.7 ± 3.4; right-handed (10); education: primary school (1), secondary school (6), University (3) SLT: once a day for 30 min, 10 days in total		the sham and control groups. HF vs control group: improvement in repetition. Follow-up: LF vs control: improvement in spontaneous speech, comprehension, repetition and naming. LF vs HF: improvement in spontaneous speech. LF vs sham: improvement in comprehension. HF vs control groups: improvement in severity of aphasia and repetition.	

Rubi-Fessen et al. (2015)	Group 1: 15 participants (5 males + 10 females); mean age (years): 67.9 ± 8.12; first ever stroke (15); stroke type: ischemic (15); localization: LMCA (15); Broca's aphasia (2), Wernicke's aphasia (8), Anomic aphasia (3), Global aphasia (2); mild (5), moderate (6), severe (4); mean time since onset of stroke (days): 41.47 ± 21.51; right-handed (15), education: no data	Group 1 (HF-rTMS + SLT): f8c coil; 1 Hz rTMS to the right pTr; 90% RMT; 20 min per day (session); 10 daily sessions in total, spread in 2 weeks, followed by 45 min of SLT (each time)	Group 2 (sham rTMS + SLT): 15 participants (9 males + 6 females); mean age (years): 69.6 ± 6.67; first ever stroke (15); stroke type: ischemic (15); localization: LMCA (15); Broca's aphasia (4), Wernicke's aphasia (5), Anomic aphasia (4), Global aphasia (2); mild (6), moderate (7), severe (2); mean time since onset of stroke (days): 41.47 ± 21.51; right-handed (15), education: no data SLT: 45 minutes, 5 days per week, 2 weeks in total	1 day before and 1 day after treatment: AAT; 60 items from Snodgrass & Vanderwart picture naming inventory (1980); ANELT-A; FIM (comprehension and expression)	Immediately post-rTMS: LF-rTMS vs sham group: significant improvement in aphasia profile score, written language, naming, comprehension and; verbal communication abilities	No data regarding side effects 0 dropouts
Wang et al. (2014)	Group 1: 15 participants (14 males + 1 female); mean age (years): 61.3 ± 13.2; first ever stroke (15); stroke type: ischemic (15); localization: LMCA (15); Broca's aphasia (9), Transcortical motor (4), Global aphasia (2); severity: no data; mean time since onset of stroke (months): 16.8 ± 6.4; right-handed (15), education (years): 11.5 ± 4.8 Group 2: 15 participants (13 males + 2 female); mean age	Group 1 (LF-rTMS + synchronous computerised naming training): f8c coil; 1 Hz rTMS to the right pTr; 90% RMT; 20 min per day (session); 10 daily sessions in total, on top of that: 60-minute SLT twice a week Group 2 (LF-rTMS	Group 3 (sham rTMS + synchronous computerised naming training, on top of that: 60-minute SLT twice a week): 15 participants (13 males + 2 female); mean age (years): 60.4 ± 11.9; first ever stroke (15); stroke type: ischemic (15); localization: LMCA (15); Broca's aphasia (6), Transcortical motor (8), Global aphasia (1); severity: no data; mean time since onset of stroke (months): 16.1 ± 7.3; right-handed (15), education	Before the first intervention, on the day of the 10^{th} session and 3 months post-treatment: CCAT (conversation, picture description, naming of objects and their use) and;	Post-rTMS: compared to groups 2 and 3, group 1 showed significant improvements in conversation, picture description and naming. No significant differences between groups 2 and 3. Follow-up: compared to groups 2 and 3, group 1 showed	1 patient reported a dull pain that subsided after 5% reduction of stimulation intensity 2 dropouts at follow-up (one from group

	(years): 62.1 ± 12.7; first ever stroke (15); stroke type: ischemic (15); localization: LMCA (15); Broca's aphasia (7), Transcortical motor (7), Global aphasia (1); severity: no data; mean time since onset of stroke (months): 15.7 ± 8.5; right-handed (15), education (years): 12.2 ± 3.9	+ asynchronous computerised naming training): f8c coil; 1 Hz rTMS to the right pTr; 90% RMT; 20 min per day , each session was followed by a 20-minute computerised naming training), 10 daily sessions in total, on top of that: 60-minute SLT twice a week	(years): 11 ± 4.1	20 objects and 20 action pictures from the IPND	significant improvements in naming. No significant differences between groups 2 and 3.	1 and one from group 2)

Barwood et al. (2013)	Group 1: 6 participants (4 males + 2 females); mean age (years): 60.8 ± 5.98; first ever stroke (no data); stroke type: ischemic (6); localization: LMCA (6); non-fluent (6); mild-moderate (2); moderate (1); moderate-severe (1); severe (2); mean time since onset of stroke (years): 3.49 ± 1.27; right-handed (6), education: 10 (2); 12 (1); 14 (1); 16 (1); 18 (1)	Group 1 (LF-rTMS): f8c coil; 1 Hz rTMS to the right pTr; 90% RMT; 20 min per day (session); 10 sessions in total	Group 2 (sham rTMS): 6 participants (5 males + 1 female); mean age (years): 67 ± 13.11; first ever stroke (no data); stroke type: ischemic (6); localization: LMCA (6); non-fluent (6); mild-moderate (2); moderate (2); moderate-severe (1); severe (1); mean time since onset of stroke (years): 3.46 ± 1.53; right-handed (6), education: 10 (1); 12 (1); 13 (2); 14 (1); 15 (1) 10 sessions in total	Post-treatment & follow-up assessments: 1 week, 2 months, 8 months & 1 year post-treatment BNT; BDAE (Cookie Theft picture, word comprehension, repetition, naming), 144 pictures (Snodgrass & Vanderwart (1980)	rTMS group versus sham group: significant improvements in naming accuracy, naming latency, repetition, picture description complexity and length of utterance, semantic errors on naming tasks and picture description tasks and, auditory commands –for the majority of subtests significant improvements were noticed between 2 and 8 months post-treatment and were maintained up to 12 months post-TMS	No data regarding side effects 0 dropouts
Heiss et al. (2013)	Group 1: 15 participants (male to female ratio: no data); mean age (years): 68.5 ± 8.19; first ever stroke (15); stroke type: ischemic (15); localization: anterior LMCA (3), posterior LMCA (5), subcortical (6); Broca's aphasia (2),	Group 1 (LF-rTMS + SLT): f8c coil; 1 Hz rTMS to the right pTr; 90% RMT; 20 min per day (session); 10 sessions in total,	Group 2 (sham rTMS + SLT): 15 participants (male to female ratio: no data); mean age (years): 69 ± 6.33; first ever stroke (15); stroke type: ischemic (15); localization: anterior LMCA (3), posterior LMCA (5), subcortical (6);	Post-treatment assessment: AAT (comprehension, Token Test, naming, writing,	rTMS group versus sham group: significant improvement in aphasia global score larger shift of	No data regarding side effects 0 dropouts

	Wernicke's (8), Amnestic (3), Global (2); severity: no data; mean time since onset of stroke (days): 39.7 ± 18.43; right-handed (15), education: no data	followed by 45 min of SLT	Broca's aphasia (4), Wernicke's (4), Amnestic (4), Global (2); severity: no data; mean time since onset of stroke (days): 50.1 ± 23.96; right-handed (15), education: no data 10 sessions in total, followed by 45 min of SLT	repetition, AAT global score)	network activity towards the left ipsilesional hemisphere	
Seniow et al. (2013)	Group 1: 20 participants (8 males + 12 females); mean age (years): 61.8 ± 11.8; first ever stroke (20); stroke type: ischemic (20); localization: anterior part of language area (7), posterior part of language area (9), anterior and posterior parts of language area (4); Broca's aphasia (3), Wernicke's (7), Mixed (9), Transcortical mixed (1); severity: mean ASRS: 1.9 ± 1; mean time since onset of stroke (days): 33.5 ± 24.1; right-handed (20), education years (mean): 13.3 ± 3.3	Group 1 (LF-rTMS + SLT): f8c coil; 1 Hz rTMS to the right pTr; 90% RMT; 30 min per day (session); 15 daily sessions spread over 3 weeks in total; followed by 45 min of SLT	Group 2 (sham rTMS + SLT): 20 participants (10 males + 10 females); mean age (years): 59.7 ± 10.7; first ever stroke (15); stroke type: ischemic (15); localization: anterior part of language area (4), posterior part of language area (7), anterior and posterior parts of language area (9); Broca's aphasia (3), Wernicke's (8), Mixed (8), Transcortical mixed (1); severity: mean ASRS: 1.7 ± 0.98; mean time since onset of stroke (days): 39.9 ± 28.9; right-handed (15), education years (mean): 11.6 ± 2.8 15 daily sessions spread over 3 weeks followed by 45 min of SLT	Post-treatment assessment & follow-up (15 weeks after treatment): Polish BDAE (naming, repetition, comprehension) and ASRS	rTMS group versus sham group: no significant differences in mean language test scores at any measurement immediately after treatment: rTMS subgroup with a lesion including the anterior part of language area: - trend towards improvement in naming Follow-up: patients with severe aphasia in the experimental group vs control	No side effects 2 dropouts in the follow-up

					group: - significant difference in repetition scores - trend towards significant difference in naming scores	
Thiel et al. (2013)	Group 1: 13 participants (male to female ratio: no data); mean age (years): 69.8 ± 7.96; first ever stroke (13); stroke type: ischemic (13); localization: anterior LMCA (2), posterior LMCA (4), anterior and posterior LMCA (1), subcortical (6); Broca's aphasia (1), Wernicke's (7), Global (2), Amnestic (3); severity: no data; mean time since onset of stroke (days): 37.5 ± 18.52; right-handed (13), education years (mean): no data	Group 1 (LF-rTMS + SLT): f8c coil; 1 Hz rTMS to the right pTr; 90% of daily defined RMT; 20 min per day (session); 10 daily sessions; followed by 45 min of SLT	Group 2 (sham rTMS + SLT): 11 participants (male to female ratio: no data); mean age (years): 71.2 ± 7.78; first ever stroke (11); stroke type: ischemic (11); localization: anterior LMCA (3), posterior LMCA (2), anterior and posterior LMCA (1), subcortical (5); Broca's aphasia (3), Wernicke's (5), Global (2), Amnestic (1); severity: no data; mean time since onset of stroke (days): 50.6 ± 22.63; right-handed (13), education years (mean): no data 10 sessions in total, followed by 45 min of SLT	Post-treatment assessment: AAT (comprehension, Token Test, naming, writing, repetition, AAT global score)	rTMS group versus sham group: significant improvement in aphasia global score - shift of network activity towards the left hemisphere in the rTMS group; consolidation of the right-hemispheric network in the sham group	No side effects 0 dropouts
Medina et al. (2012)	Group 1: 5 participants (3 males + 2 females); mean age (years): 60.6 ± 7.1; first ever stroke (5); stroke type:	Group 1 (LF-rTMS): f8c coil; 1 Hz rTMS to the right pTr (4), 1 Hz	Group 2 (sham rTMS): 5 participants (3 males + 2 females); mean age (years): 62.6 ± 10.1; first ever stroke	Follow-up assessment: Cookie Theft	rTMS group versus sham group: significant	No side effects 0 dropouts

	ischemic (5); localization: large MCA cortical & subcortical, including BA44, BA45 & BA47 (2), fronto-parietal cortex, subcortical, including internal capsule, basal ganglia, BA44, BA45 & BA47 (1), fronto-temporo-parietal, subcortical greater than cortical, including internal capsule, basal ganglia & thalamus, M1 & IFG spared (1), small fronto-temporo-parietal cortical and subcortical, minor involvement of corona radiate, IFG and insula spared (1); non-fluent aphasia (5); severity: mild to moderate (5); mean time since onset of stroke (months): 49.8 ± 29.6; right-handed: no data, education years (mean): 18.4 ± 3.6	rTMS to the right POr (1); 90% of daily defined RMT; 20 min per day (session); 10 daily sessions spread over 2 weeks (weekends excluded)	(5); stroke type: ischemic (5); localization: subcortical, including corona radiata, internal capsule, basal ganglia & thalamus, IFG spared (1), large MCA cortical & subcortical, including BA44, BA45 & BA47 (1), cortical & subcortical, including internal capsule, basal ganglia, thalamus, M1 and BA44, spared: BA45 & BA47 spared (1), large MCA cortical & subcortical, including BA44, BA45 & BA47 (1), fronto-temporo-parietal subcortical, including corona radiata but sparing internal capsule and deep grey structures, spared: IFG (1); non-fluent aphasia (5); severity: mild to moderate (5); mean time since onset of stroke (months): 48.6 ± 34.8; right-handed: no data, education years (mean): 14.4 ± 2.6	from BDAE: - discourse productivity (narrative words, closed-class words, open-class words) - sentence productivity - grammatical accuracy - lexical selection	improvement in the use of closed-class words of discourse productivity trend towards improvement in: narrative words, unique words, unique nouns, unique verbs, open-class words and correct information units	
Waldowski et al. (2012)	Group 1: 13 participants (6 males + 7 females); mean age (years): 62.31 ± 11.03; first ever stroke (13); stroke type: ischemic (13); localization: anterior language area (5),	Group 1 (LF-rTMS + SLT): f8c coil; 1 Hz rTMS to the right pTr and 1 Hz rTMS to the right pOp (15 minutes in	Group 2 (sham rTMS + SLT): Group 1: 13 participants (7 males + 6 females); mean age (years): 60.15 ± 10.58; first ever stroke (13); stroke type: ischemic (13); localization:	Immediately after treatment and 15 weeks post-treatment (follow-up):	rTMS group versus sham group: no significant differences in mean	No side effects 0 dropouts

	posterior language area (5), anterior and posterior language areas (3); Broca's aphasia (3), Wernicke's (2), Mixed (7), Transcortical mixed (1); severity: mean ASRS: 2.23 ± 1.01; mean time since onset of stroke (days): 28.92 ± 19.39; right-handed (13), education years (mean): 13.23 ± 3.92	each area) ; 90% of RMT; 30 min per day (session); 15 sessions in total, spread over 3 weeks (weekends excluded), followed by 45 min of SLT	anterior language area (4), posterior language area (3), anterior and posterior language areas (6); Broca's aphasia (3), Wernicke's (4), Mixed (5), Transcortical mixed (1); severity: mean ASRS: 2.08 ± 1.4; mean time since onset of stroke (days): 48.54 ± 32.33; right-handed (13), education years (mean): 11 ± 2 15 sessions in total, spread over 3 weeks (weekends excluded), followed by 45 min of SLT	CPNT, BDAE (naming, repetition, auditory comprehension), ASRS	language test scores at any measurement immediately after treatment: - trend towards improvement in average reaction time in naming rTMS subgroup with a lesion including the anterior part of language area: immediately after treatment: - trend towards greater improvement in average reaction time in naming follow-up: experimental vs controls: - significant improvement in average naming reaction time - significant	

					improvement in aphasia severity - trend towards greater improvement in naming	
Weiduschat et al. (2011)	Group 1: 6 participants (1 male + 5 females); mean age (years): 66.6 (no SD); first ever stroke (6); stroke type: ischemic or hemorrhagic (6); localization: posterior superior temporal gyrus (1), putamen, external capsule, posterior insula (1), posterior superior temporal gyrus, angular gyrus (1), frontal operculum, posterior inferior frontal gyrus, anterior insula (1), putamen, external capsule, anterior insula (1), posterior superior temporal gyrus, angular gyrus (1); Wernicke's aphasia (4), Global (1), Amnestic (1); severity: no data; mean time since onset of stroke (days): 45.2 (no SD); right-handed (6), education years (mean): no data	Group 1 (LF-rTMS + SLT): f8c coil; 1 Hz rTMS to the right pTr; 90% of daily defined RMT; 20 min per day (session); 8-10 sessions spread over 2 weeks (weekends excluded); followed by 45 min of SLT Mean decreases in intensity in 2 participants: 15% (on 2 out of 10 sessions) and 30% (on 7 out of 10 sessions)	Group 2 (sham rTMS + SLT): 4 participants (4 males); mean age (years): 63.75 (no SD); first ever stroke (4); stroke type: ischemic or hemorrhagic (4); localization: frontal operculum, inferior precentral gyrus (1), supramarginal gyrus, posterior superior temporal gyrus (1), entire MCA territory (1), frontal operculum, posterior inferior frontal gyrus, anterior insula (1); Wernicke's aphasia (1), Global (1), Broca's (2); severity: no data; mean time since onset of stroke (days): 57.5 (no SD); right-handed (4), education years (mean): no data 8-10 sessions in total, followed by 45 min of SLT	Post-treatment assessment: AAT (spontaneous language production, Token Test, comprehension of spoken and written language, confrontation naming, writing, repetition, AAT total score)	rTMS group versus sham group: significant improvement in aphasia profile score greater right hemispheric activity in the sham group	No side effects – 0 dropouts

Key: RCT: randomised control trial; yo: years old; vs: versus; HF-rTMS: high frequency rTMS; LF-rTMS: low frequency rTMS; RMT: Resting Motor Threshold; IFG: inferior frontal gyrus; pTr: pars Triangularis; pOp: pars Opercularis; POr: pars Orbitalis; LMCA: left middle cerebral artery; SLT: Speech & Language Therapy; WAB: Western Aphasia Battery; WBA-R: Western Aphasia Battery-Revised; AAT: Aachen Aphasia Test; ANELT-A: Amsterdam-Nijmegen Everyday Language Test-A scale; FIM: Functional Independence Measure; K-WAB: Korean Western Aphasia Battery; CCAT: Concise Chinese Aphasia Test; IPND: International Picture Naming Database; ASRS: Aphasia Severity Rating Scale; BDAE: Boston Diagnostic Aphasia Examination; f8c: figure of 8; BA: Brodmann's area; CPNT: Computerized Picture Naming Test; SD: standard deviation

Outcomes

The major findings with regards to the effectiveness of rTMS on language gains post-stroke varied. In summary, with regards to short-term effects, all studies but two (Seniow et al., 2013, Waldowski et al., 2012) found significant improvement in at least some, if not all, language measures in the experimental versus control groups (see table 3-3). Seniow et al. (2013) and Waldowski et al. (2012) did not find any significant differences in mean language test scores at any measurement between the experimental and control groups post-treatment. Seniow et al. (2013) further found that in the experimental group, participants with anterior lesions showed a trend towards improvement in naming. Waldowski et al. (2012) found a trend towards improvement in average reaction time in CPNT in the experimental versus control group and a trend towards greater improvement in average reaction time in naming in favor of the experimental subgroup with a lesion including the anterior part of language area compared to the rest of participants in the experimental group. At the follow-up stage, Hu et al. (2018) found significant improvement in several language domains in the experimental vs control groups; Wang et al. (2014) showed significant improvements in IPND naming in the experimental versus control group; Seniow et al. (2013) found significant improvement in repetition scores and a trend towards improvement in naming scores only in participants with severe aphasia belonging to the experimental group; Medina, Hamilton, Norise, Turkeltaub and Coslett (2012) found significant improvement in the use of closed-class words of discourse productivity and a trend towards improvement in other word classes in the experimental versus control group and; Waldowski et al. (2012) found significant improvements in average reaction time and ASRS ratings and a trend towards improvement in naming in favor of the rTMS group. Barwood et al. (2013) reported significant improvements in naming and other expressive language behaviours up to 12 months post-TMS (see table 3-3).

Dropouts and side effects

With regards to dropouts, two studies reported two dropouts each at the follow-up stage (Wang et al., 2014; Seniow et al., 2013). Regarding side effects, Haghighi et al. (2018), Barwood et al. (2013), Heiss et al. (2013) and Rubi-Fessen et al. (2015) did not provide any data; Hu et al. (2018) reported that one patient experienced dizziness

during their first treatment; Wang et al. (2014) reported that one participant experienced a dull pain that subsided after 5% reduction of stimulation intensity and; the rest of the studies (Seniow et al., 2013; Thiel et al., 2013; Medina et al., 2012; Waldowski et al., 2012; Weiduschat et al., 2011) reported that there were no side effects in their studies.

Key Themes

1. Specific demographic information

We considered 10 types of demographic variables to be inherent to aphasia rTMS studies: *male-female ratio, mean age, handedness, number of previous strokes, time since onset of stroke, stroke type, localization of stroke, types of aphasia, severity of aphasia, and education level of participants*. Only two studies (Seniow et al., 2013; Waldowski et al., 2012) reported all 10 demographic variables; four studies (Hu et al., 2018; Rubi-Fessen et al., 2015; Wang et al., 2014; Medina et al., 2012) reported nine variable, one study reported eight variables (Barwood et al., 2013) and; four studies (Haghighi et al., 2018; Heiss et al., 2013; Thiel et al., 2013; Weiduschat et al., 2011) reported seven demographic variables.

2. Stimulation parameters (method of determination of RMT, % RMT, frequency, duration of stimulation, number of sessions, timeline of treatment)

Analysis revealed that stimulation parameters varied across studies. With regards to the method used to determine RMT, five studies used electromyography (EMG) (Hu et al., 2018; Wang et al., 2014; Barwood et al., 2013; Seniow et al., 2013; Waldowski et al., 2012); one study used visible contraction (Rubi-Fessen et al., 2015) and; five studies did not report their method (Haghighi et al., 2018; Heiss et al., 2013; Thiel et al., 2013; Medina et al., 2012; Weiduschat et al., 2011). Regarding the percentage of RMT used in stimulation, one study used 80% (Hu et al., 2018); one study used 100% (Haghighi et al., 2018); six studies used 90% (Rubi-Fessen et al., 2015; Wang et al., 2014; Barwood et al., 2013; Seniow et al., 2013; Medina et al., 2012; Waldowski et al., 2012) and; three studies used 90% of the daily defined RMT (Heiss et al., 2013; Thiel et al., 2013; Weiduschat et al., 2011). The chosen frequency of stimulation converged in all studies. They all used 1 Hz rTMS. In addition to that, one study (Hu et al., 2018) used an additional 10 Hz rTMS stimulation in one group. The duration of

stimulation in each session was similar for most of the studies. One study (Hu et al., 2018) used a 10-minute stimulation protocol; two studies (Seniow et al., 2013; Waldowski et al., 2012) used a 30-minute protocol and the remaining eight studies used a 20-minute daily stimulation protocol. Regarding the number of sessions, two studies (Seniow et al., 2013; Waldowski et al., 2012) applied a 15 session-protocol; one study (Weiduschat et al., 2011) used an 8-10 sessions protocol (as not everyone completed the 10 day protocol) and; the rest of studies (eight in total) used a 10-day protocol. Finally, regarding the timeline of treatment, seven studies (Haghighi et al., 2018; Rubi-Fessen et al., 2015; Barwood et al., 2013; Seniow et al., 2013; Medina et al., 2012; Waldowski et al., 2012; Weiduschat et al., 2011) excluded weekends from treatment (i.e. treatment was not consecutive) and four studies did not provide detailed information regarding the timeline of their protocols (Hu et al., 2018; Wang et al., 2014; Heiss et al., 2013; Thiel et al., 2013).

3. Stimulation site

Apart from two studies reporting that stimulation was over the homologue of Broca's area (Hu et al., 2018; Haghighi et al., 2018), the rest of the studies stimulated the right pTr. In addition to stimulating the right pTr, Waldowski et al. (2012) also stimulated the right pOp in all participants and Medina et al. (2012) stimulated the right pOr in one patient and the pTr in four patients.

4. Method of localization of stimulation site

One study used the international 10-20 EEG method (Hu et al., 2018) and two studies used a frameless stereotaxic system (Barwood et al., 2013; Wang et al. 2014). Four studies (Rubi-Fessen et al., 2015; Heiss et al., 2013; Thiel et al., 2013; Weiduschat et al., 2011) used surface distance measurements: reference lines defined on the reconstruction of the respective patient's head from MRIs were transferred to the patient's head. Two studies (Seniow et al., 2013; Waldowski et al., 2012) used spatial coordinates: the stimulation site was 2,5 cm posterior to the canthus along the canther-tragus line and 3 cm superior to the line. Finally, one study (Haghighi et al., 2018) did not provide any data on the method of localization of stimulation site.

5. Characteristics/approach of adjuvant SLT

There were two studies (Barwood et al., 2013; Medina et al., 2012) that assessed the efficacy of rTMS as a standalone treatment. The rest of the studies used SLT as an adjuvant therapy. This key theme was the most inconsistent as the type and intensity of SLT varied significantly across studies. Particularly, one study (Hu et al., 2018) used a post-rTMS 30-minute SLT regimen focusing on naming. One study (Rubi-Fessen et al., 2015) applied a post-rTMS 45-minute SLT program aiming at reactivation of word retrieval. One study (Wang et al., 2014) used a 60-minute SLT program twice a week emphasising verbal expressive skills. Five studies (Haghighi et al., 2018; Heiss et al., 2013; Seniow et al., 2013; Thiel et al., 2013; Weiduschat et al., 2011) applied a 45-minute SLT program following rTMS focusing on individual language problems. Finally, one study (Waldowski et al., 2012) applied a 45-minute post-rTMS SLT program focusing on expression and comprehension of spoken language. Crucially, all controls received the same type, frequency and intensity of SLT as participants in the experimental groups that they were compared to.

6. Outcome measures, post-treatment assessments and durations of follow-up

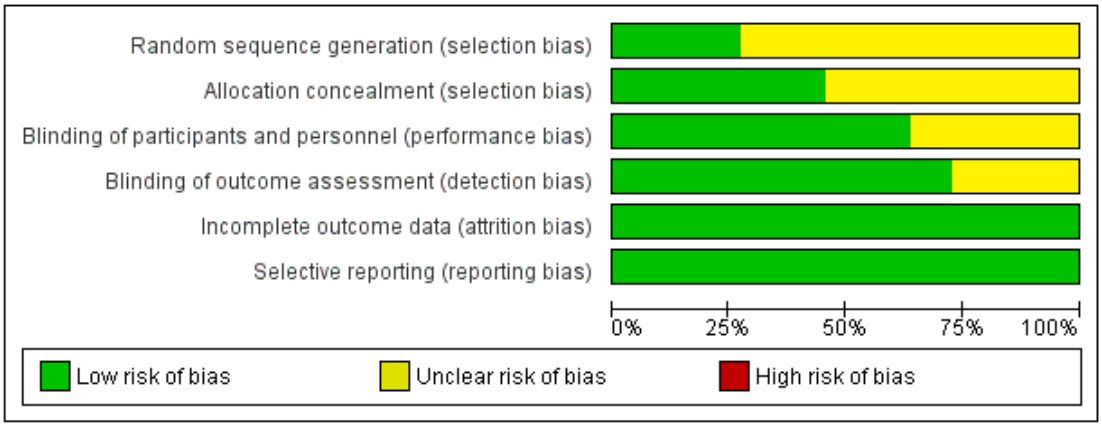
The outcomes measures used for language assessment varied across studies. Hu et al. (2018) used the Chinese versions of WAB; Haghighi et al. (2018) used the Farsi version of WAB-R; Rubi-Fessen et al. (2015) used AAT, Vanderwart picture naming inventory, ANELT-A and FIM. Wang et al. (2014) used CCAT and IPND; Barwood et al. (2013) used BNT, BDAE (Cookie Theft picture, word comprehension, repetition, naming) and the Snodgrass & Vanderwart (1980) naming inventory; Heiss et al. (2013) used AAT; Seniow et al. (2013) used the Polish BDAE and ASRS; Thiel et al. (2013) used AAT; Medina used “Cookie Theft” from BDAE; Waldowski et al. (2012) used CPNT, BDAE and ASRS and; Weiduschat et al. (2011) used AAT. All studies used standardized language measures and only two (Barwood et al., 2013; Medina et al., 2012) assessed functional communication of participants through narratives production. With regards to post-treatment assessments, seven studies (Haghighi et al., 2018; Hu et al., 2018; Heiss et al., 2013; Seniow et al., 2013; Thiel et al., 2013; Waldowksi et al., 2012; Weiduschat et al., 2011) did not report how immediate the post-treatment assessments were (e.g. on the day of the last session vs 1 day after treatment); one study (Rubi-Fessen et al., 2015) assessed its participants

the day after treatment was concluded; one study (Wang et al., 2014) performed the assessment on the day of the last session) and; one study did not perform a post-treatment assessment (Medina et al., 2012). With regards to follow-up, five studies (Haghighi et al., 2018; Rubi-Fessen et al., 2015; Heiss et al., 2013; Thiel et al., 2013; Weiduschat et al., 2011) did not follow their participants to assess possible long-term effects of treatment. Two studies (Hu et al., 2018; Medina et al., 2018) did a 2-month follow-up assessment; one study (Wang et al., 2014) did a 3-month follow-up assessment and; two studies (Seniow et al., 2013; Waldowski et al., 2012) performed a 15-week follow-up assessment. Barwood et al. (2013) was the largest longitudinal, placebo-controlled study that examined the effects of TMS on post-stroke aphasia up to 12 months post-stimulation. Last but not least, one study (Medina et al., 2012) assessed only the long-term effects of rTMS.

7. Quality assessment

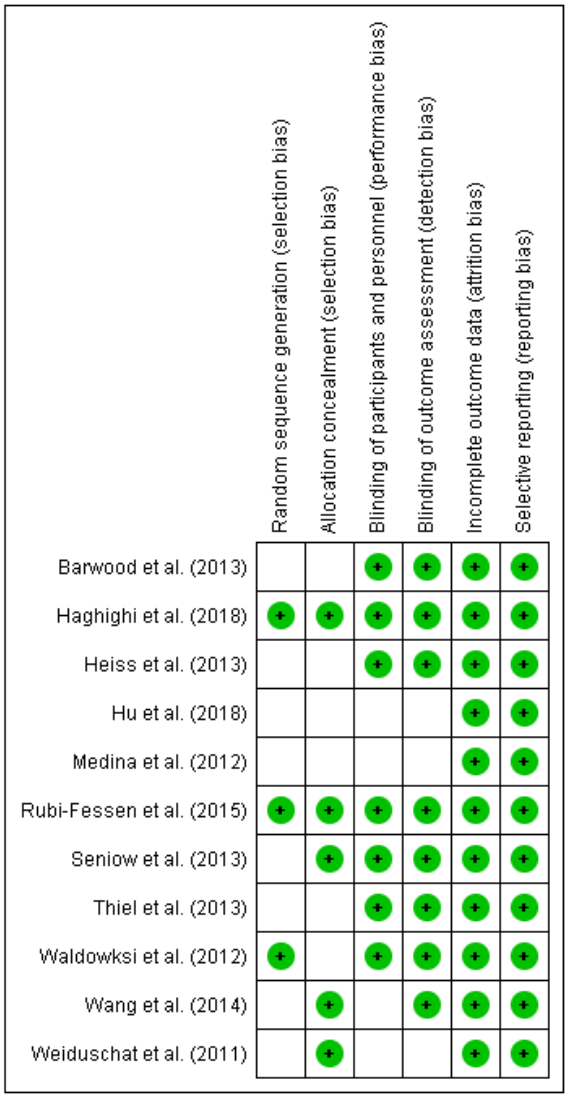
Overall, the random sequence generation bias risk was low for 27% of the included studies, whereas for 73% of the studies the risk was unclear. The risk for allocation concealment was low for 45% of the studies and unclear for the rest 55%. The risk of bias for blinding of participants and personnel bias was low for 63% of the studies and unclear for the rest 37%. The risk for detection bias was low for 73% of the studies and unclear for 27% of the included studies. Finally, the risk for attrition bias and reporting bias was low for 100% of the studies. More analytically, in the reporting bias and attrition bias items, all studies scored “low risk of bias”. With regards to detection bias, three studies (Hu et al., 2018; Medina et al., 2012; Weiduschat et al., 2011) were rated to have an “unclear risk of bias” and the rest of studies were rated to have a low risk of bias. In performance bias, the risk of bias was “unclear” for four studies (Hu et al., 2018; Wang et al., 2014; Medina et al.; Weiduschat et al., 2011) and low for the remaining studies. As for allocation concealment (selection bias), six studies were rated as having “unclear risk of bias” (Hu et al., 2018; Barwood et al., 2013; Heiss et al., 2013; Thiel et al., 2013; Medina et al., 2012; Waldowski et al., 2012) and the rest as having a “low risk of bias”. Finally, the risk for random sequence generation (selection bias) bias was “unclear” for eight studies (Hu et al., 2018; Wang et al., 2014; Barwood et al., 2013; Heiss et al., 2013; Seniow et al., 2013; Thiel et al., 2013; Medina et al., 2012; Weiduschat et al., 2011) and “low” for the rest

of the studies. Details for the risk of bias of the included studies are provided in figures 2 and 3.



Key: U = unclear; L = low; H = high

Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Key: blank square= unclear; + = low; - = high

Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Discussion

The aim of this systematic review was to examine all RCTs assessing the effects of rTMS for post-stroke aphasia rehabilitation to provide rigorous, transparent and comprehensive summaries of the best available evidence on this topic. Previous systematic reviews evaluating the effects of rTMS for post-stroke aphasia rehabilitation (Sebastianelli et al., 2017; Gadenz et al., 2015; Li et al., 2015; Ren et al., 2014) have identified 12 original studies in total. The present systematic review incorporated newer studies that do not appear in previous reviews. In total, we identified 11 RCTs that were included in our analysis. The evaluation of the methodological quality of the included papers was organised in seven key themes. We suggest that those key concepts relating to aphasia rTMS research, can be used as a guide when planning and reporting research data in this field to increase methodological rigor and to allow comparability across studies.

Starting off, our first key concept is linked to the annotation of specific demographic variables. We considered 10 important demographic variables to be inherent to aphasia rTMS studies: *male-female ratio, mean age, handedness, number of previous strokes, time since onset of stroke, stroke type, localization of stroke, types of aphasia, severity of aphasia, and education level of participants*. Demographics are independent values that determine whether or not participants constitute a representative sample of the target population, allow the comparability amongst studies and if samples are large enough, they may reveal inter-individual variations that could help researchers understand and possibly predict why and how some people respond, or respond better, and others do not respond, or respond less to treatment.

The second key concept analysis (stimulation parameters) revealed that stimulation parameters varied across studies. As there is no standardized rTMS protocol for aphasia rehabilitation, it is reasonable for this variability to exist. Notwithstanding, the method used to determine RMT in aphasia rTMS needs careful consideration. In this review we found that five studies did not report the method used to determine RMT, one study used visible contraction and five studies used EMG as a method. The International Federation of Clinical Neurophysiology (IFCN) has described how to determine RMT of a muscle using EMG (see Rothwell et al., 1999). Using EMG to

determine RMT has the advantage that it provides quantitative data for muscle response and crucially, IFCN guidelines for the safe use of TMS are based on EMG methodologies (Rossi et al., 2009). Even though visually detected movements are convenient and simple to perform, they yield significantly higher RMTs compared to EMG and this may compromise safety in some people (Westin, Bassi, Lisanby & Luber, 2014). For all the above reasons, it is recommended that future researchers should use EMG recordings to determine RMT in rTMS post-stroke aphasia studies.

With regards to stimulation site, apart from two studies that reported that they stimulated the homologue of Broca's area (Haghighi et al., 2018; Hu et al., 2018), the rest of the studies specified the site of stimulation in Broca's area. Broca's area comprises both pTr and pOp and therefore, the information that Broca's area was stimulated is not sufficient and could also be considered erroneous as it is not possible for someone to stimulate both areas simultaneously with one f8c coil. In addition to that, there is evidence that the suppression of the right pTr but not pOp improves naming in aphasia and that those two areas have different functional roles (Naeser et al., 2011). Currently there exists a published protocol that details the steps for identifying a responsive target site in the right hemisphere in patients with chronic non-fluent aphasia (see Garcia, Norise, Faseyitan, Naeser & Hamilton, 2013) that highlights the importance of individual site identification. Medina et al. (2012) was the only study in this review that used this method in five participants and found that the best responsive site in four participants was the pTr and in one participant it was the pOr. For the above reasons, it is highly recommended that researchers should apply the protocol of Garcia et al. (2013) for individual site identification prior to rTMS treatment.

Regarding the method of localization of the stimulation site, only two study (Wang et al., 2014; Barwood et al., 2013) used a frameless stereotaxy system. This technology is compatible with all modern rTMS devices and has several advantages over the three methods used by the other studies (i.e. 10-20 EEG, spatial coordinates and surface distance measurements methods). The use of neuronavigation systems is highly recommended for identifying the site of stimulation as it allows accurate planning,

consistent and precise targeting, precise coil orientation, monitoring of brain stimulation and reliable stimulation at targets defined in previous sessions.

With regards to characteristics/approach of adjuvant SLT, a great variability was also observed among studies. Particularly, there were two studies (Barwood et al., 2013; Medina et al., 2012) that assessed the efficacy of rTMS as a standalone treatment and in both studies long-term improvements in several language domains were noticed. The rest of the studies used SLT as an adjuvant therapy, but the SLT type and intensity varied significantly among studies (see table 3-3). Speech and language therapy is currently considered the gold standard for aphasia rehabilitation (Breitenstein et al., 2017) as it improves language skills in all aphasia severities and stages (Saxena & Hillis, 2017). Nonetheless, the optimum time for SLT initiation (Nouwens et al., 2015) and the optimal approach, duration, frequency and format of SLT (Brady et al., 2016) are yet to be established. Also, it has been reported that the benefit offered by SLT declines over weeks to months and crucially, there is little convincing evidence that the addition of SLT is a significant determinant of response to TMS for aphasia rehabilitation (Coslett, 2016). Therefore, first we need to establish the SLT regimes that lead to neuroplastic and behavioural effects in post-stroke aphasia and then incorporate them into rTMS studies. Otherwise, it is difficult to assess i) the contribution of each treatment modality separately to post-stroke aphasia rehabilitation and ii) the possible synergistic effects of the two treatment modalities in post-stroke aphasia recovery.

As for the outcome measures used for language assessment, all studies used standardized language measures and only two (Barwood et al., 2013; Medina et al., 2012) assessed functional communication of participants through narrative production. Functional communication is based on production of phrases, sentences and on narration and for that reason it is highly recommended that in future studies, researchers should employ an assessment of narrative production to explore not only the effects of rTMS on experimental language tasks, but also on an everyday life task.

Present findings on the effectiveness of rTMS on language gains post-stroke also varied across studies. Regarding short-term effects, all studies but two (Seniow et al.,

2013, Waldowski et al., 2012) found significant improvement in at least some, if not all, language measures in the experimental versus the control groups. Seniow et al. (2013) and Waldowski et al. (2012) did not confirm the hypothesis that low-frequency rTMS to the homologous pTr (Seniow et al., 2013) and Broca's area homologue (Waldowksi et al., 2012) improves naming, repetition and comprehension post-treatment in early post-stroke aphasia. On the other hand, both studies found trends towards language improvements in specific groups of patients. Seniow et al. (2013) found that in the experimental group, participants with anterior lesions showed a trend towards improvement in naming. Waldowski et al. (2012) found a trend towards improvement in average reaction time in naming in the experimental versus control group and a trend towards greater improvement in average reaction time in naming in favor of the experimental subgroup with a lesion including the anterior part of language area compared to the rest of participants in the experimental group. However, seven studies (Haghighi et al., 2018; Hu et al., 2018; Heiss et al., 2013; Seniow et al., 2013; Thiel et al., 2013; Waldowksi et al., 2012; Weiduschat et al., 2011) did not report how immediate the post-treatment assessments were (e.g. on the day of the last session vs 1 day after treatment); one study (Rubi-Fessen et al., 2015) assessed its participants the day after treatment was concluded; one study (Wang et al., 2014) performed the assessment on the day of the last session) and; two studies did not perform a post-treatment assessment (Barwood et al., 2013; Medina et al., 2012). In vitro evidence has shown that short rTMS effects induced by low frequency stimulations can last only for 30 to 60 minutes (Hoogendam, Ramakers, Di Lazzaro, 2010); and 40 seconds of cTBS depresses MEPs for about 1 hour (Klomjai, Katz & Lackmy-Vallee, 2015). Also, human in vivo motor cortex research supports that changes exerted by TBS protocols (iTBS and cTBS) last for about 30-120 minutes (Huang, Rothwell, Edwards & Chen, 2018). Therefore, to explore the immediate behavioural effects or rTMS it is important to assess participants upon cessation of the last session. Findings from the follow-up stage assessments also varied between studies. Five studies (Haghighi et al., 2018; Rubi-Fessen et al., 2015; Heiss et al., 2013; Thiel et al., 2013; Weiduschat et al., 2011) did not follow their participants to assess possible long-term effects of treatment. Prior evidence (e.g. Hamilton et al., 2010) has shown rTMS related language gains at two months post-treatment. All six studies that performed follow-up assessments report improvements in several

language domains, providing evidence that rTMS has the potential to induce long-lasting language gains in post-stroke aphasia. In particular, the research of Barwood and colleagues (2013) reported language gains up to 12 months post-TMS. This evidence necessitates future follow-up assessments that extends beyond 12 months to accurately characterise long-term effects of TMS on aphasia post-stroke. Overall, the variability noticed in language performance among studies both at the short- and long-term post TMS, necessitates the need for research on biomarkers and functional markers of good and non-responders to TMS. This is the key that in the future will lead to individualised TMS treatment.

To assess the trustworthiness of the information provided in the included studies the "risk of bias" for six domains (see figures 2 & 3) in each study was assessed separately. Figure 2 allows readers to gain an at-a-glance impression of the risk of bias and figure 3 provides a deeper understanding of the risks of bias for each study. The studies of Haghighi et al. (2018) and Rubi-Fessen et al. (2015) were rated to have a low risk of bias in all six domains. In the study of Waldowski et al. (2012), all six domains but one (allocation concealment) were rated to have a low risk of bias. Their method of concealment though was not described to allow a definite judgement and for that reason it was judged as having an unclear risk of bias. Seniow et al. (2013) were rated to have a low risk of bias in all six domains but one (random sequence generation). The researchers did not describe the generation of a randomized sequence to allow a definite judgement and for that reason this domain was judged as having an unclear risk of bias. Wang et al. (2014) had a low risk of bias in all but two (random sequence generation, blinding of participants and personnel) components. The investigators did not describe the generation of a randomized sequence and whether participants were blind to groups allocation to allow a definite judgement and for that reason those two domains were judged as having an unclear risk of bias. Barwood et al. (2013), Heiss et al. (2013) and Thiel et al. (2013) had a low risk of bias in all six domains apart from random sequence generation and allocation concealment. The researchers did not describe generation of a randomized sequence and method of concealment to allow a definite judgement and for that reason those domains were judged to have an unclear risk of bias. Hu et al. (2018) and Medina et al. (2012) had a low risk of bias for "incomplete outcome" data and "selective reporting" domains.

However, the researchers did not describe the processes of “random sequence generation”, “allocation concealment”, “blinding of personnel” and “blinding of outcome” to allow a definite judgement and for that reason those domains were judged as having an unclear risk of bias. Finally, Weiduschat and colleagues (2011) were rated as having a low risk of bias for “allocation concealment”, “incomplete outcome data” and “selective reporting”. However, they did not describe the processes of “random sequence generation”, “blinding of participants and personnel” and “blinding of outcome assessments” to allow a definite judgement and for that reason those domains were judged to have an unclear risk of bias. Overall, only two (Haghighi et al., 2018; Rubi-Fessen et al., 2015) out of the eleven included studies presented with trustworthy results. The rest of the studies showed at least some systematic errors related to internal validity and this means that there is a likelihood for the results of those studies to be erroneous. On the other hand, the poor reporting that we identified does not necessarily reflect what investigators really did, but it definitely undermines methodological rigour.

The present review was based on guidelines following AMASTAR 2 (Shea et al., 2017). To maximise the comparability of studies and to minimize confounding stimulation effects introduced by the application of multiple rTMS paradigms in one intervention, only published RCTs in which researchers compared unilateral stimulation of any rTMS protocol (excitatory, inhibitory, TBS) with sham TMS for post-stroke aphasia rehabilitation were included. One-real-rTMS-session-cross-over studies (two identified studies) and studies that applied bilateral stimulation (one identified study) were excluded from the present analysis.

Overall, only two studies (Haghighi et al., 2018; Rubi-Fessen et al., 2015) presented 100% trustworthy results. Two studies with high methodological rigor (Seniow et al., 2013; Waldowksi et al., 2012) provided contradictory data about the effectiveness of low-frequency rTMS for post-stroke aphasia showing that not all patients with post-stroke aphasia benefit from low-frequency rTMS. It turns out that studies were not fully comparable. As rTMS is a novel treatment and there are no standardized protocols, it is reasonable why protocol variables may vary across studies. Nonetheless, there are specific parameters inherent to study design and protocol used

in trials that can be consistent across studies. Based on the reported seven key theme analysis, it is hereby suggested that the following parameters should be taken into consideration in future TMS research: *reporting all 10 demographic variables analysed in this review; using EMG recordings for determination of RMT; reporting the method used to determine RMTs; using published protocols (e.g. Garcia et al., 2013) for individual site identification prior to rTMS treatment; using neuronavigation systems for identification of the site of stimulation; applying SLT approaches for which there is strong evidence that they have neuroplastic and behavioural effects in post-stroke aphasia; doing follow-up assessments that extend beyond 12 months post-treatment.*

Last but not least, to improve the completeness of reporting and replicability of rTMS aphasia studies, the use of the published "Template for Intervention Description and Replication" (TIDieR) 12 item checklist and guide (Hoffmann et al., 2014) is strongly suggested.

Conclusions

The present systematic review revealed that the evidence for the effectiveness of rTMS for post-stroke aphasia rehabilitation is inconclusive and identifies the need for more and larger RCTs that are methodologically rigorous. It is hereby suggested that rTMS aphasia researchers can empower the methodological rigor of their studies in three ways. First, by using published risk of bias tools; second by using published templates for intervention description and replication tools and; third by taking into consideration all seven key themes that were identified in this systematic review.

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CHAPTER 4: Methods

Previous chapters presented the theoretical background and current evidence regarding rTMS as a treatment method for improvement of communication problems in patients with aphasia post-stroke. Based on the two systematic reviews it was concluded that the level of evidence for rTMS as a beneficial intervention for post-stroke aphasia is low. So far, studies have not demonstrated conclusive results with regards to optimum stimulation parameters and outcomes. This chapter explains why the single study experimental design (SSED) was applied to the study of the thesis, describes eligibility criteria for participation to the study and outlines the applied research procedures and protocols.

4.1 Study Design

The study was undertaken at the University Rehabilitation Clinic of the Department of Rehabilitation Sciences at the Cyprus University of Technology (CUT). Adult patients who had suffered a single left hemispheric stroke at least six months before participating in the study were actively sought for recruitment. The initial plan was to conduct a double blind randomized control trial in which two experimental and one control group (i.e. cTBS – 1 Hz (low frequency) rTMS – sham TMS) of people suffering from chronic aphasia post-stroke would be compared and contrasted with each other to explore the effects of TMS on language performance in this population. However, the sample size of the main study was finally very small (i.e. six participants in total recruited over 15 months) and having three groups of two participants in each group would not allow the detection of possible effects of TMS on language performance in this sample. The lack of blinding in this trial was a clinically relevant and realistic way of assessing the effects of TMS on language performance in stroke patients in Cyprus. This is because Cyprus is a very small country (approximately 850000 native Greek speaking residents) and recruitment of people with disabilities in intervention studies is very problematic. For that reason, an open label randomized controlled trial, incorporating a single subject experimental design (SSED), was conducted. The decision was that this study design would be more appropriate to yield statistically significant results based on the literature (see Howard et al., 2015 including references and commentaries within). In particular, two

types of rTMS treatment were used: cTBS (T1) versus 1 Hz (low frequency) rTMS (T2). Since an open label study was implemented, the investigator and participants were not blinded to treatment allocation. The six participants were equally and randomly (drawing lots in sealed envelopes) allocated to two groups (three participants in each group) with each group receiving only one treatment type (T1 or T2). This way, the study was not liable to allocation bias and allocation concealment bias. The Template for Intervention Description and Replication (TIDieR) 12 item checklist and guide (Hoffmann et al., 2014) (Appendix 3) was used to improve the reporting and the replicability of both the pilot and main study.

4.2 Ethical Approval, Research Documentation & Recruitment

Permission was sought from the Cyprus National Bioethics Committee (CNBC) to conduct the intended research (Appendix 4). An open call was made to the media (Appendix 5) outlining the aim of the study with a request for assistance with patient recruitment. A research flyer outlining the study, explaining the reasons for the research, and inviting participation (Appendix 6) was i) uploaded on the Cyprus University of Technology facebook page and ii) disseminated to the Rehabilitation Centre “Melathron Agoniston EOKA” in Limassol, Limassol General Hospital, Ygia Polyclinic Private Hospital in Limassol, five neurologists in Limassol and across 30 pharmacies in Limassol. Recruitment was on a rolling basis for 15 months and interested participants were invited to take part in the study. Informed consents were sought prior to recruitment (Appendix 7). The original signed consent forms were kept in a file and only the primary investigator had access to them. Copies of the signed consent forms were given to all participants. All documentation and identifiable data were stored at the Department of Rehabilitation Sciences in a secure cabinet. Data from the patients’ medical notes were entered into an electronic database located on a password protected University computer. All data on this database were pseudo-anonymised using a patient identification (ID) number against the assigned study subject ID number. Data entry was undertaken by the principal investigator (PhD candidate). Upon study recruitment closure, the documents were archived for a minimum of 5 years according to the CNBC guidelines. Regarding data collection and management, the Data Protection Act 1998 was followed at all times.

Results obtained from the study have been published in reputable journals in the field, and/or presented at appropriate medical forums.

4.3 Participants' Examinations

For all participants, a recent brain magnetic resonance imaging (MRI) was needed to confirm the diagnosis; to rule out any additional structural abnormalities and for use by the neuronavigation system for precise localization of the area of interest for TMS. All MRI expenses were covered by Cyprus University of Technology. Also, participants of the main study underwent speech and language therapy evaluations by the author of this thesis and all language data that were gathered were analysed by one certified speech-language pathologist and one linguist that were blinded to the study.

4.4 Inclusion and Exclusion Criteria

The TMS related criteria listed below are current, expert based and rely on safety of conventional TMS protocols (2009 International Federation of Clinical Neurophysiology). In addition to the criteria listed below, a key prerequisite for participation in the study was the willingness to withdraw from any speech and language therapy for the whole duration of the program (i.e. 3 months).

4.4.1.1 Inclusion Criteria

- 18 – 75 years of age
- Native speakers of (Cypriot) Greek
- Only one stroke and located in the left hemisphere (on MRI or CT scan)
- Chronic aphasia (>6 months post-stroke)
- Stroke induced disability
- Presence of mild/moderate/severe expressive aphasia with/without mild/moderate comprehension problems as diagnosed by the Greek version of the Boston Diagnostic Aphasia Examination – Short Form (BDAE-SF)
- Mild/moderate/severe apraxia of speech
- Mild/moderate dysarthria
- No intellectual disability
- No history of dementia (on MOCA) or other neurological illnesses

- No substance abuse
- Health stability

4.4.1.2 Exclusion Criteria

- Non-native Greek speakers
- Prior cerebrovascular accidents (CVAs)
- Standard MR imaging and TMS exclusion criteria:
    - Aneurysm clips or coils
    - Stents in the neck or brain
    - Implanted stimulators
    - Cardiac pacemakers or implantable cardioverter defibrillator (ICD)
    - Electrodes to monitor brain activity
    - Metallic implants in the ears and eyes
    - Shrapnel or bullet fragments in or near the head
    - Facial tattoos with metallic or magnetic-sensitive ink
    - Other metal devices or object implanted in or near the head
    - Severe scalp skin lesions
    - Epilepsy
    - Uncontrolled seizures
- Severe dysarthria affecting intelligibility
- Any neuro- or psycho- active medications without concomitant administration of anticonvulsant drugs
- Any other neurological condition affecting the sensorimotor system (e.g. brain tumour)
- Renal or liver failure
- Current neuropsychiatric associations, apart from depression
- Progressive neurological disorder (e.g. Dementia, Parkinson's Disease, Multiple Sclerosis)
- Severe or recent heart disease
- Life-threatening diseases
- Auditory or visual deficits (Albert's test) that impair testing
- Requiring palliative care

- Medication that alerts brain excitability
- Cognitive disorders known before the stroke

The above exclusion criteria regarding medication were applied to avoid pharmacological influences on TMS, as there is evidence that the extent and direction of NIBS induced plasticity can be highly significantly modulated by many neuropharmacological agents (Ridding & Ziemann, 2010).

4.5 Pilot Study

The first two participants who expressed their interest for participation in the study, were recruited for the pilot study. The study was undertaken to ensure that all pre-therapy and therapy procedures were appropriate for prospective participants of the main study. In particular, the two participants were first assessed to see whether they fulfilled the inclusion criteria and if so, they were recruited to the pilot study. The pilot study is analysed in chapter 5.

4.6 Main Study

Results of the pilot study showed that all pre-therapy and therapy procedures were appropriate for participants of the main study. Following completion of the pilot study, the main study commenced and was completed within 18 months from the first call. The experiments lasted approximately 3 months in total for each participant. Out of the 18 patients that were recruited to the main study, only 6 took part and completed the rTMS sessions. For the remainder:

- seven patients did not participate due to caregivers' reluctance/refusal
- five patients withdrew from the study (with the fear of manifesting seizures during sessions (three) and claustrophobia (they refused to do MRI scans) (two))

4.7 Outcome Measures and Timeline of Assessments

There is congruent evidence that rTMS has potential to bring about language improvements in people that have suffered a stroke and exhibit language problems. To investigate whether similar results could be found in the present study, it was decided to choose the best outcome measures that would allow the detection of significant

changes, if any, in language performance after TMS. With regards to the selection of appropriate outcome measures, reliability and validity should not be the only factors to consider. Coster (2013) suggests researchers create a causal model of the intervention process being tested, and further provides a set of guidelines (Appendix 8) to help investigators appraise the match amongst the purpose of the study, its population and tools. The author of this thesis abided by those suggestions and guidelines and created a model (see figure 4-1) to drive the research focus, and allow appropriate selection of targeted outcome measures. The selected outcome measures were, to the writer's knowledge, in accordance, as much as possible, with those guidelines.

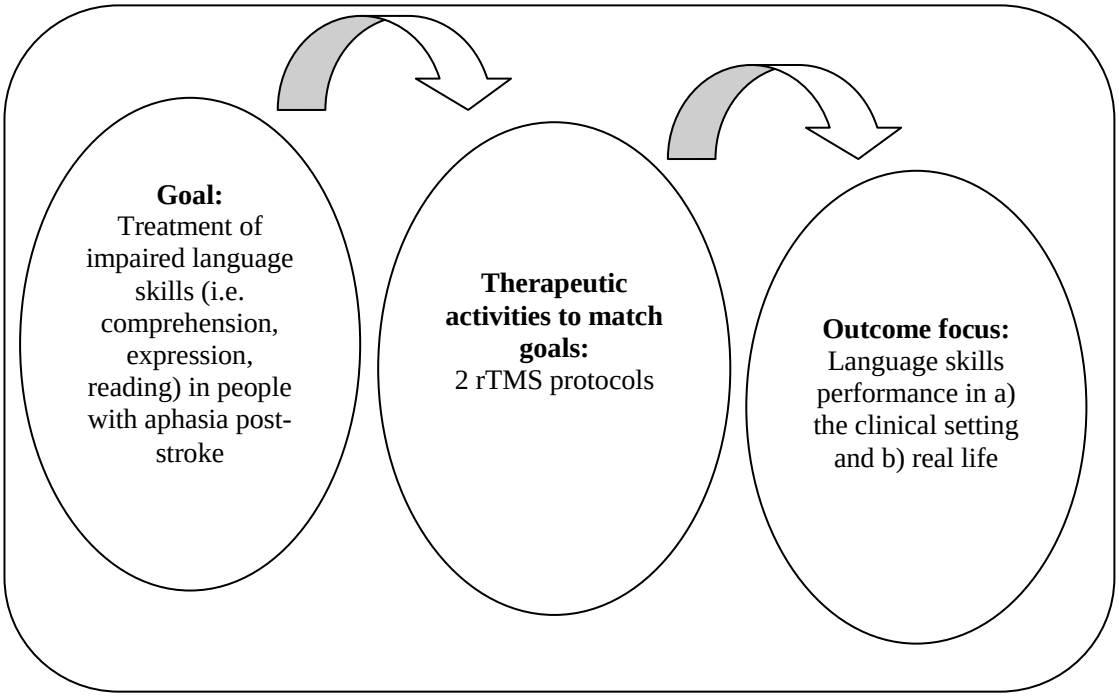

Figure 4-1: Causal model for a rTMS study on post-Stroke Aphasia

Participants in the pilot study were assessed at three points in time (i.e. 1 day pre-treatment, 1 day post-treatment and 3 months post-rTMS) with three outcome measures in total (i.e. Boston Diagnostic Aphasia Examination-Short Form (BDAE-SF), Multilingual Assessment Instrument for Narratives (MAIN) and Stroke and Aphasia Quality of Life scale-39 item (SAQOL-39g)) (see chapter 5)) as the goal of that trial was to assess the feasibility and acceptability, on behalf of participants, of the study's procedures. In the main study, however, participants were assessed at four

points in time with additional language tools to increase the amount of language data available for analysis. Four language diagnostic tools served as dependent measures: the Boston Diagnostic Aphasia Examination-Short Form (BDAE-SF); the Peabody Picture Vocabulary Test-Revised (PPVT-R); the Greek Object and Action Test (GOAT) and the Multilingual Assessment Instrument for Narratives (MAIN). Also, the Raven's Coloured Progressive Matrices (RCPM) a measure that assesses cognition (i.e. problem solving skills), and the Stroke and Aphasia Quality of Life scale-39 item (SAQOL-39g) were administered.

All language tools and the RCPM (control variable) were used at four time points during the study (i.e. 12 days and 1 day before treatment for (2) baseline measurements, one day after treatment and two months post treatment). The tools were administered twice, at the pre-therapy baseline phase to establish the level of performance prior to treatment and rule out spontaneous recovery. Even though currently the optimal number of pre-therapy probes is not clear, it is suggested that two probes are sufficient to provide an estimate of both level of performance and rate of change (Howard, Best & Nickels, 2015).

In addition to multiple assessments of the dependent language variables, equal multiple assessments of the control variable (i.e. RCPM) were applied. This was done because it was assumed that if a change in language skills was noticed but the control variable (i.e. problem solving skills) remained stable, then i) the chances that TMS leads to language specific gains are increased and ii) the possibilities for the placebo and training effects are reduced. With regards to the QoL assessment tool in particular, it was used one day before the beginning of treatment and also two months post treatment to assess the effects of treatment on the QoL of participants. The QoL of participants was assessed by analyzing proxy reports: sister for P1; daughter for P2; daughter for P3; wife for P4; sister for P5 and; mother for P6.

4.7.1.1 Background Measures: Speech & Language History Form – Face Sheet – Screening for TMS eligibility – Hemispatial Neglect Test – Handedness Inventory (Short Form) (Appendices 9-13)

Information gathered from all those tools was important as it determined eligibility for the study. Hence, all were used at one point in time; that is, before the beginning of treatment –in particular 12 days before the commencement of treatment.

Hemispatial Neglect Test

Albert's Test (1973) is a screening tool for unilateral spatial neglect (USN). The test asks to cross out lines placed in random orientations on a piece of paper. Unilateral spatial neglect is indicated if lines are left uncrossed on the same side of the page as the patient's motor deficit or brain lesion is located. For this study, the *Modified version of Albert's Test* was employed. This version varies only slightly from the original version and consists of 40 black lines (25 mm long, 0.5 or 1.2 mm thick) of various orientations dispersed randomly on a 297 x 210 mm sheet of white paper. Each side of the stimulus sheet contains 18 lines divided into 3 columns of 6 lines. The columns are numbered as 1 to 6 from left to right. The test takes less than 5 minutes to complete and cannot be completed by proxies. The test is used as a screening tool and not for clinical diagnosis of USN, as performance may be influenced by or can be indicative of other syndromes besides spatial neglect, such as hemianopia. The test has been found to have excellent test-retest reliability (Chen-Sea & Henderson, 1994), excellent convergent validity (Agrell, Dehlin & Dahlgren, 1997; Azouvi et al., 1996) and can distinguish patients with neglect from patients without neglect (Potter et al., 2000).

Handedness Inventory (Short Form)

The Edinburgh Handedness Inventory – Short Form (Veale, 2014) is a validated, brief and easily understood inventory of 4 items that address handedness with simple instructions. Despite its brevity, it has very good reliability, factor score determinacy and correlation with scores on the 10-item inventory (Veale, 2014). As this is a notably less burdensome to participants tool, it was used to assess handedness in our participants. Time administration is less than 1 minute and people are classified into one of three groups (i.e. left, mixed or right handers) according to their "Laterality

Quotient". The Greek translated tool of the original "Edinburgh Handedness Inventory – Short Form" was developed for the present study. All items of the scale were translated into Greek by the PhD candidate. Then, the questionnaire was translated back into English by two Greek – English bilinguals that was compared to the original questionnaire. The equivalence of the original text to the translated text was high (i.e. 100%).

4.7.1.2 Language Outcome Measures

The Boston Diagnostic Aphasia Examination – Short Form (BDAE-SF)

The Boston Diagnostic Aphasia Examination (BDAE) (Goodglass, Kaplan & Barresi, 2001) is a commonly used assessment tool for people suspected to have aphasia. The battery includes evaluation of language comprehension (e.g., words, commands, small paragraphs), expressive language (spontaneous speech, picture description, naming, word and sentence repetition, automatised sequences) reading and writing. Obtained scores can be converted into a language deficit score and a measure of aphasia severity. For the purposes of the study, the primary outcome measure that determined the presence, type and severity of aphasia was the Greek version of the BDAE short form (BDAE-SF) (Messinis, Kastellakis, Panagea & Papathanasopoulos, 2013). The tool has been adapted to the Greek language and culture and is used for screening for aphasia and language functioning assessment in acute and sub-acute stroke. It has satisfactory psychometric properties (Messinis et al., 2013). For the purposes of the study, written language was not assessed and therefore, time administration for the tool was approximately 30 minutes in total.

The Peabody Picture Vocabulary Test–Revised (PPVT-R)

Auditory comprehension is a principal component of general language ability and many people with aphasia exhibit comprehension deficits. Generally, auditory comprehension is assessed at the word and at the sentence level. In addition to BDAE-SF that was used to assess comprehension at both single word and sentence level, another tool was used to assess comprehension at the word level. Peabody Picture Vocabulary Test–Revised (PPVT-R) is a measure that assesses receptive vocabulary at the word level for children (Dunn & Dunn, 1981) and for the purposes of the study, the short version of the Greek PPVT-R (Simos, Sideridis, Protopapas & Mouzaki,

2011) was used. This measure has 32 stimulus plates. Participants are asked to point to the picture out of four that matches the word said by the examiner. Each participant's score is converted to a z-score and percentile taking age and level of education into consideration. The full and short versions of the PPVT-R are equivalent and constitute reliable and valid assessment tools of vocabulary for Greek students and immigrants who speak Greek (Simos et al., 2011).

The Greek Object and Action Test (GOAT)

The Greek Object and Action Test (GOAT) (Kambanaros, 2004) in its generic form is administered to assess naming of nouns and verbs for assessment and/or research purposes for Greek-speakers. It contains 84 coloured photographs, 10-14 cm in size representing 42 actions (verbs) and 42 objects (nouns). The test in total (production and comprehension subtests) takes under an hour to administer. The GOAT is reported in published studies investigating verb-noun grammatical dissociations across language-impaired populations for Greek-speakers (Grohmann & Kambanaros, 2016). For the purposes of the study, 19 informative verbs were used. "Informative" means that those 19 verbs are able to distinguish language impaired from non-impaired groups. This informative version was produced based on a new algorithm (ALNOVE) proposed to dismiss redundant/non-informative items from the tool (Phinikettos & Kambanaros, 2017).

The Multilingual Assessment Instrument for Narratives (MAIN)

To increase the reliability of our assessment regarding functional language limitations, in addition to BDAE-SF used for language diagnostics, an additional outcome measure was used for assessment of spontaneous speech (DV). The Multilingual Assessment Instrument for Narratives (MAIN) was used (Gagarina et al., 2012). In this study, the Greek version of MAIN developed within the European Cooperation in Science and Technology (COST) Action (IS0804) that started in 2008, was used to evaluate production of narrative skills at the macro- and microstructure levels. This study employed this ecologically valid measure to assess not only the effects of rTMS in experimental linguistic, but also in everyday life tasks, as functional communication is based on production of phrases, sentences and on narration. The tool evaluates both comprehension and production of narratives. It consists of four

parallel and comparable stimuli sets of six-picture (wordless) stories (Baby Birds, Baby Goats, Cat, and Dog) similar to Aesop's fables hence suitable for adult populations. The instrument has been developed on the basis of extensive piloting with more than 550 monolingual and bilingual children aged three to 10, for 15 different languages and language combinations. Scoring involves different components and is not about reaching the maximum score on the test. This tool includes both qualitative and quantitative aspects of evaluating narration and takes 15-20 minutes to administer. A low score does not necessarily indicate poor narrative ability. The quality of narrative performance depends on micro- and macrostructure performance. For the purposes of this study, only one story (i.e. Baby Goats) was used. The comprehension questions that form Part II of MAIN were not asked. Participants were allowed time to study the sequence of events unfolded in the six image panels. The investigator then prompted participants to tell the story and participants' story telling were audio recorded. No leading questions were asked by the investigator. This narrative assessment task takes 2-5 minutes. For the analysis, the "Quantitative Production Analysis" (QPA) protocol (Saffran et al., 1989) as adopted by Varkanitsa (2012) was applied. The QPA measures the formal/structural characteristics of a patient's production, yielding structural complexity scores and description of error types. The speech was transcribed in standard orthography and in phonemic transcription by a linguist, native speaker of Cypriot Greek, and the production was segmented following the QPA guidelines as adapted for Modern Greek by Varkanitsa (2012). The narrative corpus was extracted from the transcription by ignoring all utterances before the story-telling began and after the patient affirmed that they had finished telling the story. Furthermore, following QPA, the following segments were discarded: all meta-narrative comments (such us "And then this happened"), questions and responses directed to the investigator (such as "How is this called?"), common stereotyped expressions (such as "slowly-slowly"), utterances immediately repaired, interrupted, or which are results of perseveration, quotative markers used to report direct speech (such as "*And he told him"* 'Leave it'), uninterpreted neologisms, and finally coordinating conjunctions (such as 'and' or 'but') that conjoin full sentences. The remaining speech was divided on utterances primarily on syntactic/structural grounds. Prosodic information and contextual cues such as the unfolding of the next panel of the stimulus set of images were used to aid

the segmentation of speech into utterances where there were doubts as to the sentence boundary. The utterances were further subdivided into sentences with verbs, sentences without verbs, and single word utterances. Following Varkanitsa (2012) proposed modification of the protocol, utterances consisting of just a single verb and no other lexical items were classified as sentences with verb, taking into account the null-subject nature of Greek. The mean length of utterance (MLU) was calculated at this point, by measuring the number of words in each utterance and calculating its average. The number of syntactically well-formed sentences with verb was recorded and a proportion was calculated by dividing the number of well-formed sentences by the total number of sentences with verb produced. For each narrative sample, the words were categorised as Nouns, Verbs, Pronouns (including strong and weak clitic forms), Adjectives, Adverbs, Prepositions, or as Closed Class Words (a grouping that included determiners, auxiliaries and other functional vocabulary which do not have full lexical meaning, and that belong to word categories that do not easily admit new members through neologism or derivation). The number of tokens that belong to each category was recorded and the proportions were calculated in relation to the total number of narrative words. This categorisation into word types allowed for the observation of differentiated performance patterns among the patients. The sentences containing a verb were further analysed by calculating the 'AUX Score' metric (as adapted for Greek by Varkanista, 2012), which is calculated by assigning one point for each of the features MODAL, TENSE, ASPECT, NEGATION as encoded by the Main (Matrix) Verb of each independent clause and calculating the average score. The AUX Score Index is the average AUX Score minus 1 (one is subtracted to account for the base form of the verb). The verbs were scored based on the presence of the feature, and not their syntactical or semantic felicity as the goal is to measure the complexity of the produced verbs (Saffran et al., 1989). Concerning the verb phrase, two more complexity scores were calculated: the Embedding Index, and the Elaboration Index. The Embedding Index was the average of embedded clauses (clauses introduced by a subordinating particle, or a relative pronoun, or clauses used as verb objects) produced across the total number of sentences. The Elaboration Index was calculated by measuring the average number of Open Class words (i.e. Nouns, Verbs, Adjectives, and Adverbs) and of Pronouns (either strong pronouns or clitics) in the Subject Noun Phrase and in the Verb Phrase. The two averages are added together

to calculate the total Elaboration Index. Additionally to the QPA, the proportion of errors-by-type produced (and left unrepaired) was calculated in each sample following Varkanitsa (2012). The error types were the following: i) phonological, ii) morphosyntactic, iii) semantic, iv) lexical, v) uninterpretable neologisms, and vi) extended circumlocutions.

4.7.1.3 Problem Solving Skills Measure

Raven's Coloured Progressive Matrices (RCPM))

Many existing cognitive screening batteries (e.g. the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005)) have been developed for dementia and target mostly orientation and memory. Even though cognitive abilities are also often compromised after stroke, they are rarely assessed in research trials (Cumming, Bernhardt & Linden, 2011). Only three out of 190 stroke treatment trials included specific measures on cognition (Anderson, Arciniegas & Filley, 2005). Most recently it was reported that screening tests assessing cognitive decline are not suitable for aphasic patients as they contain items with a strictly verbal response (Barnay et al., 2014). The Raven's Coloured Progressive Matrices (RCPM) (Raven, Raven & Court, 1998) consists of 36 items in three sets of 12 and is used to assess problem solving skills. For each item, participants are asked to pinpoint the missing picture that best complements the given pattern. The first RCPM version was published in 1938 (Raven, 1938) and a revised version in 1956 (Raven, 1956). The tool is designed for use with young and old people with/without disabilities (e.g. aphasia) and it has been described as 'culture-free' (Cattell, 1940), 'culture-fair' (Cattell & Cattell, 1963), and 'culture-reduced' (Jensen, 1980). It has good concurrent validity (Rohde & Thompson, 2007); predictive validity (Rushton, Skuy & Fridjhon, 2003); as well as split-half reliability (Raven & Raven, 2003). Test-retest reliability appears to be weak for intervals longer than 1 year (e.g., Raven & Raven, 2003; Kazlauskaite & Lynn, 2002). In this study the maximum interval was 2 months.

4.7.1.4 Quality of Life Measure

Stroke and Aphasia Quality of Life scale-39 item (SAQOL-39g)

A problem with traditional applications of rTMS in aphasia is the use of language tasks as dependent measures to assess performance in cross sectional designs. The

problem with this approach is that it fails to capture possible improvements in everyday language, and thus fails to assess the possible effects of rTMS treatment on the QoL of people with aphasia (e.g. improved communication, increased job productivity, etc.). In this study, the Greek version of the Stroke and Aphasia Quality of Life scale-39 item (SAQOL-39) (Kartsona & Hilari, 2007) was used to assess the effects of TMS on the QoL of participants. This tool has been adapted and linguistically validated for measurement of QoL in Greek speaking people with chronic aphasia after stroke. The psychometric properties of the Greek version of the tool have been tested in its generic form (SAQOL-39g) (i.e. the exact same tool tested with a generic stroke population with and without aphasia) and it has been found that it is a valid and reliable scale that can be used as an outcome measurement, treatment prioritization and service evaluation (Efstratiadou et al., 2012). For the purposes of this study, the generic form of the tool (i.e. SAQOL-39g) was used. The SAQOL-39g is an interviewer administered self-report measure designated to assess QoL in individuals that have suffered a stroke, including those with aphasia, of any severity of expressive aphasia. For patients with receptive aphasia, it has been established that those with a score of $\geq$ 7/15 on the receptive domains of the Frenchay Aphasia Screening Test (FAST) (Enderby, Wood & Wade, 1987) (moderate or mild receptive aphasia) are able to self-report reliably on the SAQOL-39 (Hilari et al., 2003). The questionnaire consists of 39 questions that cover three domains: physical (16 items), communication (7 items) and psychosocial (16 items). The response format varies from 1= ‘definitely yes’ to 5= ‘definitely no’ and “last week” is the time frame for all questions. The tool is printed in large font (min. 14), with key words in bold and only a few items per page. The title, general instructions, practice items and transition sentences are printed in bordered pages and are highlighted in grey. Questions are printed in plain white pages. The scoring sheet is used by the interviewer to read the items to the respondent and mark the respondent’s answers, and to derive scores marked on the scoring sheet. The overall SAQOL-39g score is a mean score, calculated by adding up all the items and dividing by the number of items. The three domain scores are calculated separately as well. Overall mean and domain scores vary from 1 to 5 and are rounded to two decimal points (e.g., 3.46). Higher scores indicate better QoL. The scoring sheet includes information on scoring. To facilitate the calculation of domain scores, there is a separate column for each domain with the

items it includes being highlighted. Individual scores on the SAQOL-39g can be compared to the distribution of scores of the sample on which the instrument was tested, i.e., people with chronic aphasia following stroke. The instrument also has potential uses in the areas of treatment and service evaluation, clinical audit and treatment prioritization of people with stroke and aphasia. The pilot study revealed that patients struggled to deal with the questionnaire because of comprehension deficits. In the main study apart from P3 and P6, the remaining four participants also struggled to deal with the questionnaire. For that reason, proxy ratings were used to evaluate the QoL of all participants. Even though unbiased self-reports are the most appropriate source of QoL, ratings by proxies can provide clinicians with useful information if patients are unable to self-report (Ignatiou et al., 2012).

4.8 Repetitive TMS (rTMS) Procedures and Protocol

The six participants were randomly (drawing lots in sealed envelopes) allocated to two groups (three participants in each group) with each group (T1 or T2) receiving only one treatment type. All participants received real rTMS. The treatment procedures that were followed are described below and are summarized in table 4-1. A schematic illustrating the experimental timeline is shown in table 4-2.

4.8.1.1 Mapping the Cortical representation of the First Dorsal Interosseous (FDI) with TMS

The assessment of RMTs was done using surface electromyography (EMG) in which leads were placed over the FDI muscle of the left hand of the participants. Then, the procedure suggested by Rothwell et al. (1999) was followed. Particularly, a standard stimulus magnitude was used, the TMS coil was moved over the scalp at sites approximately 1 cm apart and the elicited Motor Evoked Potential (MEP) at each site was measured. This produced a map of MEPs with variable amplitudes and the site with the maximal amplitude was then chosen to be the “hot spot” for the assessment of Resting Motor Threshold (RMT).

4.8.1.2 Assessment of Resting Motor Threshold (RMT)

After finding the “hot spot”, to find the RMT of the FDI, the standard stimulus magnitude used for mapping of the FDI was used and then, the stimulus intensity was

progressively reduced in 2% or 5% steps until the minimum single-pulse stimulator output intensity resulting in motor evoked potentials (MEPs) of at least 50 μV peak-to-peak amplitude in ≥50% of pursued trials was found. The rate of stimulation was more than 3 secs between consecutive stimuli. Motor threshold levels were used to determine stimulation parameters, not because it was assumed that levels used for motor thresholds are directly translatable to levels for use in rehabilitation of language function but because motor threshold levels were considered as an indication of cortical excitability.

4.8.1.3 Repetitive TMS (rTMS) Stimulation Parameters

After obtaining RMTs, participants underwent rTMS at 80% of their individual RMT, using Magstim Rapid2® (Magstim Co., Wales, UK) connected to a 70mm Double Air Film Coil. Stimulation parameters were in accordance with the guidelines proposed by Wassermann (1998). The position of the coil was guided by a frameless stereotactic neuronavigation system (ANT NEURO) that uses the individual patients' MRI scan to precisely localize the target area for stimulation. Before stimulation, a T1-weighted MRI image was obtained from each patient to locate the optimal coil position.

4.8.1.4 Group T1 – continuous Theta Burst Stimulation (cTBS) over the right pars Triangularis (pTr)

Participants in this group (P1, P2 & P3) received inhibitory rTMS (continuous theta burst stimulation paradigm, cTBS) to the pTr in the right inferior frontal gyrus (homologous BA45), following the protocol suggested by Huang et al., (2005). This paradigm uses a Theta Burst Stimulation pattern (TBS) in which 3 pulses of stimulation are given at 50 Hz, repeated every 200 ms. A 40 sec train of uninterrupted TBS is given (600 pulses in total). In total, the program for each patient consisted of 10 daily stimulation treatments (10 consecutive days).

4.8.1.5 Group T2 – 1 Hz (low frequency) rTMS over the right pars Triangularis (pTr)

Participants in this group (P4, P5 & P6) received 20 minutes of 1-Hz rTMS over the right pTr (1200 pulses) (Rubi-Fessen et al., 2015). In total, the program for each patient consisted of 10 daily stimulation treatments (10 consecutive days).

Table 4-1: Summary of Intervention characteristics for each Participant

Participants	Intervention
1	cTBS: f8c coil; 80% RMT; 3 pulses of stimulation given at 50 Hz repeated every 200 ms to the right pTr; 40 sec train of uninterrupted TBS; 600 pulses in total; 10 consecutive daily sessions in total
2	cTBS: f8c coil; 80% RMT; 3 pulses of stimulation given at 50 Hz repeated every 200 ms to the right pTr; 40 sec train of uninterrupted TBS; 600 pulses in total; 10 consecutive daily sessions in total
3	cTBS: f8c coil; 80% RMT; 3 pulses of stimulation given at 50 Hz repeated every 200 ms to the right pTr; 40 sec train of uninterrupted TBS; 600 pulses in total; 10 consecutive daily sessions in total
4	LF-rTMS: f8c coil; 80% RMT; 1 Hz rTMS to the right pTr; 20 min per day (session); 1200 pulses in total; 10 consecutive daily sessions in total
5	LF-rTMS: f8c coil; 80% RMT; 1 Hz rTMS to the right pTr; 20 min per day (session); 1200 pulses in total; 10 consecutive daily sessions in total
6	LF-rTMS: f8c coil; 80% RMT; 1 Hz rTMS to the right pTr; 20 min per day (session); 1200 pulses in total; 10 consecutive daily sessions in total
Key: cTBS=continuous Theta Burst Stimulation; f8c=figure of 8; RMT=resting motor threshold; pTr=pars triangularis; LF=low frequency	

Table 4-2: Experimental Timeline

Pre rTMS sessions	**rTMS sessions (10 consecutive days)**	**Post rTMS sessions**
• Background measures • MRI scan • Language testing (BDAE-SF; PPVT-R; GOAT; (MAIN) • Cognitive testing (problem solving skills) (RCPM) • QoL assessment (SAQOL-39g)	**<u>Group 1</u>** 50 Hz neuronavigated cTBS at 80% RMT applied at right pTr **<u>Group 2</u>** 1 Hz neuronavigated rTMS at 80% RMT applied at right pTr	• Language testing (BDAE-SF; PPVT-R; GOAT; MAIN) • Cognitive testing (problem solving skills) (RCPM) • QoL assessment (SAQOL-39g)
Time (relative to start of treatment)		
– 12 & – 1 days (baseline 1 & 2)	0 days (rTMS therapy)	+ 1 day & + 2 months (post rTMS)
Note: Participants were assessed with the background measures 12 days prior to treatment; underwent an MRI scan during the week prior to treatment and; underwent language and cognitive testing 12 days and again 1 day prior to treatment and QoL assessment 1 day before treatment. Then, all participants received a 10-consecutive day rTMS treatment; underwent language and cognitive testing again 1 day after and 2 months post treatment and; underwent QoL assessment 2 months post treatment.		

The research protocol that was followed in this research is summarized in table 4-3.

Table 4-3: Pre- & Post- Therapy Procedures for all Participants

Step 1: Background Measures:

Patient Consent – Speech & Language History Form – Face Sheet – Screening for TMS eligibility – Hemispatial Neglect Test – Handedness Inventory

↓

Step 2: Recent Structural Brain MRI

↓

Step 3: Language Outcome Measures (Greek BDAE-SF, PPVT-R, GOAT, MAIN) – RCPM – SAQOL-39g

↓

Step 4: Therapeutic Procedures:

cTBS /1 Hz (low frequency) rTMS

↓

Step 5: Language Outcome Measures – RCPM – SAQOL-39g

↓

Data Analysis

4.9 Data Analyses

For the pilot study all outcomes for all baseline, post-treatment and follow-up measures were reported. For the main study, Weighted Statistics (WEST) and in particular the procedures “West-Trend” and “West-ROC” (one tailed) as suggested by Howard, Best and Nickels (2015) were applied. This method has been recently used by Kambanaros, Michaelides and Grohmann (2016) in a treatment study of a single participant using multiple baselines. Such method is suitable for studies with small sample sizes, heterogeneous participants and does not exclude any participant from receiving treatment. The rationale behind this concept is to establish the level of performance prior to treatment in order to evaluate the effects of treatment on the stimuli. Although currently the optimal number of pre-therapy probes is not clear, it is suggested that two probes are sufficient to provide an estimate of both level of

performance and rate of change (Howard et al., 2015). The West-Trend procedure tests whether there is a linear trend in improvement, while West-ROC analyses the amount of change in the treated versus the untreated periods. For the purposes of this study, those statistical procedures were conducted to evaluate a) the significance of treatment versus non-treatment (short-term effects of cTBS and rTMS (Pre 1 – Pre 2 – Post 1) and b) the short-term vs long-term effects of treatment (cTBS and rTMS) (Pre 2 – Post 1 – Follow-up). Weighted statistics were used to analyze data from the Greek BDAE-SF; PPVT-R; GOAT and RCPM. Outcomes from the MAIN and SAQOL-39g assessments were reported and described for each participant individually and no statistical analyses were performed.

4.10 Chapter Summary

This chapter detailed the trial methods and procedures relevant to this study. These included ethical considerations, the trial design, eligibility criteria for participants, settings, location, intervention, outcome measures and planned statistical analyses.

CHAPTER 5: Neuronavigated Theta Burst Stimulation for Chronic Aphasia: Two exploratory case studies [published 24/01/2019 in *Clinical Linguistics & Phonetics*]

Authors:

Anastasios M. Georgiou, Nikos Konstantinou, Ioannis Phinikettos, Maria Kambanaros

Affiliation for all authors:

Cyprus University of Technology

Department of Rehabilitation Sciences

Limassol, Cyprus

Abstract:

The present study reports the findings of a 10-day neuronavigated continuous theta burst stimulation (cTBS) over the right pars triangularis for two individuals with chronic aphasia after a single left hemispheric stroke. Baseline language and quality of life measures were collected prior to the treatment study, post-treatment and at 3-months follow-up. Therapy was tolerated well by both participants and no side effects were noticed during and after treatment. Results from one individual showed potential for positive change in performance in comprehension and expressive language both post-treatment and at the follow-up stage. Also, a trend towards improvement post-treatment was noticed in discourse and sentence productivity, and grammatical accuracy. In the follow-up stage, grammatical accuracy showed a trend towards improvement; discourse productivity decreased and; sentence productivity skills showed mixed results. Results from the other participant showed potential for positive change in comprehension post-treatment, that was maintained at the follow-up stage. However, a decline in expressive language post-treatment and at follow-up, stronger post-treatment, was noticed. Regarding QoL measurements, participant one appeared to have improved as his performance increased in the overall, physical and communication domains, but decreased slightly in the psychosocial domain. The second participant improved in the physical and communication domains and declined

overall and in the psychosocial domains. Findings from this study indicate that cTBS over the right pars triangularis may have the potential to improve various language skills in patients suffering from chronic aphasia post-stroke. However, the potential benefits of this fast, noninvasive brain stimulation protocol on improvement of language abilities post-stroke need further exploration.

Keywords: transcranial magnetic stimulation (TMS), neuronavigation, receptive and expressive language, quality of life, case-based approach

Introduction

Aphasia is an acquired communication disorder resulting from damage to brain areas responsible for language comprehension and/or production in spoken and written form. Being a significant sequela of stroke, aphasia affects more than a third of all stroke survivors (Heiss & Thiel, 2016; Dickey et al., 2010). In the context of Cyprus where this research was carried out, prevalence of post-stroke aphasia is unknown yet, on average 1200-1400 people each year suffer a stroke and years of healthy life lost due to stroke disability is estimated between 20-30 years (Cyprus WHO, 2015). Aphasia is associated with limitations in activities of daily living, loss of independence and a decrease in social participation (Northcott, Marshall & Hilari, 2016). If aphasia does not improve over time and becomes chronic, this leads to long-term disability (Gialanella, Bertolinelli, Lissi, & Prometti, 2011) and dependency (American Heart Association, 2008), increased societal burden (Northcott, Moss, Harrison & Hilari, 2016), family carer strain (Kniepmann & Cupler, 2014) and poor quality of life (Hilari, Needle & Harrison, 2012). Speech and language therapy (SLT) robustly remains the gold standard treatment for rehabilitation of aphasia. Intensive SLT is known to improve language skills in all stages post-stroke independent of severity and aphasia type (Saxena & Hillis, 2017). Nonetheless, more research is needed to define the optimal approach, type, frequency and duration of SLT (Brady et al., 2016). Currently, there is a need to develop novel cost-effective treatments to address the impact of aphasia.

Rehabilitation research exploring non-invasive brain stimulation techniques (NIBS), such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) as a treatment method for language deficits as consequence of stroke is on the rise (Georgiou, Lada & Kambanaros, in submission). This is because even if SLT is proven to be efficacious, many patients are left with residual language and communication deficits (Saxena & Hillis, 2017) upon discharge from speech and language therapy services. Depending on the frequency, intensity, and duration of the stimulation, TMS can lead to transient increases or decreases in excitability of the affected brain areas. When multiple TMS stimuli are delivered in trains (repeated single magnetic pulses of the same intensity), the term "repetitive TMS (rTMS)" is used. Results on MEP measurements in healthy people have led to the consensus that low frequency stimulation (≤ 1 Hz) induces inhibition, whereas high frequencies (≥ 5 Hz) induce excitation (Lefaucheur et al., 2014). It is assumed that excitation and inhibition represent changes in synaptic efficacy that are related to the after-effects of rTMS (Lenz, Muller-Dalhaus & Vlachos, 2016).

For treatment of aphasia post-stroke, both high and low frequency paradigms have been used. Inhibitory rTMS has been applied to the right hemisphere in order to increase language activity of the undamaged left hemisphere structures by suppressing competing right hemisphere language activation or simply by diminishing inhibitory processes in the right hemisphere. Most studies use a frequency between 1-4 Hz of rTMS to inhibit increased activation of the homologous BA45 and others have targeted right superior temporal areas (Priyanka, Shah-Basak & Hamilton, 2016). Over the last few years, there is robust evidence for the positive effects of low frequency (1 Hz) rTMS over the right triangular part of the inferior frontal gyrus (IFG) on language abilities (e.g. naming) as measured by standardized language tests in individuals with aphasia in the sub-acute phase after first-time stroke (Rubi-Fessen et al., 2015; Weiduschat et al., 2011; Thiel et al., 2006). Significant improvement following rTMS treatment, either inhibitory or excitatory, is reported in the literature also for naming accuracy (Thiel et al., 2006); language comprehension (Kakuda, Abo, Momosaki & Morooka, 2011); spontaneous speech (Naeser et al., 2012); and fluency (Abo et al., 2012). Several of the most recent rTMS studies for aphasia neurorehabilitation combine TMS with SLT (e.g. Rubi-Fessen et al., 2015; Seniow et

al., 2013; Naeser et al., 2012). Providing SLT as an adjunct treatment to rTMS may have a truly synergic outcome and boost language abilities, but it can also mask the actual therapeutic effects of rTMS.

Of major clinical interests are the positive findings from recent studies using short rTMS burst protocols, such as theta burst stimulation (TBS) paradigms, that have shown positive results in aphasia recovery (e.g. Griffis, Nenert, Allendorfer & Szaflarski, 2016; Vuksanovic et al., 2015; Kindler et al., 2012). The TBS paradigm was first introduced by Huang et al. in 2005. It was developed in animal experiments to mimic the normal pattern of neuronal firing in the hippocampus of the rodent (Huang & Rothwell, 2007). Research in humans (Oberman, Edwards, Eldaief & Pascual-Leone, 2011) has revealed that TBS protocols promote sustained changes in cortical activity that last well beyond the duration of TMS conditioning. TBS protocols are speedier than other rTMS paradigms which require much longer periods of conditioning and higher stimulus intensities in order to elicit changes in cortical excitability of a similar duration to TBS (Huang & Rothwell, 2007). There are two TBS paradigms; (i) intermittent TBS (iTBS), the basic TBS pattern delivered in a short train lasting for 2 seconds (secs) (i.e. 10 bursts in total), repeated every 10 secs for 20 cycles for a total of 600 pulses and (ii) continuous TBS (cTBS) that delivers the basic TBS pattern in a continuous, uninterrupted train lasting for a total of 40 secs (i.e. 200 bursts with a total 600 pulses). Huang et al. (2005) have demonstrated that in the iTBS pattern, motor evoked potential (MEP) size is facilitated for about 15 minutes, whereas in the cTBS paradigm, an important reduction of MEP size is observed which lasts for close to 60 minutes.

Recent TBS studies provide evidence that this quick NIBS protocol induces positive functional language changes. Griffis et al. (2016) applied iTBS over the residual language responsive cortex in or near the left inferior frontal gyrus (IFG), as identified using an fMRI language task, for five consecutive days over the course of two weeks. One-week post-iTBS, the researchers found that treatment was associated with (i) increases in left IFG activation magnitudes and decreases in right IFG activation magnitudes during covert verb generation, (ii) reduced right to left IFG connectivity during covert verb generation, and improvements in fluency. Vuksanovic et al. (2015)

applied for 15 daily sessions, cTBS over the Broca's area homologue of the right hemisphere and immediately after, applied iTBS over the left hemisphere Broca's area in a right-handed patient with chronic non-fluent aphasia post-stroke. The researchers found improvement in several language functions, most notably in propositional speech, semantic fluency, short-term verbal memory, and verbal learning. Kindler et al. (2012) applied cTBS over the right Broca's homologue in18 patients with aphasia in different post-stroke phases. Their cTBS protocol included 801 pulses delivered in 267 bursts and each burst contained 3 pulses at 30Hz, repeated with an interburst interval of 100 ms. Total duration of a train was 44 seconds. The researchers found that naming performance was significantly better, and naming latency was significantly shorter post-cTBS than post sham intervention.

The aim of this research was the investigation of possible changes in language performance using cTBS as a standalone treatment for aphasia rehabilitation in two patients with chronic aphasia post-stroke. We hereby report language and quality of life outcomes at pre-therapy (baseline), post-therapy and follow-up (three months post-treatment). In this exploratory research an rTMS protocol similar to Kindler et al. (2012) was followed.

Materials and Methods

The Template for Intervention Description and Replication (TIDieR) 12 item checklist and guide (Hoffmann et al., 2014) was adhered to improve the reporting of the intervention study, and for the future replicability of the study (see Appendix 1 for the TIDieR checklist completed by the authors). Ethical approval was given by the Cyprus National Bioethics Committee prior to the commencement of the research.

Participant 1

The first participant was a 61-year-old male who had suffered a left middle cerebral artery (MCA) stroke 20 months prior. He presented with mild to moderate anomic aphasia, had attended twice weekly speech and language therapy sessions for 8-months, and withdrew from treatment two weeks before enrolling in the present study.

Participant 2

The second participant was a 39-year-old female who had suffered a left MCA stroke 25 months prior. She presented with severe global aphasia. She had attended twice weekly speech and language therapy sessions for ten months and withdrew from therapy two weeks before enrolling in this study. Table 1 presents the background demographics of the participants.

Table 1. Demographic and clinical characteristics of the PWA participating in the research.

Participant	**Sex**	**Age (years)**	**Education (years)**	**Months post stroke**	**Lesion site**	**Type of Aphasia**	**Severity of Aphasia**	**SLT prior to enrolment**	**Termination of SLT**
1	M	61	12	20	LMCA	Anomic	mild to moderate	8 months – 2 times per week – 45 min of SLT	15 days before enrolment
2	F	39	12	25	LMCA	Global	severe	10 months – 2 times per week – 45 min of SLT	15 days before enrolment
Note: LMCA= Left Middle Cerebral Artery; PWA=people with aphasia; SLT=speech and language therapy									

Both participants were enrolled in the study as they met the following inclusion criteria: (1) they were native speakers of (Cypriot) Greek (to avoid confounding the study with bilingual issues); (2) a recent brain magnetic resonance imaging (MRI) confirmed a first-ever stroke in the left (dominant) hemisphere; (3) they had chronic aphasia (time elapsed since stroke > 6 months); (4) the presence of aphasia was diagnosed using the Greek version of the Boston Diagnostic Aphasia Examination – Short Form (BDAE-SF) (Messinis, Kastellakis, Panagea & Papathanasopoulos, 2013); (5) chronological age was no greater than 75 years. In addition, a key prerequisite for participation in the study was the willingness to withdraw from any speech and language therapy for the whole duration of the program (i.e. four months). Exclusion criteria were as follows: (1) non- native Greek speakers; (2) symptomatic prior cerebrovascular accidents (CVAs); (3) standard MR imaging, TMS and tDCS exclusion criteria; (4) severe comprehension deficits; (5) severe apraxia of speech or

dysarthria affecting intelligibility; (6) auditory or visual deficits and; (6) cognitive disorders known before the stroke.

Background Language Measures

The Boston Diagnostic Aphasia Examination (BDAE-SF)

For the purposes of the study, the primary outcome measure that determined the presence, type and severity of aphasia was the Greek BDAE-SF (Messinis et al., 2013). The battery includes evaluation of language comprehension (e.g., words, commands, small paragraphs), expressive language (spontaneous speech, picture description, naming, word and sentence repetition, automatised sequences) reading and writing. Obtained scores can be converted into a language deficit score and a measure of aphasia severity for language functioning assessment in acute and sub-acute stroke. The tool has satisfactory psychometric properties (Messinis et al., 2013). For the purposes of the present study, written language was not assessed.

Multilingual Assessment Instrument for Narratives (MAIN) and Quantitative Production Analysis (QPA) protocol

The Multilingual Assessment Instrument for Narratives (MAIN) (Gagarina et al., 2012) was used to measure spontaneous language abilities. Narratives are considered an ecologically valid measure that represent functional communication or language (production of phrases, sentences) as used in everyday life tasks (Brady et al., 2016). For the purposes of this study, both participants were asked to tell the experimenter the 'Baby Goat' story using a series of six-coloured pictures presented in a cartoon strip. See Appendix 1. The MAIN Baby Goat story depicts a mother goat saving her baby goat from drowning and from a hungry fox, that is also chased away from eating the baby goat by a bird. The story is controlled for cognitive and linguistic complexity and has a moral meaning similar to an Aesop fable. The MAIN was developed for children but can also be used with adults as the pictures are appropriate for adults (see Appendix 1). The story has episodic structure and provides macrostructure and microstructure information (Gagarina et al., 2012).

Spontaneous speech samples from the MAIN were audio-recorded, then transcribed in standard orthography and in phonemic transcription by a linguist, native speaker of

Cypriot Greek, and later analysed using the "Quantitative Production Analysis" (QPA) protocol (Saffran et al., 1989) as adapted by Varkanitsa (2012). The QPA measures the formal/structural characteristics of language production, yielding structural complexity scores and description of error types. For the two participants with aphasia, utterances were subdivided into sentences with verbs, sentences without verbs, and single word utterances. Following on from Varkanitsa's proposed modification of the protocol, utterances consisting of just a single verb and no other lexical items were classified as sentences with verb, taking into account the null-subject nature of Greek. The mean length of utterance (MLU) was calculated by measuring the number of words in each utterance and calculating its average. The number of syntactically well-formed sentences with verb was recorded and a proportion was calculated by dividing the number of well-formed sentences by the total number of sentences produced with a verb. For each narrative sample, the words were categorised as nouns, verbs, pronouns (including strong and weak clitic forms), adjectives, adverbs, prepositions, or as closed class words (a grouping that included determiners, auxiliaries and other functional vocabulary which do not have full lexical meaning, and that belong to word categories that do not easily admit new members through neologism or derivation). The number of tokens that belonged to each category was recorded and the proportions were calculated in relation to the total number of narrative words. This categorisation into word types allowed for the observation of differentiated performance patterns between the two participants. The sentences containing a verb were further analysed by calculating the 'AUX Score' metric (as adapted for Greek by Varkanista, 2012), which is calculated by assigning one point for each of the features MODAL, TENSE, ASPECT, NEGATION as encoded by the Main (Matrix) Verb of each independent clause and calculating the average score. The AUX Score Index is the average AUX Score minus one (one is subtracted to account for the base form of the verb). The verbs were scored based on the presence of the feature, and not their syntactical or semantic felicity as the goal is to measure the complexity of the produced verbs (Saffran et al., 1989). Concerning the verb phrase, two more complexity scores were calculated: the Embedding Index, and the Elaboration Index. The Embedding Index was the average of embedded clauses (clauses introduced by a subordinating particle, or a relative pronoun, or clauses used as verb objects) produced across the total number of sentences. The Elaboration Index

was calculated by measuring the average number of Open Class words (i.e. Nouns, Verbs, Adjectives, and Adverbs) and of Pronouns (either strong pronouns or clitics) in the Subject Noun Phrase and in the Verb Phrase. The two averages are added together to calculate the total Elaboration Index. In addition to the QPA, we followed Varkanitsa (2012) and calculated the proportion of errors-by-type produced (and left unrepaired) in each sample. The error types were the following: i) phonological, ii) morphosyntactic, iii) semantic, iv) lexical, v) uninterpretable neologisms, and vi) extended circumlocutions. The two samples recorded before the treatment were averaged to produce a baseline score for comparison with the post-treatment and follow-up performance.

Stroke and aphasia quality of life scale-39 item (SAQOL-39g)

The Greek version of the SAQOL-39 was administered (Kartsona & Hilari, 2007). This questionnaire has been adapted and linguistically validated as a measurement of QoL in Greek speaking people with aphasia after stroke. The psychometric properties of the Greek version have been tested in its generic form (SAQOL-39g) (i.e. the exact same tool tested with a generic stroke population with and without aphasia) and was found to be a valid and reliable scale that can be used as an outcome measure (Efstratiadou et al., 2012).

Procedures

The pre- and post- therapy procedures were the same for both participants. A certified speech and language pathologist, blind to the study, carried out the language assessment and QoL measures (baseline, post-treatment, follow-up), and later analyzed the data for all time points. The first author administered the rTMS protocol. Specifically, QoL measurements were obtained at two time points: baseline and at follow-up. Both participants struggled to respond to the SAQOL-39g questions because of mild-moderate comprehension deficits, so proxy (spouses) ratings were used to evaluate QoL. Even though unbiased self-reports are the most appropriate source of QoL, ratings by proxies can provide clinicians with useful information if patients are unable to self-report (Ignatiou et al., 2012).

After completion of the treatment period (10 consecutive days), participants were asked not to participate in any formal aphasia rehabilitation program. Instead, they were encouraged to actively engage in conversations with their families and friends. Such activities were not monitored by the researchers.

cTBS treatment

Resting motor threshold (RMT) was assessed using surface electromyography (EMG) for which electrodes were placed over the first dorsal interosseous (FDI) muscle of the left hand. The coil was then placed over the right primary motor cortex and stimulated, with a single-pulse, at the optimal site for obtaining a motor evoked potential (MEP) of at least 50μV in five or more of 10 consecutive stimulations of the FDI of the left hand. Motor threshold levels were used to determine stimulation parameters as they are considered an indication of cortical excitability.

After obtaining RMTs, participants underwent cTBS at 80% of their individual RMT, using the Magstim Rapid2® stimulator (Magstim Co., Wales, UK) connected to a 70mm Double Air Film Coil. Stimulation parameters were in accordance with the guidelines proposed by Wassermann (1998). However, before stimulation, a T1-weighted MRI image was obtained from each patient. The position of the stimulation coil was guided by a frameless stereotactic neuronavigation system (ANT NEURO) that used the individual patient's MRI scan to precisely localize the target area for stimulation. Both participants received inhibitory rTMS (cTBS) to the pars triangularis (Tr) of the right inferior frontal gyrus (homologous BA45) following the protocol suggested by Huang et al. (2005). This paradigm uses a theta burst stimulation pattern (TBS) in which three pulses of stimulation are given at 50 Hz, repeated every 200 ms. In the cTBS, a 40 sec train of uninterrupted TBS is given (600 pulses in total). In total, the program for each patient consisted of 10 daily stimulation treatments (10 consecutive days). To ensure treatment fidelity, we monitored and measured how well the treatment protocol was implemented using the TIDieR checklist as reported in Appendix 2.

Results

Language outcome measures are reported in table 2 for both participants.

Table 2. Language outcomes at post-treatment and follow-up compared to baseline for each participant.

	Participant 1				**Participant 2**			
Item	Baseline scores	Post TMS scores	Follow-up scores	Normal Controls (age 60-82)	Baseline scores	Post TMS scores	Follow-up scores	Normal Controls (age 25-39)
Auditory comprehension	25/32	26/32	27/32	30.97/32 (*SD*=1.02)	14/32	17/32	17,5/32	31.91/32 (*SD*=.28)
Expressive language (Boston naming test – excluded)	19/35	25/435	21/35	32.45/33 (*SD*=1.00)	11/48	7/48	9/48	33/33 (*SD*=.000)
Boston naming test – Accuracy	10/15	10/15	10/15	14.76/15 (*SD*=.622)	2/15	1/15	1/15	15/15 (*SD*=.000)

Participant 1

Auditory comprehension showed a trend towards improvement post-treatment that was sustained in the follow-up stage. Expressive language improved significantly post-treatment and even though it decreased in the follow-up stage, it was slightly higher compared to baseline. Naming scores remained stable post-treatment and in the follow-up. Regarding narration analysis (see table 3), compared to baseline, the participant produced a higher number of narrative words in the post-treatment assessment. The elaboration index of sentence productivity showed a trend in increase for the embedding index. The proportion of well-formed utterances increased, and the AUX complexity index remained stable. The proportion of errors remained stable. In the follow-up stage, the number of narrative words decreased compared to baseline. Regarding sentence productivity, the elaboration index remained increased as in the post-treatment phase and the embedding index reverted to baseline. The proportion of

well-formed utterances increased compared to baseline and post-treatment phases and the proportion of errors remained stable.

Table 3. A detailed linguistic analysis of spontaneous language for participant 1.

Category	Participant 1		
Lexical Selection	**1**	**Post**	**Follow-up**
Closed class:	23	24	11
Nouns:	13	16	11
Adjectives:	0	0	2
Prepositions:	9	9	5
Adverbs:	0	2	2
Pronouns:	7	17	8
Verbs:	21	23	13
Sentence Productivity			
MLU:	5,21	5,06	4,73
Elaboration Index:	1,5	2,06	2
Embedding Index:	0,3	0,39	0,27
Discourse Productivity			
Narrative words:	73	91	52
Grammatical Accuracy			
Prop of S with V:	14	17	10
Prop of U w/o V:	0	1	1
Prop of Single Word U:	0	0	0
Prop of well-formed U:	0,36	0,47	0,6
AUX Complexity Index:	1,00	1,00	1,00
Error Types:			
Phonological:	0	1	1
Morphosyntactic:	1	0	3
Semantic:	0	1	0
Lexical:	2	5	1
Neologisms:	2	0	0
Circumlocution:	0	0	0
Phonological %:	0,00	0,01	0,01
Morphosyntactic %:	0,01	0,00	0,06
Semantic %:	0,00	0,01	0,00
Lexical %:	0,03	0,05	0,01
Neologisms %:	0,03	0,00	0,00
Circumlocution %:	0,00	0,00	0,00
All Errors %:	0,07	0,07	0,08

Key: prop=proportion; s=sentences; V=verbs; U=utterances; w/o=without

The QoL for this participant improved post TMS as it was higher in all areas assessed compared to baseline, but the psychosocial score had decreased. Outcomes for QoL measures are shown in table 4.

Participant 2

Auditory comprehension improved post-treatment and this improvement was sustained in the follow-up stage. Expressive language decreased significantly post-treatment, but at follow-up showed a trend towards improvement. Naming scores decreased slightly post-treatment and during follow-up. With regards to the narrative analysis, the samples could not be analysed because they consisted only of one pronoun "toutos" (translation 'him'), and some automatized expressions. Spontaneous speech samples for both participants are reported in Appendix 3.

In terms of her QoL scores, outcomes showed that the psychosocial score had significantly decreased. Outcomes for QoL measures are shown in table 4.

Table 4. Quality of life for each participant at pre-treatment (baseline) and at 3 months follow-up using the SAQOL-39g.

	Participant 1		**Participant 2**	
Item (maximum score: 5)	**Baseline measure**	**3 months post TMS** (follow-up)	**Baseline measure**	**3 months post TMS** (follow-up)
SAQOL – 39g Mean score	3.61	3.92	2.89	2.56
Physical score	3.25	3.93	2.68	3.00
Communicate score	4.28	4.71	1.71	2.00
Psychosocial score	3.68	3.56	3.62	2.37

Discussion

In this explorative study, two participants were recruited to pilot whether cTBS as a standalone treatment (without SLT) has the potential to improve language symptoms in the chronic stage of aphasia. We followed a similar protocol to Kindler et al. (2012) but differed in that we used neuronavigated TMS and more sessions in total. Therapy was tolerated well by both participants and no side effects were noticed during and

after treatment. The first participant had mild to moderate anomic aphasia and showed potential for positive change in performance in comprehension and expressive language both post-treatment and at the follow-up stage. The change in expressive language performance was stronger post-treatment. Naming accuracy remained stable throughout treatment. Narration analysis revealed that post-treatment the participant showed a positive trend towards improvement in discourse, sentence productivity, and grammatical accuracy. In the follow-up stage, discourse productivity decreased and; the elaboration index of sentence productivity increased, while the embedding index reverted to baseline. Grammatical accuracy also showed a trend towards improvement. Regarding QoL measurements, participant 1 appeared to have improved as his performance in the overall, physical and communication domains increased, but in the psychosocial domain it decreased. The second participant had global aphasia and showed potential for positive change in comprehension post-treatment, that was maintained at the follow-up stage. However, she showed a decline in expressive language post-treatment and at follow-up, that was stronger post-treatment. Naming accuracy scores also showed a trend towards decline post-treatment and follow-up. Analysis of narratives was not possible for this participant because of her limited verbal output. However, she showed improvement in the QoL physical and communication domains but a decline in the psychosocial domain.

Considering the unequal demographic variables (e.g. age), aphasia types (anomic vs. global) and only two participants an attempt to draw conclusions on cTBS effects in chronic aphasia would be problematic. However, the trend towards improvement that was noticed in comprehension (in both participants) and expression (in one participant) in our study is in accordance with findings from recent TBS studies, either iTBS (Griffis et al., 2016; Szaflarski et al., 2011), cTBS (Kindler et al., 2012) or bilateral iTBS and cTBS (Vuksanovic et al., 2015) that support positive changes in various language domains post-stroke. Particularly relevant to our study, Kindler et al. (2012) investigated the effects of cTBS in one group of stroke patients that were in the subacute phase of stroke recovery compared to a second group of stroke patients in the chronic phase. Both groups significantly improved and the subacute group showed a greater improvement in naming accuracy and reaction time compared to the group with chronic aphasia compared to a sham group. Even though the findings of

this study favoured the use of cTBS for treatment of aphasia post-stroke, the lack of a follow-up assessment was an important drawback since the possible long-term effects of this type of therapy are unknown, and the contribution of spontaneous recovery cannot be excluded.

Positive changes (Rubi-Fessen et al., 2015; Weiduschat et al., 2011; Naeser et al., 2005) and trends toward improvements in specific groups of patients with aphasia (Seniow et al., 2013, Waldowski et al., 2012) in several language domains are also associated with other inhibitory rTMS protocols applied in aphasia post-stroke. There are several reasons reported for the variability in response to TMS amongst different patients with aphasia, such as aphasia type, aphasia chronicity, site of stimulation, TMS stimulation parameters, and the use of SLT combined with TMS (Coslett, 2016); and even age, gender and genetics can also play a role in the biological and clinical effects of rTMS protocols (Lefaucheur et al., 2014). Therefore, the failure or success of rTMS protocols can be attributed to either extrinsic and/or intrinsic therapeutic factors.

With regards to stimulation parameters in particular, the dichotomy between low frequency stimulation ($\leq$ 1 Hz) related induced inhibition and high frequencies ($\geq$ 5 Hz) related induced excitation is not 100% correct as there is evidence that both conditions can have mixed excitatory and inhibitory results (Houdayer et al., 2008). For instance, doubling the duration of stimulation on the motor cortex can reverse excitation to inhibition and vice versa (Gamboa, Antal, Moliadze & Paulus, 2010). In addition, the cellular and molecular mechanisms underpinning rTMS based therapies are not fully understood in clinical populations (Muller-Dahlaus & Vlachos, 2013). What complicates the elucidation of such mechanisms even more is that in chronic patients, when prolonged therapeutic effects (i.e. up to several months) are observed, placebo effects (that reflect a complex mixture of neurobiological effects (Benedetti, 2010; Krummenacher et al., 2010), should also be taken into consideration (Lefaucheur et al., 2014). In our case, our first participant was highly motivated to take part to the study and hoped to improve post-treatment.

People with aphasia form a highly heterogeneous group with large individual differences in post-stroke linguistic profiles, severity, type of aphasia, and recovery patterns (Brady et al., 2016), making accurate prognosis difficult. Generally, several factors are thought to influence recovery of language functions, but the evidence so far is not straightforward. For example, conflicting evidence exists in relation to the impact of sex (Sohrabji, Park & Mahnke, 2017), age (Lazzarino, Palmer, Bottle & Aylin, 2011), handedness and educational background (Henseler, Regenbrecht & Obrig, 2014) on language recovery. Also, there is research that places additional importance on the initial aphasia profile (severity, modalities involved) as a contributing factor of the type of language recovery (Gialanella & Prometti, 2009).

In our study, in addition to standardized language assessments, we also employed an assessment of narrative production as we aimed at assessing not only the effects of rTMS on experimental language tasks, but also on an everyday life task, as functional communication is based on production of phrases, sentences and on narration. To our knowledge, only Medina et al. (2012) assessed discourse productivity (narrative words, closed-class words, open-class words), sentence productivity, grammatical accuracy and lexical selection. The use of QPA in this study exhibited some predictive power, but some concerns about its applicability to Greek arose: the AUX score measure, even with the modifications by Varkanista (2012), relies on the rate of omission of verb features such as tense and aspect to score their complexity. Unlike English, tense and aspect omissions are not common, since the morphemes that express it are obligatory parts of the verb and not auxiliaries. Additionally, tense in Greek verbs is expressed syncretically with person and number, which might make it more salient and less likely to be omitted. Moreover, complex subject noun phrases containing subordinated clauses were not present, since those were not elicited directly even though opportunities for them to be used were provided by the story the participants were asked to tell. This measure was later removed from the elaboration index formula we used since there was no effect.

Overall, the trends towards improvement in specific language domains from baseline to post-treatment and follow-up assessments (comprehension in both participants

post-treatment and at follow-up and; expressive language in one participant post-treatment and at follow-up) might be due to the TBS treatment.

Conclusion

Continuous TBS was successfully applied to two individuals with chronic aphasia post-stroke and no adverse effects were noticed during treatment and follow-up periods. We tentatively suggest that TBS shows potential to facilitate recovery of language abilities in chronic aphasia despite its short application. Further investigation is warranted and specific functional markers and biomarkers of good responders to noninvasive brain stimulation methods need to be explored and established.

"Disclosure of interest"

The authors report no conflict of interest.

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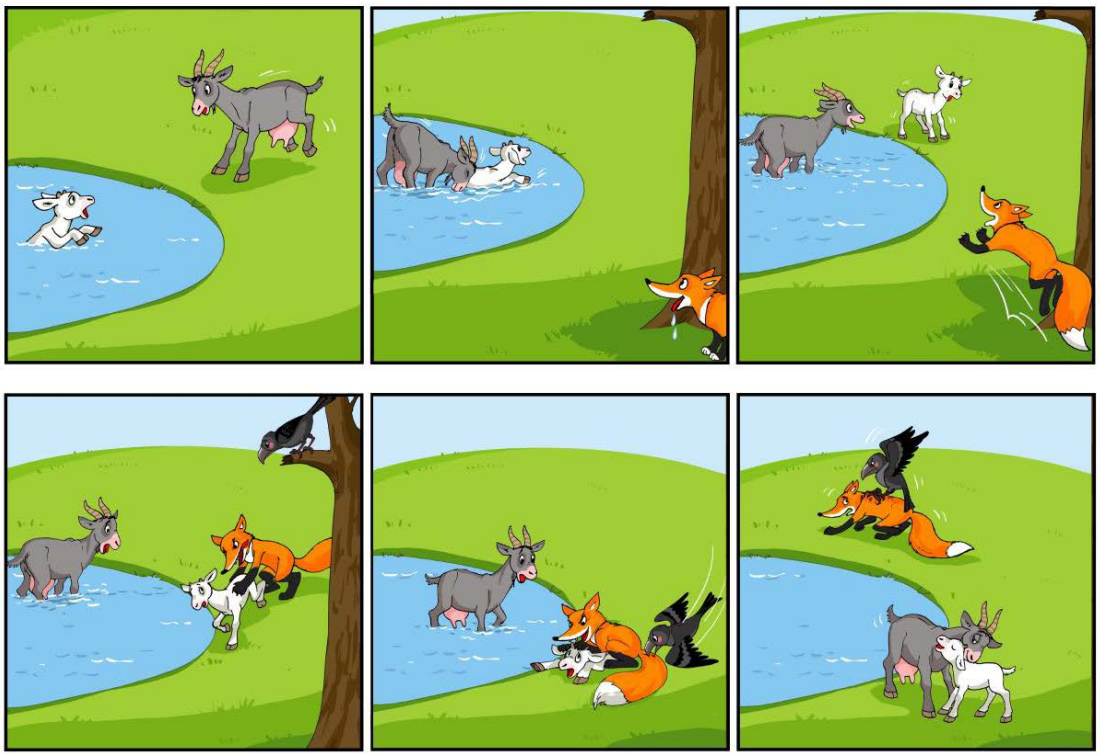
Appendix 1: The pictures of the MAIN ‘Baby Goat Story’



Appendix 2: Evaluation of the study using the TIDieR checklist

The TIDieR (Template for Intervention Description and Replication) Checklist

	BRIEF NAME
1.	Neuronavigated Theta Burst Stimulation for Chronic Aphasia
	WHY
2.	To determine whether cTBS as a standalone treatment has the potential to improve language symptoms of aphasia and subsequently quality of life.
	WHAT
3.	Materials: A certified speech and language pathologist, blind to the study, assessed and analysed the data. The first author administered the rTMS protocol. Language measurements were obtained at 3 time points; at baseline, immediately after treatment and at 3 months post-treatment (follow-up assessment). Quality of life measurements were obtained at baseline and at follow-up. Both participants struggled to deal with SAQOL-39g due to comprehension deficits, so proxy (spouses) ratings were used to evaluate QoL. After completion of the treatment period (10 consecutive days), participants were asked not to participate in any formal aphasia rehabilitation program but; they were encouraged to actively engage in conversations with their families and friends. Such activities were not monitored by the researchers.
4.	Procedures: We assessed resting motor threshold (RMT) using surface electromyography (EMG). After obtaining RMTs, participants underwent the cTBS at 80% of their individual RMT, using a Magstim Rapid2® stimulator (Magstim Co., Wales, UK) connected to a 70mm Double Air Film Coil. Stimulation parameters were in accordance with the guidelines proposed by Wassermann (1998). The position of the coil was guided by a frameless stereotactic neuronavigation system (ANT NEURO) that uses the individual patients' MRI scan to precisely localize the target area for stimulation. Before stimulation, a T1-weighted MRI image was obtained from each patient to locate the optimal coil position. Both participants received inhibitory rTMS (cTBS) to the pars triangularis (Tr) at the right inferior frontal gyrus (homologous BA45) following the protocol suggested by Huang et al. (2005). This paradigm uses a theta burst stimulation pattern (TBS) in which 3 pulses of stimulation are given at 50 Hz, repeated every 200 ms. In the cTBS, a 40 sec train of uninterrupted TBS is given (600 pulses in total). In total, the program for each patient consisted of 10 daily stimulation treatments (10 consecutive days).
	WHO PROVIDED

5.	Speech & Language Assessments: Certified Speech & Language Pathologist with expertise in Aphasia rTMS: Certified Speech & Language Pathologist with expertise in neuronavigated rTMS for aphasia rehabilitation
	HOW
6.	The intervention was provided to one participant at a time and was delivered face to face. During treatment, participants sat comfortably on a chair. During the TMS treatments participants were monitored for potential side effects (e.g. pain, discomfort) and were asked (using thumb gestures) if they felt well before during and after the treatment.
	WHERE
7.	Cyprus University of Technology, University Rehabilitation Clinic, Neurorehabilitation Lab
	WHEN and HOW MUCH
8.	A 40 sec train of uninterrupted TBS was given (600 pulses in total). In total, the program for each patient consisted of 10 daily stimulation treatments (10 consecutive days).
	TAILORING
9.	No
	MODIFICATIONS
10.	No
	HOW WELL
11.	Planned: Inclusion and exclusion criteria were clearly predetermined. Treatment was devised by (Huang & Rothwell, 2007) based on neuroplasticity theory. Intended assessment and active therapy ingredients were reported before study initiation. All therapists adhered to the same protocol to ensure standardised delivery across participants. The fourth author provided expert consultation. Therapies were delivered on site. Before commencement of the exploratory trial, a non-aphasic participant acted as a "sample" participant to ensure that all TMS related procedures could be implemented as planned.
12.	Actual: All TMS sessions were monitored by two people (second author and a senior speech and language therapy student) to ensure that therapy was implemented as planned. The delivered intervention did not vary at all from the intended intervention.

Appendix 3: Spontaneous language samples

Participant 1

Pre–treatment narrative production (translated and transcribed)
Η κατσίκα ε: ε: η κατσίκα το μωρό ήταν μες το νερό εβού- ε: επήε να το φκάλει έξω.
i katsíka e: e: i katsíka to moro ítan mes to neró evu:- e: epíe na to fkáli ékso
The goat um um the goat the baby was in the water (it) rushe- um (it) went to get it out.

Τζι όπως ήταν δαμαί ο η κατσονι- κατσικόραινα που το που το έπεσε τζι έπκιασεν τον λύκο τζι έφυε τζιαι το ε το τζιείνο.
Τζιαι όπως ήταν έξω έπκιασεν το τζι έφεφκε.
tʃe ópos ítan ðamé o i katsóni- katsikórena pu to pu to épese tʃ épcasen ton líko tʃ éfie tʃe to e to tʃino. tʃe ópos ítan ékso épcasen to tʃ éfefke.
And as he- she was here, the goa- *goat-ess that- that *felled it and caught the wolf and left and that um *the that. And as she was outside she caught it and *was leaving.

Post–treatment narrative production (translated and transcribed)
Έφυεν μες το νερόν η αίγα και προσπαθεί να το βγάλει έξω. Τζιαι που μπροστά έσιει έναν λύκο που – νάμπου να κάμει.
éfien mes to nerón i éɣa ce prospaθí na to vɣáli ékso. tʃ pu mbrostá éʃi énan líko pu námpu na kámi.
She *left in the water the goat (formal name) and she tries to get it out. And at the front there's a wolf who what to do.

Ο: ο λύκος το είδε, το άρπαξε, μια – πούντη;
o: o líkos to íðe, to árpakse, mɲa púndi?
The wolf saw it, got hold of it, an – where is she?

Follow-up narrative production (translated and transcribed)
Βλέπει το κατσικάκι μες το νερό τζιαι β-β-β μπόρει να το φκάλει έξω.
vlépi to katsikáci mes to neró tʃe [v v v] mbóri na to fkáli ékso.
She sees the kid in the water and [v v v] can get it out.

Τζιαι μόλις το μουντάρει η – η μόλις το φκάλει έξω μουντά' η κατσικορώνα ε: κάμει το.
tʃe mólis to mundári i – i mólis to fkáli ékso mundá- i katsikórona e kámi to.
And as the – the attacks – As she gets it out *attack the *magpie um *does it.

Μόλις το βάλει στο στόμαν του, η κατσικορώνα ε: τον μουντάρει τζιαι πκιάει τον τζιαι φεύφκει.
mólis to váli sto stóman tu, i katsikoróna e: ton mundárei tʃe pcái ton tʃe féfkei
As he puts it in his mounth, the *magpie um attacks him and get *him and leaves.

Participant 2:

Pre–treatment narrative production (translated and transcribed)
Μπε μπε μπε
mbe mbe mbe
Baa baa baa

Τούτο έλα έλα έλα
túto éla éla éla
This come! come! come!

Κρα κρα κρα
kra kra kra
Caw caw caw

Άλατέ το
álate to
[álate] this (Novel word, uninterpretable)

Post–treatment narrative production (translated and transcribed)
Έλα έλα έλα
éla éla éla
come! come! come!

Για τάμμουμε;
ja tám:ume?
Lets [tám:ume]? (possibly “Let’s see” /na ðúme/)

Ντάξει;
ndáksi?
OK?

Follow-up sample narration production (translated and transcribed)
Έξω έξω
ékso ékso
Out out

Κύριε ‘λέησον
círie léison
Good lord (expression of surprise)

Για να δούμε για να μούμε
ja na ðúme ja na múme (phonological substitution)
Let’s see let’s see

CHAPTER 6: Results (Main Study)

This chapter presents baseline demographic and clinical characteristics of participants that took part in the main study; presents the results of the statistical analyses of standardized language and cognitive measures (i.e. BDAE-SF, PPVT-R, GOAT & RCPM) and also reports outcome summaries for MAIN and SAQOL-39g for all participants, individually.

6.1 Baseline Demographic and Clinical characteristics of Participants

Two of the six participants were females. All participants had suffered a first ischemic stroke at least 6 months before enrolment to the study. Participant characteristics are provided in table 6-1.

Participant 1

The first participant was a 74-year-old female who had suffered a left middle cerebral artery (MCA) stroke 48 months prior. She presented with severe global aphasia, had attended 2 weekly speech and language therapy sessions for 20 months, and withdrew from treatment 2 years before enrolling in the present study.

Participant 2

The second participant was a 61-year-old male who had suffered a left middle cerebral artery (MCA) stroke 9 months prior. He presented with moderate-severe, had attended 2 weekly speech and language therapy sessions for 6 months, and withdrew from treatment 2 months before enrolling in the present study.

Participant 3

The third participant was a 48-year-old male who had suffered a left middle cerebral artery (MCA) stroke 11 months prior. He presented with moderate-severe Broca's aphasia, had attended 4 weekly speech and language therapy sessions for 8 months, and withdrew from treatment 10 days before enrolling in the present study.

Participant 4

The fourth participant was a 72-year-old female who had suffered a left middle cerebral artery (MCA) stroke 50 months prior. She presented with moderate-severe anomic aphasia, had attended 2 weekly speech and language therapy sessions for 24 months, and withdrew from treatment 2 years before enrolling in the present study.

Participant 5

The fifth participant was a 55-year-old male who had suffered a left middle cerebral artery (MCA) stroke 8 months prior. He presented with severe global aphasia, had attended 4 weekly speech and language therapy sessions for 4 months, and withdrew from treatment 10 days before enrolling in the present study.

Participant 6

The sixth participant was a 26-year-old male who had suffered a left middle cerebral artery (MCA) stroke 109 months prior. He presented with mild anomic aphasia, had attended 4 weekly speech and language therapy sessions for 10 months, and withdrew from treatment 7 years before enrolling in the present study.

Table 6-1: Demographic and Clinical characteristics of the PWA participating in the study

Participant	Sex	Age (years)	Handedness	Education (years)	Type of stroke	Months post stroke	Lesion site (left hemisphere)	Type of Aphasia	Severity of Aphasia	SLT prior to enrolment	Termination of SLT
1	F	74	right	6	ischemic	48	diffuse frontal, parietal and temporal (middle and superior gyri) lobes; insula; basal ganglia	global	severe	20 months – 2 times per week – 45 min of SLT	2 years before enrolment
2	M	61	right	12	ischemic	9	Broca's and Wernicke's areas; arcuate fasciculus; insula; inferior precentral gyrus; temporal pole	anomic	moderate-severe	6 months – 2 times per week – 45 min of SLT	2 months before enrolment
3	M	48	right	15	ischemic	11	IFG; internal capsule; insula; caudate nucleus; putamen; inferior precentral gyrus	Broca's	moderate-severe	8 months – 4 times per week – 45 minutes	10 days before enrolment
4	F	72	right	12	ischemic	50	Broca's and Wernicke's areas; arcuate fasciculus; insula; superior posterior temporal gyrus; middle posterior temporal gyrus	anomic	moderate-severe	24 months – 2 times per week – 45 min of SLT	2 years before enrolment
5	M	55	right	17	ischemic	8	precentral gyrus; post central gyrus; arcuate fasciculus; internal capsule; caudate nucleus; putamen	global	severe	4 months – 4 times per week – 45 minutes	10 days before enrolment
6	M	26	right	16	ischemic	109	IFG; MFG; insula; basal ganglia; arcuate fasciculus; internal capsule; anterior temporal lobe; Wernicke's area	anomic	mild	10 months – 4 times per week – 45 minutes	7 years before enrolment

Key: PWA: people with aphasia; IFG: inferior frontal gyrus; MFG: middle frontal gyrus; SLT: speech and language therapy

6.2 Short- and long-term Outcomes on Standardized Language and Cognitive Measures (Greek BDAE-SF; PPVT-R; GOAT; RCPM)

Short-term (i.e. pre-treatment 1st measurement, pre-treatment 2nd assessment and 1-day post-treatment measurement) and long-term (i.e. pre-treatment 2nd measurement, 1-day post-treatment measurement and 2 months post-treatment measurement) assessments were conducted for each participant separately. A summary of intervention outcomes for each participant on all standardized language and cognitive measures is reported in table 6-2.

Table 6-2: Summary of Intervention Outcomes on Standardized Language and Cognitive Measures

Participant characteristics (all right handed)	**Greek BDAE-SF; PPVT-R; GOAT; RCPM (comprehension; expressive language; naming accuracy; reading; problem solving skills)**
P1: female; 74 years old; severe global aphasia; 48 months post-stroke (ischemic); 6 years of education **cTBS**	Short-term effects of cTBS (Pre 1 – Pre 2 – Post 1) • Trend towards improvement in expressive language Long-term effects of cTBS (Pre 2 – Post 1 – Follow-up) • Overall improvement in comprehension and reading
P2: male; 61 years old; moderate-severe anomic aphasia; 9 months post-stroke (ischemic); 12 years of education **cTBS**	Short-term effects of cTBS (Pre 1 – Pre 2 – Post 1) • Trend towards improvement in reading Long-term effects of cTBS (Pre 2 – Post 1 – Follow-up) • Trend towards improvement in comprehension and naming
P3: male; 48 years old; moderate-severe Broca's aphasia; 11 months post-stroke (ischemic); 15 years of education **cTBS**	Short-term effects of cTBS (Pre 1 – Pre 2 – Post 1) • Trend towards improvement in naming Long-term effects of cTBS (Pre 2 – Post 1 – Follow-up) • No trend/improvement in any domain
P4: female; 72 years old; moderate-severe anomic aphasia; 50 months post-stroke (ischemic); 12 years of education **1 Hz rTMS**	Short-term effects of 1 Hz rTMS (Pre 1 – Pre 2 – Post 1) • Trend towards improvement in comprehension and naming Long-term effects of 1 Hz rTMS (Pre 2 – Post 1 – Follow-up) • No trend/improvement in any domain
P5: male; 55 years old; severe global aphasia; 8 months post-stroke (ischemic); 17 years of education **1 Hz rTMS**	Short-term effects of 1 Hz rTMS (Pre 1 – Pre 2 – Post 1) • No trend/improvement in any domain Long-term effects of 1 Hz rTMS (Pre 2 – Post 1 – Follow-up) • Trend towards improvement in comprehension
P6: male; 26 years old; mild anomic aphasia; 109 months post-stroke (ischemic); 16 years of education **1 Hz rTMS**	Short-term effects of 1 Hz rTMS (Pre 1 – Pre 2 – Post 1) • Trend towards improvement in comprehension and reading Long-term effects of 1 Hz rTMS (Pre 2 – Post 1 – Follow-up) • Trend towards improvement in comprehension

Key: P: participant; Pre 1= baseline one; Pre 2=baseline 2; Post 1=immediately post-treatment; cTBS: continuous Theta Burst Stimulation; rTMS: repetitive Transcranial Magnetic Stimulation; BDAE-SF: Boston Diagnostic Aphasia Examination –Short Form; PPVT-R: Peabody Picture Vocabulary Test-Revised; GOAT: Greek Object and Action Test; RCPM: Raven's Coloured Progressive Matrices

6.2.1.1 Participant 1

Short-term effects of cTBS (Pre 1 – Pre 2 – Post 1)

Participant 1 did not show an overall improvement in cognition (problem solving skills), comprehension ($t(63) = 0.44$, $p = .32$), naming and reading. However, she showed an overall improvement in expressive language ($t(25) = 1.79$, $p = .04$), but the improvement was not higher in the treated versus the untreated period ($t(25) = .90$, $p = .19$). Results for the short-term effects of cTBS are shown in figure 6-1.

Short-term vs. long-term effects of cTBS (Pre 2 – Post 1 – Follow-up)

Participant 1 did not show an overall improvement in cognition (problem solving skills), expressive language ($t(25) = .57$, $p = .28$) and naming. However, she showed an overall improvement in comprehension ($t(63) = 3.66$, $p < .001$) and reading ($t(28) = 1.79$, $p = .04$) and this improvement was greater during the follow-up period compared to short-term for both comprehension ($t(63) = 2.61$, $p < .01$) and reading ($t(28) = 1.79$, $p = .04$). Results for the long-term effects of cTBS are shown in figure 6-1.

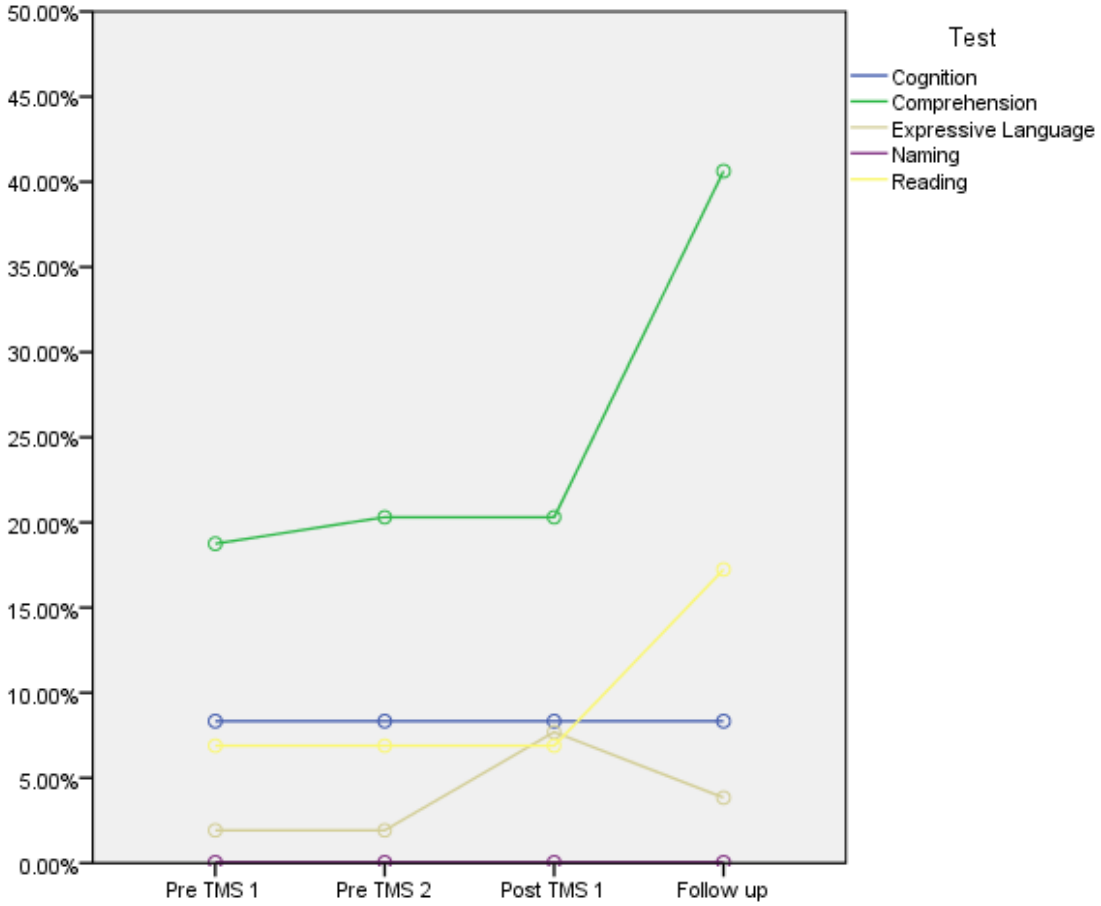


Figure 6-1: Short-term and long-term effects of cTBS for Participant 1

6.2.1.2 Participant 2

Short-term effects of cTBS (Pre 1 – Pre 2 – Post 1)

Participant 2 did not show an overall improvement in cognition (problem solving skills) ($t(35) = 0.32$, $p = .37$), comprehension ($t(63) = 1.52$, $p = .07$), expressive language ($t(25) = 0.46$, $p = .32$) and naming ($t(33) = -0.81$, $p = .79$). However, he showed an overall improvement in reading ($t(28) = 1.79$, $p = .04$), but the improvement was not higher in the treated versus the untreated period ($t(28) = 0.91$, $p = .187$). Results for the short- term effects of cTBS are shown in figure 6-2.

Short-term vs. long-term effects of cTBS (Pre 2 – Post 1 – Follow-up)

Participant 2 did not show an overall improvement in cognition (problem solving skills) ($t(35) = 0.37$, $p = .35$), expressive language ($t(25) = 0.63$, $p = .27$) and reading ($t(28) = 0.81$, $p = .21$). However, he showed an overall improvement in comprehension ($t(63) = 1.76$, $p = .041$) and naming ($t(33) = 1.75$, $p = .04$). However, this improvement was not higher in the follow-up stage compared to the short-term for either comprehension ($t(63) = 0.12$, $p = .45$) or naming ($t(33) = 1.07$, $p = .14$). Results for the long-term effects of cTBS are shown in figure 6-2.

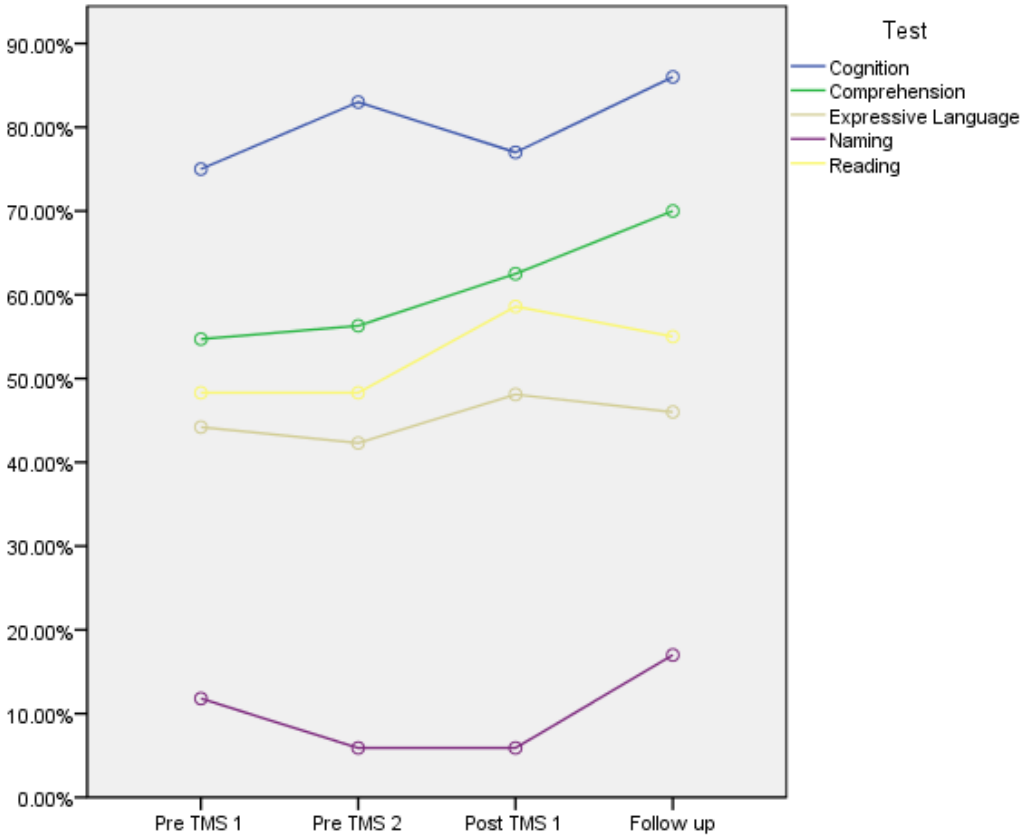


Figure 6-2: Short-term and long-term effects of cTBS for Participant 2

6.2.1.3 Participant 3

Short-term effects of 1 cTBS (Pre 1 – Pre 2 – Post 1)

Participant 3 did not show an overall improvement in cognition (problem solving skills) ($t(35) = -1.43$, $p = .91$), comprehension ($t(63) = 1.13$, $p = .13$), expressive language, and reading ($t(28) = 1$, $p = .17$). However, he showed an overall improvement in naming ($t(33) = 3.01$, $p < .01$), but the improvement was not higher in the treated versus the untreated period ($t(33) = -.55$, $p = .71$). Results for the short-term effects of cTBS are shown in figure 6-3.

Short-term vs. long-term effects of cTBS (Pre 2 – Post 1 – Follow-up)

Participant 3 did not show an overall improvement in cognition (problem solving skills) ($t(35) = 0.57$, $p = .28$), comprehension ($t(63) = 0.33$, $p = .37$), expressive language ($t(25) = 0.33$, $p = .37$), naming ($t(33) = 1.22$, $p < .01$) and reading ($t(28) = 0$, $p = .50$). Results for the long-term effects of cTBS are shown in figure 6-3.

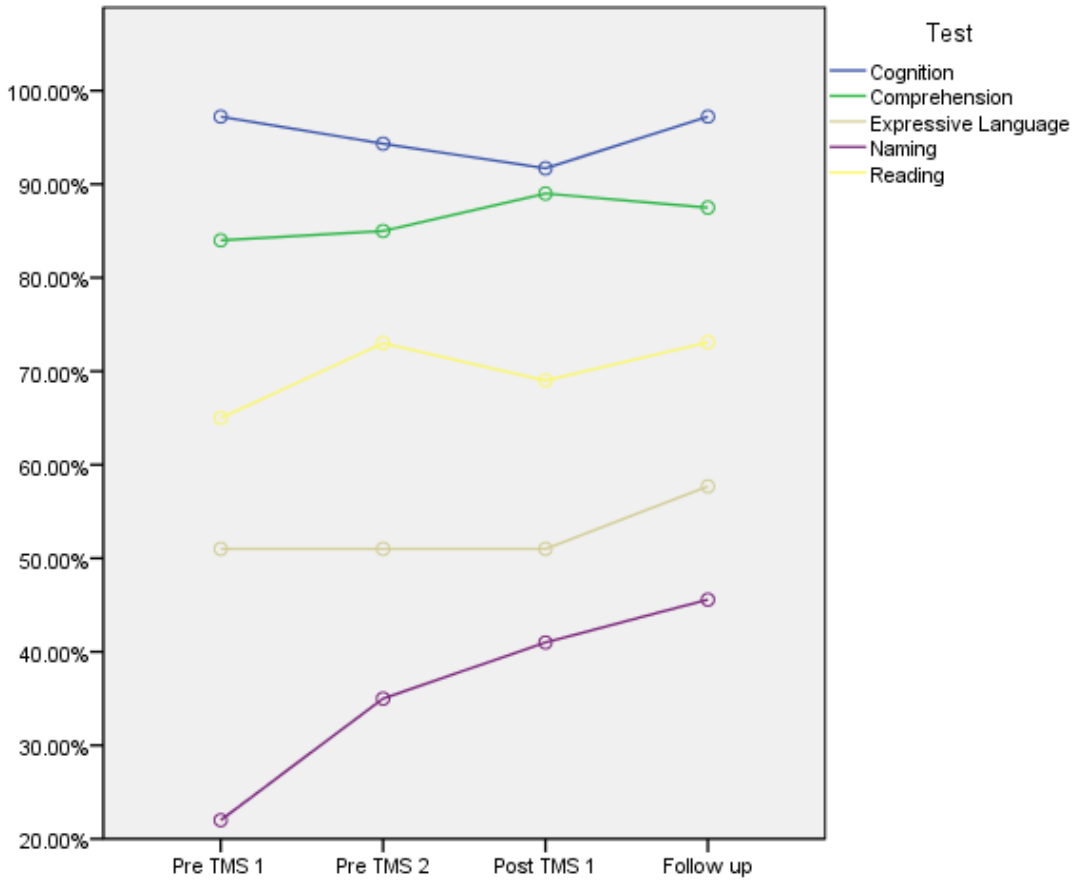


Figure 6-3: Short-term and long-term effects of cTBS for Participant 3

6.2.1.4 Participant 4

Short-term effects of 1 Hz rTMS (Pre 1 – Pre 2 – Post 1)

Participant 4 did not show an overall improvement in cognition (problem solving skills) ($t(35) = 1.07$, $p = .14$), expressive language ($t(25) = 0$, $p = .50$) and reading ($t(28) = 0$, $p = .50$). However, she showed an overall improvement in comprehension ($t(63) = 3.37$, $p < .001$) and naming ($t(33) = 2.31$, $p = 0.01$), but the improvement was not higher in the treated versus the untreated period for either comprehension ($t(63) = -.13$, $p = .55$) or naming ($t(25) = 1.09$, $p = .14$). Results for the short-term effects of 1 Hz rTMS are shown in figure 6-4.

Short-term vs. long-term effects of 1 Hz rTMS (Pre 2 – Post 1 – Follow-up)

Participant 4 did not show an overall improvement in cognition (problem solving skills) ($t(35) = -2.23$, $p = .98$), comprehension ($t(63) = -.046$, $p = .67$), expressive language ($t(25) = -1$, $p = .83$), naming ($t(33) = -0.29$, $p = .61$) and reading ($t(28) = 1.44$, $p = .08$). Results for the long-term effects of 1 Hz rTMS are shown in figure 6-4.

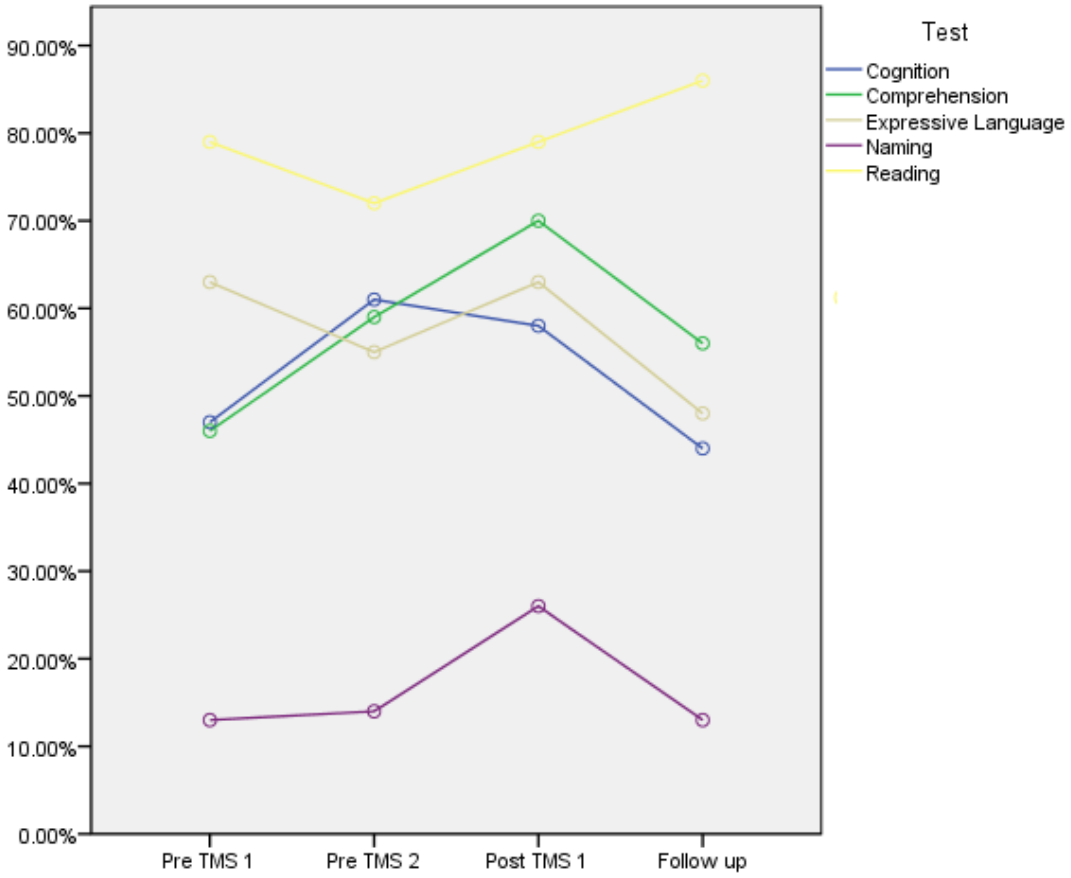


Figure 6-4: Short-term and long-term effects of 1 Hz rTMS for Participant 4

6.2.1.5 Participant 5

Short-term effects of 1 Hz rTMS (Pre 1 – Pre 2 – Post 1)

Participant 5 did not show an overall improvement in cognition (problem solving skills) ($t(35) = 0.43$, $p = .33$), comprehension ($t(63) = 0.46$, $p = .32$), expressive language, naming, and reading ($t(28) = 1.36$, $p = .09$). Results for the short-term effects of 1 Hz rTMS are shown in figure 6-5.

Short-term vs. long-term effects of 1 Hz rTMS (Pre 2 – Post 1 – Follow-up)

Participant 5 did not show an overall improvement in cognition (problem solving skills) ($t(35) = 1$, $p = .16$), expressive language, naming, and reading ($t(28) = 0$, $p = .50$). However, he showed an overall improvement in comprehension ($t(63) = 2.72$, $p < .01$), but this improvement was not higher in the follow-up stage compared to the short-term ($t(63) = 1.15$, $p = .12$). Results for the long-term effects of 1 Hz rTMS are shown in figure 6-5.

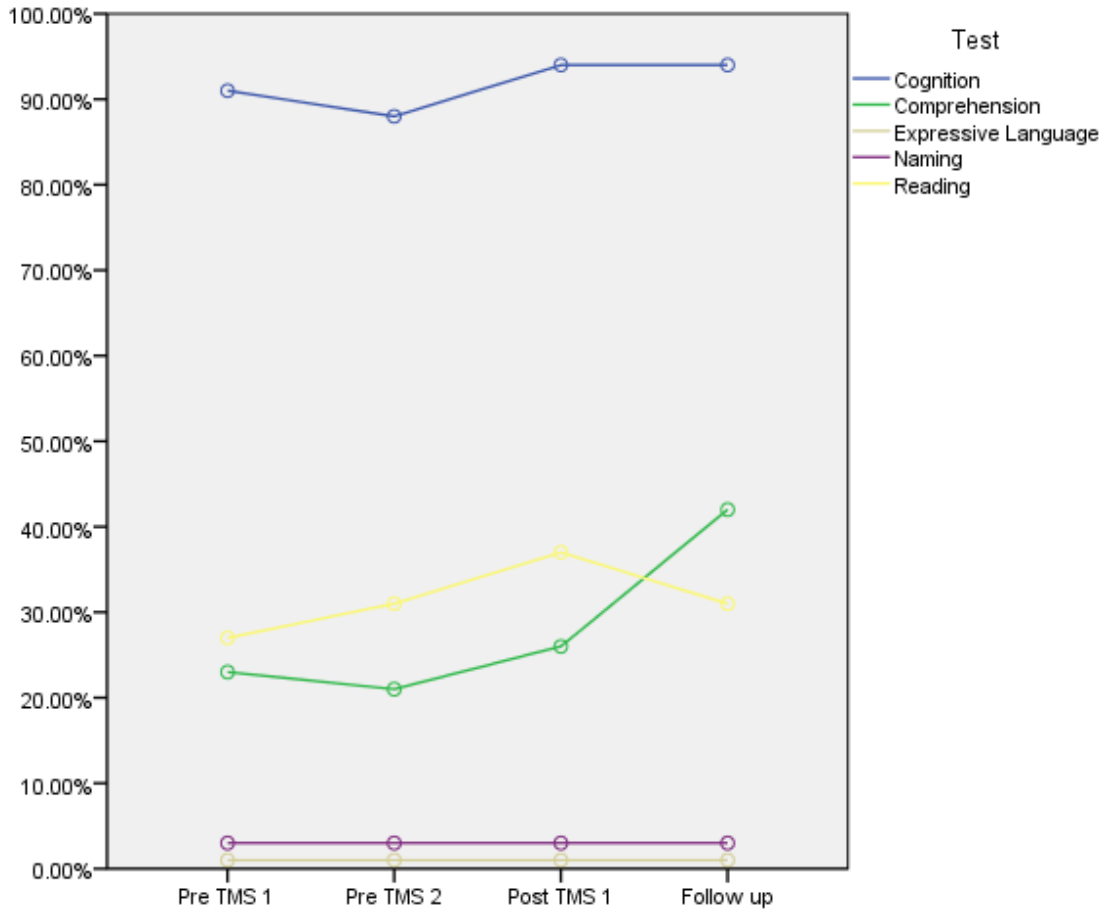


Figure 6-5: Short-term and long-term effects of 1 HZ rTMS for Participant 5

6.2.1.6 Participant 6

Short-term effects of 1 Hz rTMS (Pre 1 – Pre 2 – Post 1)

Participant 6 did not show an overall improvement in cognition (problem solving skills) ($t(35) = 0$, $p = 0.5$), expressive language ($t(25) = 0.70$, $p = .25$) and naming ($t(33) = 0.37$, $p = .35$). However, he showed an overall improvement in comprehension ($t(63) = 2.60$, $p < .001$) and reading ($t(28) = 2.25$, $p = .02$), but the improvement was not higher in the treated versus the untreated period for either comprehension ($t(63) = 0.77$, $p = .21$) or reading ($t(28) = -0.15$, $p = .44$). Results for the short-term effects of 1 Hz rTMS are shown in figure 6-6.

Short-term vs. long-term effects of 1 Hz rTMS (Pre 2 – Post 1 – Follow-up)

Participant 6 did not show an overall improvement in cognition (problem solving skills) ($t(35) = 1$, $p = .16$), expressive language ($t(25) = 1$, $p = .16$), naming ($t(33) = 1.49$, $p = .07$) and reading ($t(28) = .44$, $p = .33$) However, he showed an overall improvement in comprehension ($t(63) = 1.69$, $p = .04$), but this improvement was not higher in the follow-up stage compared to the short-term ($t(63) = -1.58$, $p = .93$). Results for the long-term effects of 1 Hz rTMS are shown in figure 6-6.

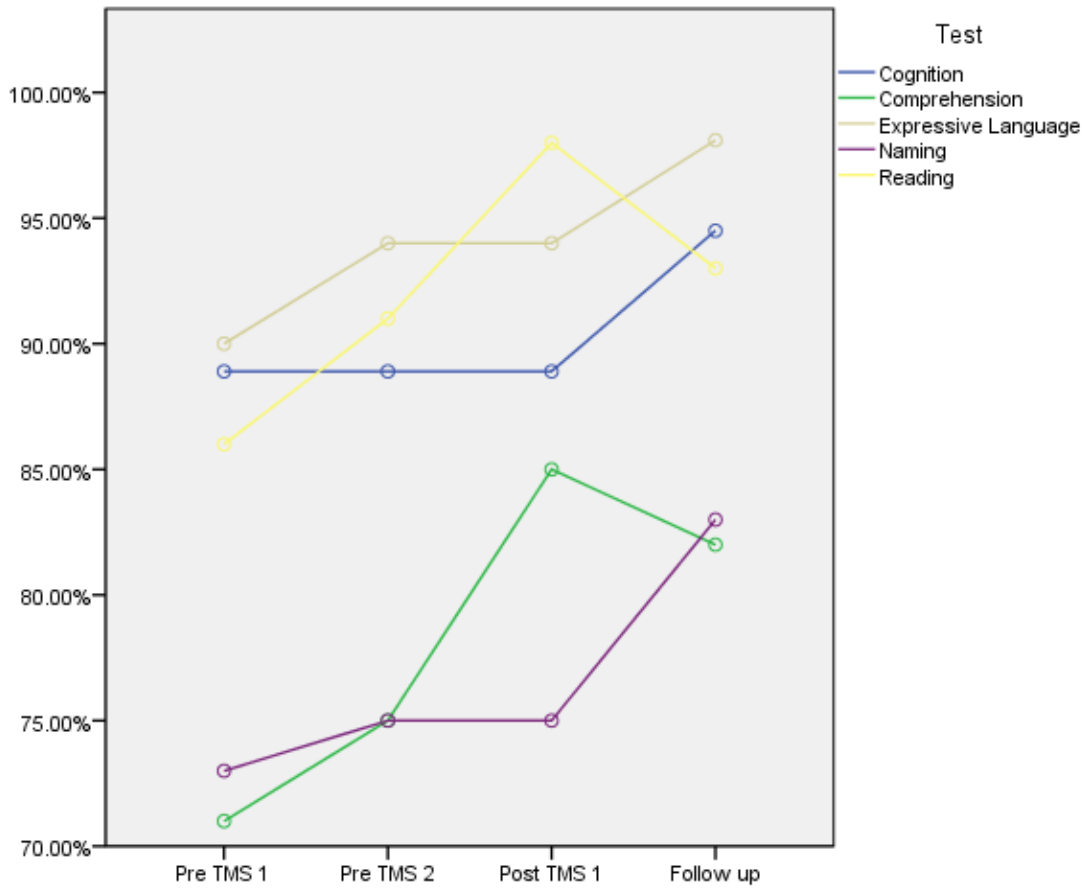


Figure 6-6: Short-term and long-term effects of 1 HZ rTMS for Participant 6

6.3 Short- and long-term Outcomes on the MAIN tool

Participants 1 and 5 had global aphasia and did not produce any narratives. Even though a baseline average score was calculated for each for the remaining participants (i.e. P2, P3, P4 & P6), for purposes of comparison only the 2nd pre-treatment assessment (baseline 2) was used as the baseline measurement because the number of narrative words was higher in baseline 2 compared to baseline 1, for all participants.

6.3.1.1 Participant 2

Baseline vs. post-treatment

Participant 2 produced a significantly higher number of narrative words (mostly adverbs and verb) in the post-treatment assessment phase compared to baseline. Sentence productivity decreased while grammatical accuracy and the proportion of errors remained stable. Results of the microstructure analysis of MAIN are shown in table 6-3.

Baseline vs. follow-up

At follow-up, P2 reverted to baseline 1 (slightly above baseline 1) with regards to the total number of narrative words. This was the case for all lexical categories except pronouns that increased at follow-up compared to baseline 2. Sentence productivity and grammatical accuracy decreased, while the proportion of errors remained stable. Results of the microstructure analysis of MAIN are shown in table 6-3.

Table 6-3: Narration outcomes for Participant 2

Category	Participant 2				
Lexical Selection	Pre 1	Pre 2	Baseline	Post	Follow -up
Closed class:	10	21	**15,50**	20	10
Nouns:	3	3	**3,00**	4	1
Adjectives:	4	7	**5,50**	11	4
Prepositions:	4	7	**5,50**	6	1
Adverbs:	1	4	**2,50**	16	5
Pronouns:	11	8	**9,50**	14	18
Verbs:	18	21	**19,50**	31	18
Sentence Productivity					
MLU:	2,55	4,44	**3,49**	3,40	3,17
Elaboration Index:	1,06	1,75	**1,40**	1,21	1,53
Embedding Index:	0,00	0,31	**0,16**	0,10	0,17
Discourse Productivity					
Narrative words:	51	71	**61,00**	102	57
Grammatical Accuracy					
Prop of S with V:	18	16	**17,00**	29	15
Prop of U w/o V:	2	0	**1,00**	0	2
Prop of Single Word U:	0	0	**0,00**	1	1
Prop of Well Formed U:	0,94	0,75	**0,85**	0,79	0,33
AUX Complexity Index:	1,06	1,07	**1,06**	1,00	1,00
Error Types:					
Phonological:	1	1	**1,00**	2	2
Morphosyntactic:	2	0	**1,00**	2	1
Semantic:	1	0	**0,50**	0	1
Lexical:	2	2	**2,00**	3	3
Neologisms:	0	0	**0,00**	0	0
Circumlocution:	0	1	**0,50**	0	1
Phonological %:	0,02	0,01	0,02	0,02	0,04
Morphosyntactic %:	0,04	0,00	0,02	0,02	0,02
Semantic %:	0,02	0,00	0,01	0,00	0,02
Lexical %:	0,04	0,03	0,03	0,03	0,05
Neologisms %:	0,00	0,00	0,00	0,00	0,00
Circumlocution %:	0,00	0,01	0,01	0,00	0,02
All Errors %:	0,12	0,06	0,08	0,07	0,14

Key: prop: proportion; s: sentences; V: verbs; U: utterances; w/o: without

6.3.1.2 Participant 3

Baseline vs. post-treatment

Participant 3 produced the same number of narrative words in the post-treatment assessment compared to baseline. Sentence productivity, grammatical accuracy and the proportion of errors remained stable. Results of the microstructure analysis of MAIN are shown in table 6-4.

Baseline vs. follow-up

At follow-up, P3 produced a significantly higher number of narrative words (mainly closed class words and nouns) compared to baseline. Sentence productivity decreased slightly and, grammatical accuracy and the proportion of errors remained stable. Results of the microstructure analysis of MAIN are shown in table 6-4.

Table 6-4: Narration outcomes for Participant 3

Category	Participant 3				
Lexical Selection	**1**	**2**	**Baseline**	**Post**	**Follow-up**
Closed class:	21	22	**21,50**	25	33
Nouns:	17	19	**18,00**	21	29
Adjectives:	4	2	**3,00**	1	5
Prepositions:	5	5	**5,00**	7	7
Adverbs:	3	2	**2,50**	0	2
Pronouns:	6	8	**7,00**	4	8
Verbs:	19	19	**19,00**	19	23
Sentence Productivity					
MLU:	5,36	6,42	**5,89**	6,42	5,35
Elaboration Index:	2,31	2,92	**2,61**	2,67	2,25
Embedding Index:	0,36	0,58	**0,47**	0,58	0,15
Discourse Productivity					
Narrative words:	75	77	**76,00**	77	107
Grammatical Accuracy					
Prop of S with V:	13	12	**12,50**	12	20
Prop of U w/o V:	1	0	**0,50**	0	0
Prop of Single Word U:	0	0	**0,00**	0	0
Prop of Well Formed U:	0,38	0,42	**0,40**	0,75	0,60
AUX Complexity Index:	1,07	1,00	**1,04**	1,17	1,05
Error Types:					
Phonological:	26	25	**25,50**	21	28
Morphosyntactic:	3	2	**2,50**	4	5
Semantic:	0	1	**0,50**	0	0
Lexical:	4	0	**2,00**	0	3
Neologisms:	4	4	**4,00**	0	0
Circumlocution:	0	0	**0,00**	0	2
Phonological %:	0,35	0,32	0,34	0,27	0,26
Morphosyntactic %:	0,04	0,03	0,03	0,05	0,05
Semantic %:	0,00	0,01	0,01	0,00	0,00
Lexical %:	0,05	0,00	0,03	0,00	0,03
Neologisms %:	0,05	0,05	0,05	0,00	0,00
Circumlocution %:	0,00	0,00	0,00	0,00	0,02
All Errors %:	0,49	0,42	0,45	0,32	0,36

Key: prop: proportion; s: sentences; V: verbs; U: utterances; w/o: without

6.3.1.3 Participant 4

Baseline vs. post-treatment

Participant 4 produced slightly fewer narrative words in the post-treatment assessment compared to baseline. Sentence productivity increased, grammatical accuracy decreased slightly and the proportion of errors remained stable. Results of the microstructure analysis of MAIN are shown in table 6-5.

Baseline vs. follow-up

At follow-up, P4 produced a significantly lower number of narrative words compared to baseline. This was the case for all lexical categories except prepositions and pronouns. Sentence productivity decreased and, grammatical accuracy and the proportion of errors remained stable. Results of the microstructure analysis of MAIN are shown in table 6-5.

Table 6-5: Narration outcomes for Participant 4

Category	Participant 4				
Lexical Selection	**1**	**2**	**Baseline**	**Post**	**Follow-up**
Closed class:	15	21	**18,00**	26	7
Nouns:	11	21	**16,00**	20	6
Adjectives:	0	7	**3,50**	2	0
Prepositions:	0	1	**0,50**	1	6
Adverbs:	1	1	**1,00**	0	0
Pronouns:	14	8	**11,00**	6	13
Verbs:	11	17	**14,00**	12	10
Sentence Productivity					
MLU:	3,50	4,00	**3,75**	4,86	3,23
Elaboration Index:	2,38	1,53	**1,95**	1,64	1,60
Embedding Index:	0,14	0,05	**0,10**	0,07	0
Discourse Productivity					
Narrative words:	52	76	**64,00**	68	42
Grammatical Accuracy					
Prop of S with V:	8	15	**11,50**	11	10
Prop of U w/o V:	3	2	**2,50**	3	1
Prop of Single Word U:	3	2	**2,50**	0	2
Prop of Well Formed U:	0,50	0,27	**0,38**	0,09	0,50
AUX Complexity Index:	1,00	1,00	**1,00**	0,90	1,00
Error Types:					
Phonological:	0	2	**1,00**	6	1
Morphosyntactic:	3	14	**8,50**	14	2
Semantic:	0	5	**2,50**	4	3
Lexical:	0	1	**0,50**	3	2
Neologisms:	1	1	**1,00**	0	1
Circumlocution:	0	0	**0,00**	1	0
Phonological %:	0,00	0,03	0,02	0,09	0,02
Morphosyntactic %:	0,06	0,18	0,13	0,21	0,05
Semantic %:	0,00	0,07	0,04	0,06	0,07
Lexical %:	0,00	0,01	0,01	0,04	0,05
Neologisms %:	0,02	0,01	0,02	0,00	0,02
Circumlocution %:	0,00	0,00	0,00	0,01	0,00
All Errors %:	0,08	0,30	0,21	0,41	0,21

Key: prop: proportion; s: sentences; V: verbs; U: utterances; w/o: without

6.3.1.4 Participant 6

Baseline vs. post-treatment

Participant 6 produced a higher number of narrative words in the post-treatment assessment compared to baseline. Sentence productivity increased significantly and, grammatical accuracy and the proportion of errors remained stable. Results of the microstructure analysis of MAIN are shown in table 6-6.

Baseline vs. follow-up

At follow-up, P6 produced a higher number of narrative words compared to baseline. Regarding sentence productivity, the elaboration index decreased but the embedding index and MLU increased. Grammatical accuracy and the proportion of errors remained stable. Results of the microstructure analysis of MAIN are shown in table 6-6.

Table 6-6: Narration outcomes for Participant 6

Category	Participant 6				
Lexical Selection	**1**	**2**	**Baseline**	**Post**	**Follow-up**
Closed class:	22	30	**26,00**	41	41
Nouns:	17	26	**21,50**	27	24
Adjectives:	3	3	**3,00**	10	12
Prepositions:	6	6	**6,00**	8	13
Adverbs:	3	3	**3,00**	3	2
Pronouns:	4	5	**4,50**	4	3
Verbs:	14	21	**17,50**	23	22
Sentence Productivity					
MLU:	6,56	6,00	**6,28**	9,67	8,83
Elaboration Index:	3,33	2,93	**3,13**	4,17	1,83
Embedding Index:	0,5	0,38	**0,44**	0,92	0,85
Discourse Productivity					
Narrative words:	69	94	**81,5**	116	117
Grammatical Accuracy					
Prop of S with V:	9	15	**12**	11	12
Prop of U w/o V:	1	1	**1**	1	1
Prop of Single Word U:	0	0	**0**	0	0
Prop of Well Formed U:	0,89	0,93	**0,91**	0,73	0,83
AUX Complexity Index:	1,11	1,07	**1,09**	1,00	1,00
Error Types:					
Phonological:	4	0	**2,00**	0	0
Morphosyntactic:	3	0	**1,50**	1	2
Semantic:	0	3	**1,50**	0	4
Lexical:	1	2	**1,50**	2	2
Neologisms:	0	0	**0,00**	0	0
Circumlocution:	0	0	**0,00**	1	0
Phonological %:	0,06	0,00	0,02	0,00	0,00
Morphosyntactic %:	0,04	0,00	0,02	0,01	0,02
Semantic %:	0,00	0,03	0,02	0,00	0,03
Lexical %:	0,01	0,02	0,02	0,02	0,02
Neologisms %:	0,00	0,00	0,00	0,00	0,00
Circumlocution %:	0,00	0,00	0,00	0,01	0,00
All Errors %:	0,12	0,05	0,08	0,03	0,07

Key: prop: proportion; s: sentences; V: verbs; U: utterances; w/o: without

6.4 Outcomes on the Quality of Life (SAQOL-39g) scale

Measurements of QoL for all participants are presented in table 6-7.

6.4.1.1 Participant 1

At follow-up, QoL scores neither improved nor decreased, compared to baseline.

6.4.1.2 Participant 2

At follow-up, QoL scores decreased slightly in the physical domain, moderately in the communication domain and more significantly in the psychosocial domain, compared to baseline.

6.4.1.3 Participant 3

At follow-up, QoL scores decreased slightly in the communication domain and moderately in the psychosocial domain, compared to baseline.

6.4.1.4 Participant 4

At follow-up, QoL scores neither improved nor decreased, compared to baseline.

6.4.1.5 Participant 5

At follow-up, QoL scores neither improved nor decreased, compared to baseline.

6.4.1.6 Participant 6

At follow-up, QoL scores improved slightly in the physical and psychosocial domains, compared to baseline.

Table 6-7: Quality of life for each Participant at the pre-treatment (baseline) stage and at 2 months follow-up using the SAQOL-39g

	Participant 1		Participant 2		Participant 3		Participant 4		Participant 5		Participant 6	
Item (maximum score: 5)	**Baseline measure**	**2 months post TMS**	**Baseline**	**2 months post TMS**	**Baseline**	**2 months post TMS**	**Baseline**	**2 months post TMS**	**Baseline**	**2 months post TMS**	**Baseline**	**2 months post TMS**
SAQOL – 39g Mean score	1.46	1.46	3.77	3.28	4.2	3.97	3.53	3.53	1.02	1.02	4.12	4.17
Physical score	1	1	4.62	4.43	5	5	4.68	4.68	1	1	4.75	4.81
Communication score	1	1	2.71	2.28	3.28	3.14	2.42	2.42	1.14	1.14	4.71	4.71
Psychosocial score	2.12	2.12	3.37	2.56	3.81	3.31	2.87	2.87	1	1	3.25	3.31

6.5 Side effects and Dropouts

Participants did not report any side effects during and after treatment. None of the participants dropped out during the whole duration of the study.

6.6 Chapter Summary

This chapter presented baseline demographic and clinical characteristics, intervention outcomes, statistical analyses of standardized language and cognitive measures, reports of outcome summaries for narratives produced by four participants and, reports of QoL outcomes as reported by proxies. Participants did not report any side effects during or after treatment. None of the participants dropped out during the study (i.e. 3 months).

CHAPTER 7: Discussion

Chapter 6 presented the results of an open label randomized controlled trial, that incorporated a single subject experimental study design (SSED), investigating the effectiveness of rTMS (1 Hz rTMS & cTBS) as a standalone treatment for chronic post-stroke induced aphasia in 6 individuals. The efficacy of the two treatment paradigms (i.e. 1 Hz rTMS & cTBS) was measured in the short- (i.e. 1-day post-treatment) and long-term (i.e. 2-months post-treatment). Results indicated that both rTMS paradigms induced trends towards improvement in several language domains either in the short- and/or long-term in all participants. Only one participant, however, showed statistically significant improvement in language performance that was evident at the follow-up stage (i.e. 2 months post-treatment) and concerned comprehension abilities and reading skills. Crucially, none of the six participants experienced side effects relating to TMS during or after stimulation sessions. Overall, this chapter discusses the findings of the present trial within the context of current evidence from TMS studies in aphasia recovery post-stroke. The limitations of the current research are highlighted and, areas considered future research priority are outlined.

7.1 Language and Cognitive outcomes

7.1.1.1 Short- and long-term Outcomes on Comprehension, Expressive Language, Naming accuracy, Reading and, Problem Solving Skills

In the short-term (i.e. one day post-treatment), overall, five participants showed trends towards improvement in different language skills. In the long-term (i.e. two months post-treatment), overall, three participants showed a trend towards improvement in different language skills. Participant 1 that had severe global aphasia manifested a trend towards improvement in expressive language in the short-term and P5 who also had severe global aphasia showed a trend towards improvement towards comprehension in the long-term. The participant with moderate-severe Broca's aphasia (P3) presented with a trend towards improvement in naming in the short-term. Participant 2 with moderate-severe anomic aphasia exhibited a trend towards improvement in reading in the short-term and a trend towards improvement in

comprehension and naming in the long-term. Participant 4 with moderate-severe anomic aphasia exhibited a trend towards improvement in comprehension and naming in the short-term. Participant 6 with mild anomic aphasia showed a trend towards improvement in comprehension and reading in the short- and long-term. All three participants with anomic aphasia exhibited trends towards improvement in comprehension (one in the short-term, one in the long-term and one in the short- and long-term); two showed trends towards improvement in reading (one in the short-term and one in the short- and long-term) and two showed trends towards improvement in naming (one in the short-term and one in the long-term). Only one participant (P1) showed an overall improvement that was observed in the long-term and concerned comprehension skills and reading ability. Notably, this was the oldest participant who had severe global aphasia resulting from diffuse lesions in the frontal, parietal and temporal (middle and superior gyri) lobes, insula and basal ganglia and also had the least years of education (i.e. six) compared to the other participants.

None of the participants showed a trend towards improvement or improvement in the control variable (i.e. problem solving skills). The control variable was assessed as many times (i.e. two) as the dependent language variables (i.e. comprehension, expression, reading and, naming accuracy) in all participants. As it remained stable in all participants, it was assumed that i) the chances that TMS led to language specific gains were increased and ii) the possibilities for the placebo and training effects were reduced.

Barwood et al (2013) assessed the effects of TMS as a standalone treatment for chronic aphasia post-stroke and found significant improvements in several language domains (i.e. naming, repetition, length of utterances, picture description tasks) that lasted up to 12 months post-treatment. Crucially, the observed magnitude of improvement was higher after the 2-month follow-ups. In contrast to the results of Barwood et al. (2013), in the present study only one participant (P1) showed significant improvement in reading and comprehension but; this improvement was noticed at the follow-up stage as in Barwood et al.'s study. As the present study was terminated after the 2-month follow-up, it is unknown whether there was any language improvement in those six participants after the 2-month follow-up stage.

Based on findings from Barwood et al. (2013) and on reports from other studies (Seniow et al. 2013; Waldowski et al., 2012; Martin et al., 2009), language improvements induced by inhibitory rTMS may occur over a period of many months. Notably, the significant language improvement observed in P1 with severe global aphasia corroborates findings of another study (Seniow et al., 2013) in which participants with severe aphasia in the experimental group (i.e. TMS group) improved significantly in repetition scores, compared to controls. The language domains (i.e. comprehension and reading skills) in which the participant of the present study showed improvement are not the same with the language domain (i.e. repetition) in which participants of Seniow et al.'s (2013) study improved but; in both studies only severely affected patients with aphasia benefited from treatment. If such findings are not coincidental, they reveal that, for some reason, individuals with severe aphasia are better responders to TMS compared to less affected individuals.

Another prominent finding of the present study is the trends towards improvement in several language domains in the short- and/or long-term that were exhibited by all six participants. This shows that TMS as a standalone treatment has potential to drive changes in language performance in chronic aphasia post-stroke. This finding corroborates results from previous studies (Seniow et al., 2013; Waldowski et al., 2012) that have also found trends towards improvement in several language domains in chronic post-stroke aphasia. In those studies though, participants where in the acute/subacute stage of recovery and TMS was used as an adjuvant to SLT.

7.1.1.2 Short- and long-term Outcomes on Narration

The application of the QPA protocol revealed two patterns of performance pre- and post-treatment. Group 1 consisting of P3 (moderate-to-severe Broca's aphasia) and P6 (mild anomic aphasia) produced more elaborate sentences compared to group 2 (P2 & P4 –both with moderate-to-severe anomic aphasia) as shown by their Elaboration and Embedding Index scores. Group 1 also produced on average more narrative words than group 2, leading to higher MLUs in the first group. Group 1 also produced a higher number of nouns than group 2, and the reverse trend held for pronouns, with the second group using more of them at the expense of lexical nouns. The error type analysis did not yield as strong predictions as the QPA, but when seen qualitatively,

group 2 produced more semantically infelicitous utterances. The above measures and the subcategories observed are also reported by Varkanista (2012). Fluent aphasia is reflected by a lower proportion of nouns and a higher proportion of pronouns, and of lower overall complexity as reflected by the less elaborate subjects and verb phrase and the lower number of embedded clauses employed. The latter also plays a role in explaining the difference in the two groups' MLUs. The fact that the above observation does not apply to the case of P6 who had fluent anomic aphasia, may be explained by the fact that this participant had mild aphasia. Aphasic speech is characterised by difficulties in planning and delivering a narrative that is structured and grammatically correct. A decrease in performance on productivity measures such as MLU and the lower proportion of lexical nouns used by one of the two emergent groups could be examined by the observations of Seifart and colleagues (2018) that showed, in typical adults across diverse languages, a tendency to slow down before nouns more than before verbs, which the researchers analyse in terms of information complexity – nouns introduce new information which is more costly to plan for. The use of QPA in this study exhibited some predictive power regarding aphasias classification, but some concerns about its applicability to Greek arose: the AUX Score measure, even with the modifications by Varkanista (2012), relies on the rate of omission of verb features such as Tense and Aspect to score their complexity. Unlike English, Tense and Aspect omissions are not common, since the morphemes that express it are obligatory parts of the verb and not auxiliaries. Additionally, Tense in Greek verbs is expressed syncretically with Person and Number, which might make it more salient and less likely to be omitted. Moreover, the experiment didn't elicit any complex Subject Noun Phrases containing subordinated clauses, since those were not elicited directly even though opportunities for them to be used were provided by the story the participants were asked to tell. This measure was removed from the Elaboration Index formula that was used since it would have no effect.

With regards to the effects of treatment on narrative skills, results varied across participants. Participant 2 showed an increase in the total number of narrative words in the short-term but this number reversed to baseline at the follow-up stage. Participant 4 showed a gradual decrease in the total number of narrative words from baseline 2 to follow-up. Participant 3 on the other hand showed an increase in the total

number of narrative words only at the follow-up stage. Finally, participant 6 showed an increase in the total number of narrative words in the short-term that was also sustained in the long-term.

Overall, two participants showed improvements in fluency in the short-term and such findings are in accordance with findings from the study of Wang et al. (2014) who also observed short-term improvements (i.e. immediately after treatment) in picture description. One of those participants together with another one exhibited an increase in the total number of narrative words at the follow-up stage –thus, one participant showed sustained improvements in fluency up to two months post-TMS. Such findings are in accordance with findings from Medina et al. (2012) who also found improvements in fluency two months post-TMS. According to the researchers, a possible explanation for this improvement could be that TMS over the right inferior frontal gyrus improves lexical-semantic access. Particularly, participants receiving TMS are better able to retrieve the appropriate representations of words and word meanings and this way they can generate more narrative utterances that are relevant to picture stimuli. This assumption is consistent with i) fMRI data in aphasia research supporting that the activation of the right BA45 is associated with semantic naming errors (Fridriksson, Baker & Moser, 2009) and; ii) studies in healthy people showing that ventral anterior regions of the left hemisphere (including BA45) are preferentially involved in lexical-semantic processing (Hagoort, 2006) and disruption of the right BA45 is not involved in lexical-semantic processing (Hartwigsen et al., 2010).

Again, as the present study was terminated after the 2-month follow-up, it is unknown whether there is any further improvement in narrative skills in those four participants after the 2-month stage.

7.2 Language related TMS Outcomes in relation to Models of post-Stroke Aphasia recovery

The brain begins to reorganize its language networks immediately after the stroke event. There are different theoretical models, not necessarily opposing to each other, that explain language related brain-reorganization post-stroke. First, the mutual and

balanced transcallosal inhibition, that is observed between the two hemispheres in the healthy brain, supports language processes. This interhemispheric balance is disturbed in stroke, leading to reduced inhibition from the affected to the unaffected hemisphere, and increased inhibition to the affected from the unaffected hemisphere. It has been reported that this process is maladaptive for language recovery post-stroke as it blocks the reactivation of brain areas in the dominant hemisphere where language processes are established (Thiel & Zumbansen, 2016). Also, it has been reported that, compared to people with small left hemispheric lesions, individuals with large left hemispheric lesions and chronic aphasia must rely on their right hemisphere for language processes (which is ineffective in compensating for language deficits) and hence they recover poorly from aphasia (Anglade et al., 2014). It is therefore suggested that suppressing the overactivated contralateral brain language areas may increase the neuronal activity of the inhibited brain areas in the affected left hemisphere and this in turn, may lead to language recovery. The trend for applying low-frequency rTMS on homotopic language areas is observed in numerous TMS post-stroke aphasia trials (e.g. Haghighi et al., 2018; Hu et al., 2018; Rubi-Fessen et al., 2015; Wang et al., 2014; Barwood et al., 2013; Heiss et al., 2013; Seniow et al., 2013; Thiel et al., 2013; Medina et al., 2012; Waldowski et al., 2012; Weiduschat et al., 2011). This theoretical model was the rationale for choosing the rTMS protocols that were applied in the studies (pilot and main) of this thesis. Two studies (Heiss et al., 2013; Thiel et al., 2013) have investigated hemispheric activities before and after TMS and have observed shifts of network activity towards the left hemisphere post-treatment. In both studies, functional improvements post-TMS were noticed in aphasia global scores.

The second theoretical model of language related brain-reorganization post-stroke suggests that perilesional regions of the left hemisphere are recruited to take over lost language functions (Norise & Hamilton, 2017). Excitatory rTMS (high frequency rTMS or iTBS) over perilesional areas of the left hemisphere has proved to be successful in several studies. Griffis and colleagues (2016) applied iTBS over residual language responsive cortex in or near the left inferior frontal gyrus (IFG), as identified through an fMRI language task, in eight participants with fluent and non-fluent aphasias, for five consecutive days over the course of two weeks. Post-iTBS, the

researchers found that treatment was associated with (i) increases in left IFG activation magnitudes and decreases in right IFG activation magnitudes during covert verb generation, (ii) reduced right to left IFG connectivity during covert verb generation and, (iii) improvements in fluency. Dammekens, Vanneste, Ost and De Ridder (2014) applied high-frequency (10 Hz) rTMS to the left IFG in a chronic patient with post-stroke aphasia and found long-lasting language gains (at least four months post-TMS) in repetition and naming tasks. Szaflarski and colleagues (2011) applied fMRI guided excitatory theta burst stimulation (TBS) to residual Broca's area of the left hemisphere in eight patients with chronic or moderate aphasia and found significant improvement in semantic fluency and an overall trend towards improvement in communication. Such findings were associated with increased activation shifts in the dominant hemisphere.

It could be argued that the aforementioned theoretical models are inherently related as they both account for and serve neuroplastic processes relating to language recovery in the dominant hemisphere. Supporting the cumulative utility of inhibiting the right hemisphere and activating the left dominant-for-language hemisphere, several studies have applied bilateral stimulation paradigms. Vuksanovic and colleagues (2015) applied cTBS over the Broca's area homologue and immediately after, iTBS over the left hemispheric Broca's area in a right-handed patient with chronic non-fluent aphasia post-stroke for 15 daily sessions. The researchers found improvement in several language functions, most notably in propositional speech, semantic fluency, short-term verbal memory and, verbal learning. Khedr et al. (2014) employed a bi-hemispheric stimulation paradigm. In their study, Broca's area was stimulated with high-frequency rTMS (20 Hz) and the homologue of Broca's area in the right hemisphere was inhibited with low-frequency rTMS (1 Hz). Compared to the sham group, the rTMS group demonstrated significant improvements in aphasia severity, comprehension, naming, repetition and fluency, post treatment and at the follow-up stages (1- and 2-months).

The third model is called "vicariation model" and supports that activity in areas of the unaffected hemisphere may contribute to functional recovery for functions that were supported, and are now lost, by damaged areas (Di Pino et al., 2014). In light of this

perspective, Chieffo et al. (2014) explored the effects of a single session of inhibitory, excitatory and sham rTMS (in a random sequence) over the right IFG with an H-coil in five right-handed patients with chronic aphasia. The H-coil targets larger and deeper brain regions than the figure-of-8 coil. The researchers showed that excitatory rTMS over the right IFG was correlated with significant improvements in naming compared to baseline performance and inhibitory rTMS. Also, the best respondent was a patient with a large lesion involving the cortical frontal regions and more severe naming difficulties. In contrast, a patient with subcortical hematoma and milder naming deficits did not show a meaningful improvement post-excitatory rTMS. Such findings are in contrast with the hypotheses that i) the left hemisphere remains best equipped to sustain effective language functions (Thompson & den Ouden, 2008) and ii) activation in homologue areas is deleterious to recovery (e.g. Szaflarski et al., 2013; Postman-Caucheteux et al., 2010; Thiel et al., 2006). Results from the study of Chieffo et al. (2014) suggest that activating the right hemisphere may facilitate language recovery post-stroke in some patients and this hypothesis is in line with research supporting the beneficial role of the right hemispheric language homologues for language recovery (e.g. Tillema et al., 2008; Musso et al., 1999; Thulborn, Carpenter & Just, 1999).

There is evidence that post-stroke, cerebral neural activation shifts over time. This implies that the reorganization of language networks post-stroke is a dynamic process. Hence, the above theoretical models should not be considered mutually exclusive, but complimentary to each other. Particularly, in the early stages cortical activity is reduced at the site of the lesion and is increased in homologue language zones and, over time language processing redistributes back to the left hemisphere (Mendonca, 2014; Saur et al., 2006). However, an interesting rTMS case study provides evidence that this argument is not 100% correct. Turkeltaub and colleagues (2012) applied inhibitory rTMS to the right pTr of a patient with chronic non-fluent aphasia after a left CVA. Improvement in naming was noticed post-treatment and was sustained two months post-TMS termination. Functional MRI confirmed a local reduction in activity in the right pTr, but not the expected increased activity in the corresponding left hemispheric areas. In addition to that, three months post treatment, the same patient suffered a right hemispheric ischemic stroke, resulting in worsening of the aphasia

without other clinical deficits. The researchers reported that this case reveals that some right hemispheric areas contribute to language recovery, whilst others interfere with it. In line with this hypothesis are findings from the study of Xing et al. (2016) who found that increased right temporoparietal gray matter volume was associated with improved language performance in patients with post-stroke aphasia even if such regions are not homotopic to patients' lesions.

Overall, the research of this thesis cannot determine which theoretical(s) model(s) best explain(s) the functional language changes that were observed in all six participants as this would require more direct measurements of brain activation and connectivity -that were not taken.

7.3 Research Outcomes in relation to factors other than Brain-reorganization Processes

The fact that the trends towards improvement observed in the present research were not translated into actual functional improvement, could imply that there was something absent from the intervention that, if applied, may have led to statistically significant results. In this study i) all six participants showed trends towards improvement in several language domains and ii) three participants showed improvement in fluency (either in the short- and/or long-term). The wide variability in language performance post rTMS is a common finding across studies. There are several reported reasons for this variability in response to TMS, such as aphasia type, aphasia chronicity, site of stimulation, TMS stimulation parameters, and the use of SLT combined with TMS (Coslett, 2016). In the systematic review of this thesis (Chapter 3), seven key themes were identified, the annotation of which, as suggested, may provide further insight into the big question over TMS response variability. Even though all those key themes were taken into consideration when planning the present study, no explanation could be given about the observed variability in TMS response among participants in the present study. Therefore, it is suggested that only large trials with homogeneous populations, as much as possible, that take into account the identified seven key themes into their designs can provide insight into TMS response variability.

What was really intriguing in the present study was that the only participant (P1) that showed significant improvement in language performance was the oldest and most linguistically challenged (i.e. she had severe global aphasia) individual. Also, the extent of brain lesions in this participant was greater compared to the rest of participants. In particular, P1 presented with diffuse lesions in the frontal, parietal and temporal (middle and superior gyri) lobes, insula and basal ganglia. There is some evidence that the capacity of NIBS induced plasticity declines with age in both healthy and neurologically impaired people (Ridding & Ziemann, 2010). However, results from this study oppose this argument. Also, P1 had the least years of education (six in total) compared to the rest of participants. It has been reported that education has no significant effects on oral naming, tactile naming, or repetition and no conclusions can be drawn on its role in aphasia recovery (Gonzalez-Fernandez et al., 2011). Findings from the present study corroborate this view.

A most critical question is whether SLT should be used as an adjuvant treatment to rTMS for aphasia rehabilitation post-stroke. There is evidence that SLT leads to considerable communication improvement in aphasia (e.g. Brady et al., 2016; Brady, Kelly, Godwin, Enderby & Campbell, 2012) and the general consensus is that SLT improves language skills for all aphasia severities and stages post-stroke even if many patients are finally left with residual deficits (Saxena & Hillis, 2017). Also, it has been reported that intensive therapy over short periods is considered superior to less intensive therapy over prolonged therapy times (Cherney, 2012). Recently, a RCT aimed to determine the ideal amount of daily practice and total duration of the training period in intensive SLT in 30 chronic (>1 year post-stroke onset) post-stroke aphasia patients (Stahl et al., 2017). Speech and language therapy frequency was three weekly sessions of four hours (group 1) or two hours (group 2) for a total of four weeks. The authors reported no additional benefit from more than two hours of daily SLT within one month, whereas a small 2-week extension of treatment duration added to the efficacy of intensive SLT. In the systematic review of this thesis (Chapter 3), two RCTs (Barwood et al., 2013; Medina et al., 2012) assessed the efficacy of rTMS as a standalone treatment in chronic post-stroke aphasia and found long-term improvements in several language domains. Crucially, so far the study of Barwood et al. (2013) is the largest longitudinal (i.e. 12-month follow-up study), placebo-

controlled rTMS post-stroke aphasia study. Findings from the present study support the results of Barwood et al. (2013) and Medina et al. (2012), that TMS as a standalone treatment has potential to lead to language gains in chronic post-stroke aphasia. Nevertheless, the weak effects (i.e. trends towards improvement in five participants and significant improvement in one) of TMS on language performance in the present study may suggest that TMS may be more effective when used in combination with SLT, rather than as an alternative treatment for aphasia post-stroke. In conclusion, even though traditional SLT is currently considered the gold standard for aphasia rehabilitation (Breitenstein et al., 2017); to add or not to add SLT as an adjuvant to TMS for aphasia rehabilitation necessitates further exploration as there is little convincing evidence that the addition of SLT is a significant determinant of response to TMS for aphasia rehabilitation Coslett (2016).

To explore the short- and long-term effects of TMS on language recovery, participants were assessed one day post-TMS and two months post-TMS, respectively. In vitro research on hippocampal slices has shown that early changes in synaptic strength resulting from LTP/LTD can last for only 30 to 60 minutes (Hoogendam, Ramakers, Di Lazzaro, 2010) and late changes may last hours, days or even weeks (Sutton & Schuman, 2006). Evidence from rTMS research in humans has shown that the longer the length of the stimulation, the longer is the duration of TMS after-effects and depending on the stimulation parameters (i.e. intensity, frequency and pulse number) facilitation of MEPs can last up to 90 minutes and depression of MEPs may last up to one hour post-stimulation (Klomjai, Katz & Lackmy-Vallee, 2015). Evidence from the main study of this thesis and other trials (e.g. Barwood et al., 2013; Seniow et al. 2013; Waldowski et al., 2012; Hamilton et al., 2010; Martin et al., 2009) suggests that TMS related language gains may last for several months post-treatment, highlighting the need for follow-up assessments by all TMS post-stroke aphasia researchers. However, the findings of the present study cannot provide any insight into the mechanisms that support the observed functional changes in language performance of the participants in the short-term and further; cannot explain how the effects of treatment accumulate in the long-term to lead to sustained language gains.

7.4 1 Hz (low frequency) rTMS versus cTBS: Findings

The two protocols that were explored in this thesis exert the same effects on the brain (i.e. neuronal suppression). However, cTBS has a duration of only 40 secs, whereas 1 Hz rTMS has a 20 min duration. As both protocols exert the same effects on brain neurons, a third objective of this research was to explore whether both protocols also bring about the same changes in language performance in post-stroke aphasia. If this is proved to be true, then the short in duration (40 secs) cTBS may outplace the long in duration (20 min) 1 Hz rTMS. Results from the present study corroborate findings from other studies that have successfully used TBS paradigms (e.g. Griffis et al., 2016; Vuksanovic et al., 2015; Szaflarski et al., 2011), suggesting that cTBS and 1 Hz rTMS bring about comparable changes in language performance in chronic post-stroke aphasia one day and two months post-TMS. Notably, P1 that showed significant improvement at the follow-up stage received cTBS.

7.5 Effects of TMS on the QoL of Participants

Stroke affects health related QoL (Towfighi & Saver, 2011) and for that reason, a main axis of stroke care is the assurance of a good QoL for stroke survivors (Teasell et al., 2014). Following this principle, in the present trial the QoL of all participants (of both the pilot and main study) was assessed using proxy ratings. Proxy ratings were used, as both participants of the pilot and P1, P2, P4 and P5 of main study struggled to respond to the SAQOL-39g questions because of comprehension deficits.

Overall, in the main study two participants showed a decrease in the overall QoL score mainly caused by decreases in the psychosocial domain. For the rest of the participants, with the exception of one participant (P6) that showed a minimal increase in the overall QoL score, the QoL reports remained stable throughout the study.

The decrease in the overall QoL score of P2 may be explained by the fact that his functional communication did not improve two months post-treatment leading to sustained psychosocial and communication problems. Participant 3 on the other hand, who showed an increase in functional communication at the follow-up stage,

exhibited a decrease mainly in the psychosocial domain, whereas the communication domain changed minimally and insignificantly. In both cases, the stroke event was recent and thus the QoL reports may reflect the perspectives and psychological status of the carers. This assumption is reinforced as data from P4 indicate no change in the QoL of the participant even though functional communication decreased two months post-treatment. Notably, this participant had suffered the stroke 50 months before she was enrolled to the study and the caregiver of this person had a lot more time to accept and adapt to the new reality. Participant 6 who showed a sustained increase in functional communication two months post-TMS, also showed a minimal increase in the overall QoL score. The QoL scores remained stable throughout the study for P1 and P5.

As the QoL forms were completed by proxies, it could be assumed that such reports reflected the perspectives and expectations of the proxies. Previous research on proxy assessments of QoL in stroke survivors indicates that proxy raters tend to report more QoL problems than patients themselves (Pinkneya, Gaylea, Mitchell-Fearonc & Mullingsb, 2017; Carod-Artal, Coral, Trizotto & Moreira, 2009; Williams et al., 2006). Therefore, proxy assessments, when used, should be evaluated with caution. In cases where unbiased patient-reports cannot be obtained though, ratings by proxies can provide clinicians with useful information (Ignatiou et al., 2012).

7.6 Limitations

All care was taken to design and conduct a study of high methodological standards. Practical issues limited the trial design, but the selected design did not exclude any participant from treatment. Also, the published “Template for Intervention Description and Replication” (TIDieR) 12-item checklist and guide (Hoffmann et al., 2014) was used to improve the completeness of reporting and replicability of the study.

A key limitation of this trial was the small sample size, and this has an impact on the generalisability of the results. Nonetheless, small sample sizes in aphasia research are inherent to the nature of the condition, as stroke survivors do not always manifest aphasia. Also, among those that suffer from aphasia, some individuals experience

severe complications and/or disability that excludes them from participation in research. After all, it is very common for rTMS aphasia studies to have small sample sizes. This was a non-randomized trial and even though the analysis of functional communication outcomes was thorough, it could not go beyond the descriptive level. Hence, in this study it was not doable to explore if the sustained improvements in functional communication were significant. Another limitation of the study was that direct measurements of brain activation and connectivity were not taken and therefore no assumptions could be made with regards to which model(s) of brain-reorganization explain(s) the observed trends and improvements. Moreover, behavioral interventions may also have long term effects and could manifest weeks following the end of treatment. Thus, enrolling participants 10 days after they had received a different behavioural therapy may confound the effects of TMS with the possible long term effects of that behavioral intervention. Another limitation of this study was that participants were followed up to two months post-treatment. This was done as two participants wanted to return to behavioural therapy (i.e. SLT) after the 2-month follow-up period. Based on findings from other studies (e.g. Barwood et al., 2013; Seniow et al. 2013; Waldowski et al., 2012; Martin et al., 2009), functional changes induced by inhibitory rTMS may occur over a period of many months and this possibility could not be investigated in this research.

7.7 Future directions

It is highly likely, that by optimizing the stimulation parameters (e.g. duration, intensity, frequency, stimulation site), the effectiveness of TMS for post-stroke aphasia rehabilitation will increase. Furthermore, there is a need for constant direct measurements of brain activation and connectivity in TMS aphasia studies, as such data may allow researchers to better understand the neuroplastic effects of TMS that underpin functional language changes. In addition to that, the combination of TMS with EEG is highly suggested for future studies as it provides an insight into i) the brain's instantaneous state, ii) TMS driven brain excitability and iii) time-resolved brain connectivity.

7.8 Conclusions

This thesis aimed to evaluate the effectiveness of rTMS (cTBS & 1 Hz rTMS) as a standalone treatment for chronic aphasia, of different types and severities, post-stroke. The present study was the first of its kind conducted in Cyprus and even though it was small in size, it was very informative as it adds to the existing body of knowledge on the topic. Also, to the knowledge of the author, it was the first study on TMS for post-stroke aphasia rehabilitation that (i) used the WEST protocol and (ii) applied thorough narratives analyses (as an index of functional communication skills) together with standardized language measures. The WEST methodology allowed the exploration of the effects of TMS gains on individual levels and is suggested to be an alternative methodology for researchers that are concerned with small sample sizes, heterogeneity of participants and paucity of data. Findings from the current trial suggest that both inhibitory rTMS paradigms (i.e. cTBS and 1 Hz rTMS), when applied as a standalone aphasia treatment over the right pTr of patients suffering from chronic aphasia post-stroke, seem to have potential to drive language changes in comprehension, expression, naming, reading and, fluency, regardless of severity and type of aphasia.

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Appendix 1

Review of Epidemiology of Stroke (Incidence and Prevalence Rates)

First name author	Aim	Findings	Conclusions
Tsai et al. (2013)	Systematic Review to explore epidemiological differences (i.e. incidence and distribution of its subtypes) between Chinese and white populations.	Since 1990 in China, compared to white people, there is a merely higher overall stroke incidence and a higher rate of ICH. What is more, important regional variations between Chinese people were also found in terms of distribution of ischaemic subtypes.	Further research to explore the distribution of ischemic subtypes amongst Chinese people is needed.
Feigin (2007)	Investigation of stroke epidemiology in developing countries.	Paucity of data (e.g. incidence, prevalence, causes, etc.).	Elucidation of etiological and risk related factors is needed to improve stroke prevention measures in developing countries.
Feigin et al. (2003)	Review of stroke incidence in developed countries.	Compared to other developed countries, there is a higher stroke incidence in Japan for unclear reasons, maybe related to environmental and genetic factors.	The review was based on white people (a limitation acknowledged by the authors). More research including all ethnicity types is needed to identify prevalence and incidence rates and give insight into etiology.
Thorvaldsen et al. (1997)	Data from the World Health Organization (WHO) Monitoring Trends and Determinants in Cardiovascular Disease (MONICA)' suggest a general tendency for decline in stroke incidence and mortality rates in 35-64 years of age.		
Bonita et al. (1990)	Investigation of stroke mortality rates in men and women 50-69 years old in 27 during 1970-1985.	Stroke mortality rates declined in 21 countries for men and 25 countries for women, especially in western Europe, Japan and North America.	International research on risk factor levels over time is needed to explain findings.

Appendix 2

Risk Factors and Causes of Ischemic & Hemorrhagic Stroke

First (and second) name author	
Miah et al. (2012)	Stroke Risk Factors in Younger: smoking - transient ischemic attack - hypertension - vulvular heart disease - oral contraceptive pill Stroke Risk Factors in Older: transient ischemic attack - stroke - hypertension - ischemic heart disease - diabetes mellitus - dyslipidemia
Moghtaderi & Alavi-Naini (2012)	In tropical areas there are some special, mainly infectious causes of stroke (e.g. Chagas' disease, cysticercosis, tuberculosis and syphilis).
Traylor et al. (2012)	A meta-analysis regarding genetic risk factors for ischaemic stroke and its subtypes provides evidence that genetic variants are associated with specific ischaemic stroke subtypes (i.e. cardioembolic and large-vessel stroke).
Turanjanin et al. (2012)	The synergistic effect of dyslipidemia, hypertension and diabetes is associated with Lacunar Ischemic Stroke.
Rajamani & Sivaswamyb (2010)	Vascular Causes of Arterial Ischemic Stroke in children include: cervicocephalic dissection - Moyamoya syndrome (and disease) - post-varicella zoster angiopathy - transient cerebral arteriopathy - fibromuscular dysplasia - vasculitis - Sickle cell disease - congenital hypoplasia - agenesis of cervicocephalic vessels.
Gschwendtner et al. (2009)	Several genetic variants are linked to ischemic stroke.
Flaherty et al. (2005)	Ethnicity is considered a risk factor for intracerebral hemorrhage.
Brott et al. (1986)	Hypertension is the most frequent risk factor for intracerebral hemorrhage.

Appendix 3

The TIDieR (Template for Intervention Description and Replication) Checklist

	BRIEF NAME
1.	Neuronavigated rTMS for Chronic Aphasia
	WHY
2.	To determine whether cTBS and 1 Hz (low frequency) rTMS as a standalone treatment has the potential to improve language symptoms of aphasia and subsequently quality of life.
	WHAT
3.	Materials: A certified speech and language pathologist, blind to the study, assessed and analysed the data. The first author administered the rTMS protocol. Language measurements were obtained at 3 time points; at baseline, immediately after treatment and at 2 months post-treatment (follow-up assessment). Quality of life measurements were obtained at baseline and at follow-up. As participants in the pilot study struggled to deal with SAQOL-39g due to comprehension deficits, proxy (spouses) ratings were used to evaluate QoL. After completion of the treatment period (10 consecutive days), participants were asked not to participate in any formal aphasia rehabilitation program but; they were encouraged to actively engage in conversations with their families and friends. Such activities were not monitored by the researchers.
4.	Procedures: We assessed resting motor threshold (RMT) using surface electromyography (EMG). After obtaining RMTs, participants in group 1 underwent the cTBS at 80% of their individual RMT, and participants in group 2 underwent 1 Hz (low frequency) rTMS using a Magstim Rapid2® stimulator (Magstim Co., Wales, UK) connected to a 70mm Double Air Film Coil. Stimulation parameters were in accordance with the guidelines proposed by Wassermann (1998). The position of the coil was guided by a frameless stereotactic neuronavigation system (ANT NEURO) that uses the individual patients' MRI scan to precisely localize the target area for stimulation. Before stimulation, a T1-weighted MRI image was obtained from each patient to locate the optimal coil position. Participants in group 1 received inhibitory rTMS (cTBS) to the pars triangularis (pTr) at the right inferior frontal gyrus (homologous BA45) following the protocol suggested by Huang et al. (2005). This paradigm uses a theta burst stimulation pattern (TBS) in which 3 pulses of stimulation are given at 50 Hz, repeated every 200 ms. In the cTBS, a 40 sec train of uninterrupted TBS is given (600 pulses in total). Participants in group 2 received 20 minutes of 1-Hz rTMS over the right pTr (Rubi-Fessen et al., 2015). In total, the program for each participant consisted of 10 daily stimulation treatments (10 consecutive days).
	WHO PROVIDED

5.	Speech & Language Assessments: Certified Speech & Language Pathologist with expertise in Aphasia rTMS: Certified Speech & Language Pathologist with expertise in neuronavigated rTMS for aphasia rehabilitation
	HOW
6.	The intervention was provided to one participant at a time and was delivered face to face. During treatment, participants sat comfortably on a chair. During the TMS treatments participants were monitored for potential side effects (e.g. pain, discomfort) and were asked (using thumb gestures) if they felt well before during and after the treatment.
	WHERE
7.	Cyprus University of Technology, University Rehabilitation Clinic, Neurorehabilitation Lab
	WHEN and HOW MUCH
8.	Group 1: A 40 sec train of uninterrupted TBS was given (600 pulses in total). Group 2: A 20 min train of uninterrupted rTMS was given (1200 pulses in total). In total, the program for each patient consisted of 10 daily stimulation treatments (10 consecutive days).
	TAILORING
9.	No
	MODIFICATIONS
10.	No
	HOW WELL
11.	Planned: Inclusion and exclusion criteria were clearly predetermined. 1 Hz (low frequency) rTMS has been reported extensively in the literature (e.g. Rubi-Fessen et al., 2015) and cTBS treatment was devised by (Huang & Rothwell, 2007) based on neuroplasticity theory. Intended assessment and active therapy ingredients were reported before study initiation. The 2 protocols used in the 2 groups were the same to ensure standardised delivery across participants. Therapies were delivered on site. Before commencement of the main trial, a pilot study ensured that all TMS related procedures could be implemented as planned.
12.	Actual: All TMS sessions were monitored by two people to ensure that therapy was implemented as planned. The delivered intervention did not vary at all from the intended intervention.

Appendix 4

Ethical Approval

ΚΥΠΡΙΑΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΕΘΝΙΚΗ ΕΠΙΤΡΟΠΗ ΒΙΟΗΘΙΚΗΣ ΚΥΠΡΟΥ

Αρ. Φακ.: ΕΕΒΚ/ΕΠ /2017/37
Αρ. Τηλ.: 22809038 / 22809039
Αρ. Φαξ: 22353878

07 Φεβρουαρίου 2018

Δρ Μαρία Καμπανάρου
Αναπληρώτρια Καθηγήτρια
Τμήμα Επιστημών Αποκατάστασης
Τεχνολογικό Πανεπιστήμιο Κύπρου
Βραγαδίνου 15
3041 Λεμεσός

Ερευνητική πρόταση με τίτλο:
« Neurorehabilitation using transcranial magnetic stimulation- Νευρολογική Αποκατάσταση με τη Χρήση Διακρανιακής Μαγνητικής Διέγερσης »

Επιθυμώ να αναφερθώ στο πιο πάνω θέμα και να σας πληροφορήσω ότι η Επιτροπή Βιοηθικής Αξιολόγησης Βιοϊατρικής Έρευνας ενεργώντας με βάση την εκχωρηθείσα σ΄ αυτήν αρμοδιότητα από την Εθνική Επιτροπή Βιοηθικής Κύπρου, να αξιολογεί βιοηθικά ερευνητικές προτάσεις που αφορούν την βιοϊατρική έρευνα στον άνθρωπο, έχει πραγματοποιήσει την βιοηθική αξιολόγηση της πιο πάνω ερευνητικής σας πρότασης, η οποία σας αποστέλλεται συνημμένα.

2. Σε σχέση με την επισήμανσή σας κατά πόσον *«ισχύει η δυνατότητα λήψης «ανοικτής συγκατάθεσης» -όπως αναφέρεται στην Γνώμη της Εθνικής Επιτροπής Βιοηθικής περί «Δημιουργίας και χρήσης βιοτραπεζών και αρχείων βιολογικών δειγμάτων ανθρώπινης προέλευσης για σκοπούς έρευνας»* όπως αναφέρεται στην Παράγραφο 7 σελίδα 10/21 και στην Παράγραφο 8 (σελίδα 11/21), όπου *«Ανοικτή» συγκατάθεση είναι εκείνη η οποία θα δίδεται για ένα συγκεκριμένο ερευνητικό πρόγραμμα αλλά οι δοτές θα δίδουν και την άδεια τους για να χρησιμοποιηθούν τα δείγματα/ουσίες τους και σε αλλά μελλοντικά προγράμματα χωρίς κατ' ανάγκη να γνωρίζουν αρκετές πληροφορίες για αυτά,* η Επιτροπή επιβεβαιώνει ότι αυτή η δυνατότητα ισχύει.

..../2....

Κέντρο Υγείας Έγκωμης, Νίκου Κρανιδιώτη, 2411 Έγκωμη, Λευκωσία
Ηλεκτρονικό Ταχυδρομείο: cnbc@bioethics.gov.cy *Ιστοσελίδα:* www.bioethics.gov.cy

3. Ωστόσο, η «ανοικτή» συγκατάθεση δεν συνεπάγεται τη φύλαξη/επεξεργασία δεδομένων επ' αόριστον, αλλά για συγκεκριμένο χρονικό διάστημα. Επισημαίνουμε, σύμφωνα με τον Νόμο 138 (1) του 2001, τον πρόσφατο Κανονισμό (ΕΕ) 2016/679 για την προστασία των φυσικών προσώπων έναντι της επεξεργασίας των δεδομένων προσωπικού χαρακτήρα και την κατάργηση της οδηγίας 95/46/ΕΚ (Γενικός Κανονισμός για την Προστασία Δεδομένων), και σύμφωνα με τις γενικές αρχές που διέπουν την προστασία των προσωπικών δεδομένων: Ο υπεύθυνος επεξεργασίας, κατά τη λήψη των δεδομένων προσωπικού χαρακτήρα, παρέχει στο υποκείμενο των δεδομένων επιπλέον πληροφορίες που είναι αναγκαίες για την εξασφάλιση θεμιτής και διαφανούς επεξεργασίας, μεταξύ των οποίων, και για το χρονικό διάστημα για το οποίο θα αποθηκευτούν τα δεδομένα προσωπικού χαρακτήρα ή, όταν αυτό είναι αδύνατο, τα κριτήρια που καθορίζουν το εν λόγω διάστημα.

Με εκτίμηση,

Δρ Μαρία Καρεκλά
Πρόεδρος
Επιτροπής Βιοηθικής Αξιολόγησης
Βιοϊατρικής Έρευνας

ΕΕΒΚ/ΕΠ/2017/37

ΕΜΠΙΣΤΕΥΤΙΚΑ ΕΓΓΡΑΦΑ

ΑΠΟΦΑΣΗ
ΕΠΙΤΡΟΠΗΣ ΒΙΟΗΘΙΚΗΣ
ΓΙΑ
ΕΓΚΡΙΣΗ Ή ΑΠΟΡΡΙΨΗ
ΠΡΟΓΡΑΜΜΑΤΟΣ

Η απόφαση της Επιτροπής Βιοηθικής θα πρέπει να κοινοποιηθεί προς την Εθνική Επιτροπή Βιοηθικής Κύπρου μαζί με όλα τα υπόλοιπα έντυπα που αφορούν το πρόγραμμα για το οποίο λήφθηκε σχετική απόφαση.

Συμπληρώνεται από την Επιτροπή Βιοηθικής

Τίτλος Προγράμματος για το οποίο γίνεται η αίτηση
«Neurorehabilitation using transcranial magnetic stimulation- Νευρολογική Αποκατάσταση με τη Χρήση Διακρανιακής Μαγνητικής Διέγερσης »
Επιστημονικός Υπεύθυνος του Προγράμματος
Δρ. Μαρία Καμπανάρου

Όνομα Επιτροπής Βιοηθικής	
Επιτροπή Βιοηθικής Αξιολόγησης Βιοϊατρικής Έρευνας στον Άνθρωπο	
Μέλη της Επιτροπής Βιοηθικής	
Όνομα	Επίθετο
Ανδρέας	Ζαχαριάδης
Γιασεμίνα	Καραγιώργη
Καλυψώ	Ιορδάνους
Μαρία	Αγγελή
Μαρία	Καρεκλά
Παύλος	Πολυκάρπου
Χρίστια	Μίτλεττον
Χριστίνα	Θεράποντος
Χρίστος	Σιαμμάς

Σχόλια από την Επιτροπή Βιοηθικής με βάση τα οποία λήφθηκε η απόφαση για την αίτηση που υποβλήθηκε
Η Επιτροπή κατά τη σημερινή συνεδρίαση της ημερομηνίας 07/02/2018, πραγματοποίησε τη βιοηθική αξιολόγηση των πρόσθετων ή/και αναθεωρημένων εγγράφων που κατατέθηκαν στις 22/01/2018 σε συνέχεια απόφασης της Επιτροπής ημερομηνίας 18/12/2017. Τα σχόλια της Επιτροπής κατά τη σημερινή συνεδρίαση παρουσιάζονται με έντονα μαύρα γράμματα. **Θερμή παράκληση της Επιτροπής όπως οι διορθώσεις/αλλαγές γίνονται με επισήμανση αλλαγών (track changes). Επίσης, να κατατίθεται καλυπτική επιστολή στην οποία θα επεξηγείται η διαχείριση του κάθε σχόλιου της Επιτροπής με αναφορά στον αριθμό του σημείου στο οποίο αναφέρονται.** **Έντυπο EEBK02:** Η Επιτροπή παρακαλεί όπως υποβληθεί το EEBK02, αναθεωρημένο, στη βάση των διευκρινήσεων της ερευνητικής ομάδας όπως παρέχονται στην καλυπτική επιστολή. **Απαντήθηκε.** 1. Στη σελ. 6 στις πληροφορίες για τη στρατολόγηση των συμμετεχόντων γίνεται αναφορά σε διάφορα πλαίσια από τα οποία θα αντληθούν επιλέξιμα άτομα. Στο πρωτόκολλο της έρευνας αναφέρεται επίσης: *«In order to participate in this study patients must present with unilateral damage subsequent to one (only) cerebrovascular accident (CVA)/stroke and fulfill the criteria outlined below».* Το πρωτόκολλο παραθέτει κριτήρια συμπερίληψης/αποκλεισμού τα

οποία περιλαμβάνουν και στοιχεία ιατρικού ιστορικού. Συνεπώς, η ερευνητική ομάδα καλείται να παράσχει περισσότερες πληροφορίες για τον τρόπο στρατολόγησης. Πώς ακριβώς θα αντληθούν αυτές οι πληροφορίες; Πώς θα προσεγγιστούν αυτά τα άτομα; Πώς θα διασφαλιστεί η αξιοπιστία των πληροφοριών, ειδικά αν αυτές υποβληθούν από τους ίδιους τους συμμετέχοντες; Επίσης, να επισυναφθούν δηλώσεις για ενδιαφέρον για συμμετοχή από τα δημόσια νοσοκομεία και τα ιδιωτικά κέντρα αποκατάστασης κτλ.

Σχόλιο 18/12/2017: Η ερευνητική ομάδα παρακαλείται όπως προχωρήσει σε προσαρμογή του εντύπου ΕΕΒΚ 03, ούτως ώστε οι συμμετέχοντες να ενημερώνονται για τη διαδικασία αξιολόγησης με χρήση των ερωτηματολογίων 1-7, που αναφέρονται στο ερευνητικό πρωτόκολλο (σ.5). **Απαντήθηκε.**

2. Στη σελ. 10 αναφέρεται ότι θα ακολουθηθούν *«safety guidelines that are designed to minimize the risk of seizures (Wassermann, 1998). Moreover, all researchers employed in the study have been trained in First Aid and are fully capable of handling a seizure in the unlikely event that one might take place.»*. Η ερευνητική ομάδα να καθορίσει ποια ακριβώς μέτρα ασφαλείας θα λάβει για να ελαχιστοποιήσει αυτή την πιθανότητα.

   Σχόλιο 18/12/2017: Απαντήθηκε. Εφόσον η ερευνητική ομάδα στην καλυπτική επιστολή (σ. 3) διευκρινίζει ότι οι θεραπείες θα διενεργούνται στην παρουσία ατόμου με δίπλωμα πρώτων βοηθειών που θα μπορεί να διαχειρίζεται επιληπτικές κρίσεις, η ερευνητική ομάδα καλείται όπως προσδιορίσει αυτό το άτομο και προωθήσει σημείωμα από το εν λόγω άτομο ότι αποδέχεται να έχει αυτό το ρόλο σε όλες τις συνεδρίες που αφορούν στη ΔΜΔ. **Απαντήθηκε.**

3. Στη σελ. 12, στις προϋποθέσεις που αφορούν τη χρήση TMS (Trained in using the specific TMS equipment, In possession of a First Aid diploma) η ερευνητική ομάδα δηλώνει ότι τα μέλη της *(«all TMS investigators»)* έχουν το σχετικό υπόβαθρο που απαιτείται. Η Επιτροπή παρακαλεί όπως η ερευνητική ομάδα τεκμηριώσει τη θέση αυτή περαιτέρω, υποβάλλοντας σχετικά έγγραφα που πιστοποιούν αυτό το υπόβαθρο (π.χ. δίπλωμα πρώτων βοηθειών). Η ερευνητική ομάδα καλείται, επίσης, να καθορίσει ονομαστικά τα άτομα αυτά. Επισημαίνεται ότι στη σελ. 2 γίνεται αναφορά μόνο στον κ. Νίκο Κωνσταντίνου ως *«Neuroscientist, responsible for neuroimaging (brain MRI) and TMS sessions»*.

   Σχόλιο 18/12/2017: Απαντήθηκε. Εφόσον η ερευνήτρια στην καλυπτική επιστολή (σ. 3) αναφέρει ότι θα ενημερώσει την ΕΕΒΚ με τα ονόματα των ερευνητών που θα είναι κάτοχοι διπλώματος Πρώτων Βοηθειών παρακαλείται όπως προχωρήσει σε σχετική ενημέρωση της Επιτροπής πριν ξεκινήσει τη διαδικασία της παρέμβασης με ΔΜΔ. **Αναμένεται η σχετική ενημέρωση, όπως διευκρινίζει σχετικά η ερευνητική ομάδα.**

4. Στη σελ. 14 επισημαίνεται ότι *«Samples will be safely destroyed five years after collection unless participants consent to the use of their samples by future studies by the principal investigator of the current study, pending approval by the Cyprus National Bioethics Committee.»* Επισημαίνεται ότι η φύλαξη των δειγμάτων για περίοδο πάνω των 5 χρόνων για αόριστο χρονικό διάστημα δεν είναι αποδεκτή από την Επιτροπή. Η ερευνητική ομάδα πρέπει

να καθορίσει επακριβώς περίοδο φύλαξης και να περιορίσει την χρήση σε μελέτες συγκεκριμένου περιεχομένου/στόχευσης.
Σχόλιο 18/12/2017: Δεν απαντήθηκε. Η ερευνητική ομάδα παρακαλείται όπως καθορίσει χρονικό διάστημα για το οποίο θα ισχύει η μελλοντική χρήση των δεδομένων, καθώς η φύλαξη για «αόριστο χρονικό διάστημα» δεν μπορεί να γίνει αποδεκτή. ***Ζητείται η συναίνεση των συμμετεχόντων για χρήση των δεδομένων για περίοδο 10 ετών.*** **Απαντήθηκε.**

Έντυπο ΕΕΒΚ03:

5. Στα έντυπα γίνεται η εξής αναφορά: «*Τα βιολογικά μου δείγματα και όλες οι λοιπές πληροφορίες που θα συλλεγούν για τους σκοπούς του παρόντος ερευνητικού προγράμματος μπορούν να κρατηθούν πέραν των 5 χρόνων και να χρησιμοποιηθούν σε μελλοντικές μελέτες αφού πρώτα εγκριθεί κάτι τέτοιο από την Εθνική Επιτροπή Βιοηθικής Κύπρου μέσω νέας αίτησης ή μετά από σχετικό αίτημα ανανέωσης σε περίπτωση επέκτασης της παρούσας μελέτης από τον υπεύθυνο ερευνητή του προγράμματος*». Επισημαίνεται στην ερευνητική ομάδα ότι μία τέτοια γενικού τύπου συναίνεση για φύλαξη βιολογικών δειγμάτων πέραν των 5 χρόνων δεν είναι αποδεκτή (σημείο πιο πάνω).
Σχόλιο 18/12/2017: Δεν απαντήθηκε. Η ερευνητική ομάδα παρακαλείται όπως καθορίσει χρονικό διάστημα για το οποίο θα ισχύει η μελλοντική χρήση των δεδομένων, καθώς η φύλαξη για «αόριστο χρονικό διάστημα» δεν μπορεί να γίνει αποδεκτή. ***Ζητείται η συναίνεση των συμμετεχόντων για χρήση των δεδομένων για περίοδο 10 ετών.*** **Απαντήθηκε.**

6. Να γίνει γλωσσικός έλεγχος στα εν λόγω έγγραφα και να γίνει διόρθωση των ορθογραφικών/συντακτικών λαθών.
Σχόλιο 18/12/2017: Απαντήθηκε. Ωστόσο, σε κάποια έντυπα συναίνεσης που αφορούν σε παρέμβαση για κινητικά προβλήματα γίνεται αναφορά σε 'Γλωσσική Αξιολόγηση'. Η ερευνητική ομάδα καλείται όπως προβεί σε προσεκτικό έλεγχο όλων των εντύπων για να διασφαλιστεί η προσαρμογή του λεκτικού σε κάθε υπο-ομάδα πληθυσμού. **Απαντήθηκε.**

7. Στο πρωτόκολλο της έρευνας αναφέρεται: «*Patients will be informed in the consent form that they can be informed about the results of the study relevant to them following completion of the study.*». Στο έντυπο συναίνεσης, ωστόσο, οι συμμετέχοντες ερωτώνται κατά πόσον θα ήθελαν να ενημερωθούν για τα αποτελέσματα της έρευνας που τους αφορούν. Η ερευνητική ομάδα να παράσχει περισσότερες πληροφορίες ως προς το είδος των αποτελεσμάτων που θα είναι προσβάσιμα σε κάθε ομάδα και τον τρόπο ενημέρωσής των συμμετεχόντων για αυτά.
Σχόλιο 18/12/2017: Η ερευνητική ομάδα έχει προβεί σε σχετικές διευκρινήσεις προς την Επιτροπή (στην επιστολή), οι οποίες θα πρέπει να ενσωματωθούν στο έντυπο ΕΕΒΚ03 για ενημέρωση των συμμετεχόντων. **Απαντήθηκε.**

Γενικά Σχόλια:

8. Η ερευνητική ομάδα να διευκρινίσει περαιτέρω ότι οι συμμετέχοντες δεν θα επιβαρυνθούν με οποιοδήποτε κόστος ως προς τη συμμετοχή τους, καθώς δεν είναι ξεκάθαρο κατά πόσον τα διαγνωστικά κέντρα θα καλύψουν με δικά τους

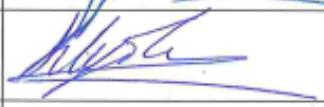
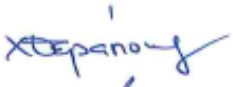
έξοδα το κόστος της μαγνητικής τομογραφίας.
Σχόλιο 18/12/2017: Η ερευνητική ομάδα παρακαλείται όπως προωθήσει στην Επιτροπή τον προϋπολογισμό του προγράμματος, εφόσον η κάλυψη των εξόδων θα γίνει από το ερευνητικό πρόγραμμα. **Έχει προωθηθεί σχετική βεβαίωση από την επιστημονική υπεύθυνη για την κάλυψη των εξόδων από εσωτερικά κονδύλια του ΤΕΠΑΚ. Απαντήθηκε.**

9. Η ερευνητική ομάδα παρακαλείται όπως διευκρινίσει πώς θα διαχειριστεί περιπτώσεις συμμετεχόντων, οι οποίοι θα παρουσιάζουν συμπτώματα κατάθλιψης ή άλλης ψυχοπαθολογίας (στη βάση των δηλώσεων τους στα ερωτηματολόγια).
Σχόλιο 18/12/2017: Δεν απαντήθηκε. Η ερευνητική ομάδα διευκρινίζει στην καλυπτική επιστολή (σ. 5) ότι θα άτομα θα ενημερώνονται για τα ευρήματα από ψυχίατρο ή κλινικό ψυχολόγο και θα παραπέμπονται για σχετική στήριξη. Η ερευνητική ομάδα παρακαλείται όπως καθορίσει αυτό το άτομο και διευκρινίσει κατά πόσον θα είναι μέλος της ερευνητικής ομάδας. Σε περίπτωση που θα είναι μέλος της ερευνητικής ομάδας θα πρέπει να προστεθεί στο έντυπο EEBK02 (και να επισυναφθεί βιογραφικό σημείωμα). Σε αντίθετη περίπτωση, να επισυναφθεί επιστολή από το άτομο αυτό ότι αποδέχεται να αναλάβει αυτό το ρόλο. **Έχει προστεθεί στην ομάδα η ψυχίατρος Στυλιανή Σπυρίδη. Απαντήθηκε.**

Συμπληρώνεται από την Επιτροπή Βιοηθικής

Έχουν δοθεί λεπτομέρειες στην Επιτροπή Βιοηθικής ή/και η Επιτροπή Βιοηθικής *έκρινε ικανοποιητικά τα κάτωθι:		
Στοιχεία	ΝΑΙ	ΟΧΙ
Βιογραφικά Στοιχεία ΟΛΩΝ των ερευνητών και των συνεργατών τους	Σχόλια	
Δήλωση μη συγκρουόμενων συμφερόντων	√	
Περιγραφή του είδους του Προγράμματος	√	
Περιγραφή του πληθυσμού που θα μελετηθεί	√	
Ο τρόπος με τον οποίο θα στρατολογηθούν άτομα για το Πρόγραμμα	√	
Μελετήθηκαν προσεκτικά τα έντυπα συγκατάθεσης (ΕΕΒΚ03);	√	
Τα έντυπα που θα χρησιμοποιηθούν για την στρατολόγηση ατόμων	√	
Ολόκληρο το πρωτόκολλο του Προγράμματος	√	
Δικαιολόγηση για την χρήση εικονικής φαρμακευτικής αγωγής	ΔΙ	
Υπεύθυνη δήλωση από όλους τους ερευνητές και συνεργάτες τους ότι τα έντυπα πληροφόρησης και συναίνεσης τους δεσμεύουν	√	
Διασφάλιση της προστασίας των δεδομένων που αφορούν τα άτομα που θα λάβουν μέρος στο Πρόγραμμα	√	
Λεπτομέρειες για την χρηματοδότηση του Προγράμματος	√	
Έχουν εκδοθεί ειδικά συμβόλαια σε σχέση με αμοιβές ;		√
Θα δίδονται αμοιβές στα άτομα που θα συμμετάσχουν στο Πρόγραμμα ;		√
Θα υπάρξουν οποιεσδήποτε οικονομικές επιβαρύνσεις για τα άτομα που θα συμμετάσχουν στο Πρόγραμμα ;		√
Οι ερευνητές ή/και συνεργάτες τους θα παίρνουν αμοιβές ;		√
Έχουν περιγραφεί τα αναμενόμενα οφέλη του Προγράμματος ;	√	
Έχει διαφανεί ότι προκύπτουν οποιαδήποτε οφέλη προς τον χρηματοδότη, τους ερευνητές και τους συνεργάτες τους από το Πρόγραμμα;	√	
Εάν πιο πάνω είναι ΝΑΙ, να εξηγηθεί:		
Έχουν τεκμηριωθεί όλες οι διευθετήσεις που έγιναν σε σχέση με τις υπηρεσίες που τυχόν θα παρασχεθούν για το Πρόγραμμα ;	√	
Θα υπάρχει συνεχής ενημέρωση για την ασφάλεια των ατόμων που θα λαμβάνουν μέρος στο Πρόγραμμα ;	√	
Υπάρχουν διαδικασίες για την υποβολή παραπόνων/καταγγελιών;	√	
Διασφαλίζονται επαρκώς τα δικαιώματα των ερευνητών για τις δημοσιεύσεις των αποτελεσμάτων ;	√	
Έχει δεσμευθεί ο/η Επιστημονικός Υπεύθυνος ότι δεν θα γίνουν οποιεσδήποτε αλλαγές στο Πρόγραμμα από την ημέρα που θα εγκριθεί από την Επιτροπή Βιοηθικής ;	√	

***Αποτελεί ευθύνη της Επιτροπής Βιοηθικής να σταθμίσει όλα τα στοιχεία που έχουν δοθεί, να δώσει την απαραίτητη βαρύτητα εκεί που χρειάζεται και να λάβει απόφαση ως προς το κατά πόσον έχουν δοθεί ικανοποιητικές επεξηγήσεις σε σχέση με το προτεινόμενο Πρόγραμμα.**

Δήλωση για «μη συγκρουόμενα συμφέροντα» από την Επιτροπή Βιοηθικής		
Εμείς τα μέλη της Επιτροπής Βιοηθικής που λάβαμε μέρος στις συνεδρίες σε σχέση με την παρούσα αίτηση, υπογράφοντας πιο κάτω δηλώνουμε υπεύθυνα ότι δεν έχουμε οποιαδήποτε άμεσα ή έμμεσα συγκρουόμενα συμφέροντα σε σχέση με το Πρόγραμμα που μελετήσαμε και εκδώσαμε σχετική απόφαση.		
Ονοματεπώνυμο	Υπογραφή	Ημερομηνία
Δρ Ανδρέας Ζαχαριάδης		07/02/2018
Δρ Γιασεμίνα Καραγιώργη		07/02/2018
Δρ Καλυψώ Ιορδάνους		07/02/2018
κα Μαρία Αγγελή		07/02/2018
Δρ Μαρία Καρεκλά		07/02/2018
κος Παύλος Πολυκάρπου		07/02/2018
κα Χρίστια Μίτλεττον		07/02/2018
Δρ Χριστίνα Θεράποντος		07/02/2018
Δρ Χρίστος Σιαμμάς		07/02/2018

Τίτλος Προγράμματος
«Neurorehabilitation using transcranial magnetic stimulation- Νευρολογική Αποκατάσταση με τη Χρήση Διακρανιακής Μαγνητικής Διέγερσης »
Αριθμός Πρωτοκόλλου Επιτροπής Βιοηθικής
ΕΕΒΚ/ΕΠ/2017/37
Απόφαση της Επιτροπής Βιοηθικής (Εγκρίνεται, Ζητούνται επιπρόσθετα στοιχεία, Απορρίπτεται)
Εγκρίνεται 1. Νοείται ότι την νομική ευθύνη της επιστημονικής εγκυρότητας, αναγκαιότητας, πληρότητας και της συνολικής επιστημονικής αξίας της προτεινομένης έρευνας έχουν οι επιστημονικοί υπεύθυνοι της έρευνας και ο Φορέας του επιστημονικού υπεύθυνου. Όλοι οι πιο πάνω έχουν επίσης την νομική ευθύνη της διεξαγωγής της έρευνας με τη δέουσα επιστημονική επιμέλεια και φροντίδ α. 2.Από 01/08/2012 η Εθνική Επιτροπή Βιοηθικής Κύπρου διενεργεί δειγματοληπτικό έλεγχο σε ερευνητικές προτάσεις που λαμβάνουν έγκριση. Περισσότερες λεπτομέρειες είναι διαθέσιμες στην ιστοσελίδα της Επιτροπής σε σχετική ανακοίνωση. 3.Το παρόν έντυπο απόφασης κοινοποιείται και στον χρηματοδότη της ερευνητικής πρότασης. 4. Οι ερευνητές υποχρεούνται να υποβάλλουν προς την Επιτροπή ανά εξάμηνο από σήμερα έκθεση για την εξέλιξη της έρευνας μέσα του εντύπου ΕΕΒΚ05. 5. Με το πέρας της έρευνας, οι ερευνητές υποχρεούνται όπως υποβάλουν στην Επιτροπή αναφορά μέσω του Εντύπου ΕΕΒΚ06. 6. Τονίζεται στους ερευνητές η υποχρέωσή τους να τηρούν τις εκάστοτε υποχρεώσεις τους με βάση την κείμενη νομοθεσία και κανονισμούς και ιδιαιτέρως η υποχρέωσή τους να ενημερώνουν άμεσα την Επιτροπή για οποιοδήποτε έκτακτο συμβάν ή οποιαδήποτε τροποποίηση στην πρόταση ως εγκρίθηκε, με την υποβολή των προνοουμένων εντύπων.
Μέλη που ήταν παρόντα στην λήψη απόφασης/Αποτέλεσμα Ψηφοφορίας
Ως αναφέρεται στην σελίδα 7 ανωτέρω και η απόφαση ήταν ομόφωνη.
Ημερομηνία έκδοσης απόφασης
Ημέρα: ……..…07…. Μήνας: ……Φεβρουαρίου….. Έτος: ……2017…….

Υπογράφει ο Πρόεδρος της Επιτροπής Βιοηθικής και ο Αναπληρωτής Πρόεδρος

Αξίωμα	Όνομα	Επίθετο	Υπογραφή
Πρόεδρος	Μαρία	Καρεκλά	
Αντιπρόεδρος	Παύλος	Πολυκάρπου	

Appendix 5

Open call to media

ΠΛΗΡΟΦΟΡΙΕΣ ΓΙΑ ΕΡΕΥΝΑ

Τίτλος Έρευνας	**Νευροαποκατάσταση Χρόνιας Αφασίας μετά από Εγκεφαλικό Επεισόδιο με τη χρήση Διακρανιακού Μαγνητικού Ερεθισμού (ΔΜΕ)**
Κύριος Ερευνητής	**Αναστάσιος Μ. Γεωργίου, Υπ. Δρ. Νευροαποκατάστασης** **Τεχνολογικό Πανεπιστήμιο Κύπρου** **Τμήμα Επιστημών Αποκατάστασης** **Λεμεσός, Κύπρος** **Τηλέφωνο Επικοινωνίας: 96 63 78 47** **Email: anastasios.georgiou@cut.a.cy**
Υπεύθυνη Προγράμματος	**Δρ. Μαρία Καμπανάρου, Αναπληρώτρια Καθηγήτρια** **Τεχνολογικό Πανεπιστήμιο Κύπρου** **Τμήμα Επιστημών Αποκατάστασης** **Λεμεσός, Κύπρος** **Email: maria.kambanaros@cut.ac.cy**

Γιατί γίνεται η έρευνα;

Η επικοινωνία είναι η σημαντικότερη ικανότητα που έχει ο άνθρωπος. Η ικανότητά μας αυτή είναι σημαντική για την επαφή μας με άλλους ανθρώπους. Επίσης, η επικοινωνία, μας προσφέρει μια καλή ποιότητα ζωής. Ένα εγκεφαλικό επεισόδιο μπορεί να προκαλέσει από ήπια έως πολύ σοβαρά προβλήματα επικοινωνίας.

Η παρούσα επιστολή αποσκοπεί στη διάδοση της είδησης ότι πραγματοποιείται μια έρευνα που έχει ως σκοπό την μελέτη και κατανόηση των πιθανών θετικών επιδράσεων του Διακρανιακού Μαγνητικού Ερεθισμού (ΔΜΕ) στη νευρολογική αποκατάσταση επίκτητων γλωσσικών ελλειμμάτων (Αφασία) μετά από εγκεφαλικό επεισόδιο.

Η συμμετοχή στην έρευνα είναι εθελοντική και άνευ κόστους.

Ποιος μπορεί να συμμετάσχει στην έρευνα;

Άτομα ηλικίας 18-75 ετών τα οποία:

- έχουν ως μητρική γλώσσα τα Ελληνικά
- έχουν πάθει 1 μόνο εγκεφαλικό στη ζωή τους στο αριστερό ημισφαίριο (το οποίο έχει διαγνωστεί με αξονική ή μαγνητική τομογραφία εγκεφάλου)
- έπαθαν το εγκεφαλικό τουλάχιστον πριν 6 ολόκληρους μήνες
- έχουν πρόβλημα λόγου

Ποιες είναι οι διαδικασίες;

1. Λήψη Ιστορικού & Χορήγηση Ερωτηματολογίων
2. Γλωσσική Αξιολόγηση – Γνωστική Αξιολόγηση – Αξιολόγηση Ποιότητας Ζωής
3. Μαγνητική Τομογραφία Εγκεφάλου
4. 10ήμερη Θεραπευτική Παρέμβαση με Διακρανιακό Μαγνητικό Ερεθισμό

Η έρευνα θα ωφελήσει τους συμμετέχοντες;

Υπάρχουν διεθνείς μελέτες που λένε ότι υπάρχουν οφέλη με τη θεραπεία με ΔΜΕ για προβλήματα επικοινωνίας μετά από εγκεφαλικό επεισόδιο. Συγκεκριμένα, υπάρχει πιθανότητα να βελτιωθεί η επικοινωνία των ατόμων με Αφασία μετά από την ολοκλήρωση της θεραπείας.

Οι πληροφορίες από αυτήν την έρευνα μπορεί στο μέλλον να βοηθήσουν άλλους συνανθρώπους μας που αντιμετωπίζουν προβλήματα επικοινωνίας μετά από εγκεφαλικό επεισόδιο. Έτσι, τα αποτελέσματα της παρούσας έρευνας αναμένεται να συμβάλουν στην επιστημονική γνώση σχετικά με την νευρολογική αποκατάσταση προβλημάτων επικοινωνίας σε ασθενείς που έχουν πάθει εγκεφαλικό επεισόδιο.

Ποιος θα έχει πρόσβαση στα αποτελέσματα;

Όλες οι πληροφορίες που θα συλλεχθούν θα παραμείνουν αυστηρώς εμπιστευτικές και **μόνο** οι ερευνητές της παρούσας έρευνας θα έχουν πρόσβαση στις πληροφορίες.

Η έρευνα έχει εγκριθεί από κάποιον οργανισμό;

Η έρευνα αυτή έχει αξιολογηθεί και έχει εγκριθεί από την Εθνική Επιτροπή Βιοηθικής Κύπρου, με αριθμό: ΕΕΒΚ/ΕΠ/2017/37

Αν γνωρίζετε κάποιο άτομο που έχει πάθει εγκεφαλικό και αντιμετωπίζει προβλήματα επικοινωνίας, παρακαλώ όπως επικοινωνήσετε με την οικογένειά του για να την ενημερώσετε για την παρούσα έρευνα.

Για περαιτέρω πληροφορίες, παρακαλώ επικοινωνήστε με τον:

κ. Γεωργίου Αναστάσιο
τηλ. 96 63 78 47

Appendix 6

Research Flyer

Αναζητούμε Εθελοντές από 18 έως 75 ετών για Συμμετοχή σε Έρευνα

Εγκεφαλικό επεισόδιο

Αναζητούμε άντρες και γυναίκες με πρόβλημα επικοινωνίας μετά από **εγκεφαλικό επεισόδιο**, για να συμμετάσχουν σε έρευνα για την πιθανή βελτίωση της επικοινωνίας τους.

Η έρευνα περιλαμβάνει:

- ✓ 2 αξιολογήσεις λόγου πριν από τη θεραπεία
- ✓ Θεραπεία περίπου 20 λεπτών με Διακρανιακό Μαγνητικό Ερεθισμό κάθε μέρα για 10 ημέρες Συνεχόμενα
- ✓ Αξιολόγηση λόγου αμέσως μετά τη θεραπεία και 2 μήνες μετά τη θεραπεία
- ✓ Μαγνητική Τομογραφία Εγκεφάλου (MRI) πριν τη θεραπεία και 2 μήνες μετά τη θεραπεία

Οι αξιολογήσεις, η θεραπεία και οι μαγνητικές τομογραφίες εγκεφάλου δεν επιβαρύνουν οικονομικά τους συμμετέχοντες.

Αν ενδιαφέρεστε να μάθετε περισσότερα

παρακαλώ επικοινωνήστε:

κ. Γεωργίου Αναστάσιος, PhD cand.: (00357) 96 63 78 47 – anastasios.georgiou@cut.ac.cy
Δρ. Καμπανάρου Μαρία, PhD: (00357) 2500 2098 – maria.kambanaros@cut.ac.cy
Τμήμα Επιστημών Αποκατάστασης

Τεχνολογικό Πανεπιστήμιο Κύπρου

Η έρευνα αυτή έχει αξιολογηθεί και έχει εγκριθεί από την Εθνική Επιτροπή Βιοηθικής Κύπρου, με αριθμό: ΕΕΒΚ/ΕΠ/2017/37

Appendix 7

Consent Form

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ για συμμετοχή σε πρόγραμμα έρευνας

(Τα έντυπα αποτελούνται συνολικά από 13 σελίδες)

Καλείστε να συμμετάσχετε σε ένα ερευνητικό πρόγραμμα. Πιο κάτω (βλ. **«Πληροφορίες για Ασθενείς ή/και Εθελοντές»**) θα σας δοθούν εξηγήσεις σε απλή γλώσσα σχετικά με το τι θα ζητηθεί από εσάς ή/και τι θα σας συμβεί σε εσάς, εάν συμφωνήσετε να συμμετάσχετε στο πρόγραμμα. Θα σας περιγραφούν οποιοιδήποτε κίνδυνοι μπορεί να υπάρξουν ή ταλαιπωρία που τυχόν θα υποστείτε από την συμμετοχή σας στο πρόγραμμα. Θα σας επεξηγηθεί με κάθε λεπτομέρεια τι θα ζητηθεί από εσάς και ποιος ή ποιοι θα έχουν πρόσβαση στις πληροφορίες ή/και άλλο υλικό που εθελοντικά θα δώσετε για το πρόγραμμα. Θα σας δοθεί η χρονική περίοδος για την οποία οι υπεύθυνοι του προγράμματος θα έχουν πρόσβαση στις πληροφορίες ή/και υλικό που θα δώσετε. Θα σας επεξηγηθεί τι ελπίζουμε να μάθουμε από το πρόγραμμα σαν αποτέλεσμα και της δικής σας συμμετοχής. Επίσης, θα σας δοθεί μία εκτίμηση για το όφελος που μπορεί να υπάρξει για τους ερευνητές ή/και χρηματοδότες αυτού του προγράμματος. **Δεν πρέπει να συμμετάσχετε, εάν δεν επιθυμείτε ή εάν έχετε οποιουσδήποτε ενδοιασμούς που αφορούν την συμμετοχή σας στο πρόγραμμα.** Εάν αποφασίσετε να συμμετάσχετε, πρέπει να αναφέρετε εάν έχετε συμμετάσχει σε οποιοδήποτε άλλο πρόγραμμα έρευνας μέσα στους τελευταίους 12 μήνες. Εάν αποφασίσετε να μην συμμετάσχετε και είστε ασθενής, η θεραπεία σας δεν θα επηρεαστεί από την απόφασή σας. **Είστε ελεύθεροι να αποσύρετε οποιαδήποτε στιγμή εσείς επιθυμείτε την συγκατάθεση για τη συμμετοχή σας στο πρόγραμμα.** Εάν είστε ασθενής, η απόφασή σας να αποσύρετε την συγκατάθεση σας, δεν θα έχει οποιεσδήποτε επιπτώσεις στην θεραπεία σας. Έχετε το δικαίωμα να υποβάλετε τυχόν παράπονα ή καταγγελίες, που αφορούν το πρόγραμμα στο οποίο συμμετέχετε, προς την Επιτροπή Βιοηθικής που ενέκρινε το πρόγραμμα ή ακόμη και στην Εθνική Επιτροπή Βιοηθικής Κύπρου. Πρέπει όλες οι σελίδες των εντύπων συγκατάθεσης να φέρουν το ονοματεπώνυμο και την υπογραφή σας.

Σύντομος Τίτλος του Προγράμματος στο οποίο καλείστε να συμμετάσχετε
Νευροαποκατάσταση Χρόνιας Αφασίας μετά από Εγκεφαλικό Επεισόδιο με τη χρήση Διακρανιακού Μαγνητικού Ερεθισμού
Υπεύθυνος του Προγράμματος στο οποίο καλείστε να συμμετάσχετε
Δρ. Μαρία Καμπανάρου, Αναπληρώτρια Καθηγήτρια, Τμήμα Επιστημών Αποκατάστασης, Τεχνολογικό Πανεπιστήμιο Κύπρου, Βραγαδίνου 15, Λεμεσός, 3041, τηλέφωνο: +35725002098, ηλεκτρονικό ταχυδρομείο (email) maria.kambanaros@cut.ac.cy

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ για συμμετοχή σε πρόγραμμα έρευνας (Τα έντυπα αποτελούνται συνολικά από 13 σελίδες)
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Δίδετε συγκατάθεση για τον εαυτό σας ή για κάποιο άλλο άτομο;	
Εάν πιο πάνω απαντήσατε για κάποιον άλλο, τότε δώσετε λεπτομέρειες και το όνομα του.	

Ερώτηση	ΝΑΙ ή ΟΧΙ
Συμπληρώσατε τα έντυπα συγκατάθεσης εσείς προσωπικά;	
Τους τελευταίους 12 μήνες έχετε συμμετάσχει σε οποιοδήποτε άλλο ερευνητικό πρόγραμμα;	
Διαβάσατε και καταλάβατε τις πληροφορίες για ασθενείς ή/και εθελοντές;	
Είχατε την ευκαιρία να ρωτήσετε ερωτήσεις και να συζητήσετε το Πρόγραμμα;	
Δόθηκαν ικανοποιητικές απαντήσεις και εξηγήσεις στα τυχόν ερωτήματά σας;	
Καταλαβαίνετε ότι μπορείτε να αποσυρθείτε από το πρόγραμμα, όποτε θέλετε;	
Καταλαβαίνετε ότι, εάν αποσυρθείτε, δεν είναι αναγκαίο να δώσετε οποιεσδήποτε εξηγήσεις για την απόφαση που πήρατε;	
(Για ασθενείς) καταλαβαίνετε ότι, εάν αποσυρθείτε, δεν θα υπάρξουν επιπτώσεις στην τυχόν θεραπεία που παίρνετε ή που μπορεί να πάρετε μελλοντικά;	
Συμφωνείτε να συμμετάσχετε στο πρόγραμμα;	
Με ποιόν υπεύθυνο μιλήσατε;	

Επίθετο:	.....	Όνομα:	.....
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ΠΛΗΡΟΦΟΡΙΕΣ ΓΙΑ ΑΣΘΕΝΕΙΣ ή/και ΕΘΕΛΟΝΤΕΣ

Τίτλος Έρευνας	**Νευροαποκατάσταση Χρόνιας Αφασίας μετά από Εγκεφαλικό Επεισόδιο με τη χρήση Διακρανιακού Μαγνητικού Ερεθισμού**
Κύριος Ερευνητής	**Αναστάσιος Μ. Γεωργίου, Υπ. Δρ. Νευροαποκατάστασης** **Τεχνολογικό Πανεπιστήμιο Κύπρου** **Τμήμα Επιστημών Αποκατάστασης** **Λεμεσός, Κύπρος** **Τηλέφωνο Επικοινωνίας: 96 63 78 47** **Email: anastasios.georgiou@cut.a.cy**
Κύριος Επόπτης Έρευνας	**Δρ. Νίκος Κωνσταντίνου, Επίκουρος Καθηγητής** **Τεχνολογικό Πανεπιστήμιο Κύπρου** **Τμήμα Επιστημών Αποκατάστασης** **Λεμεσός, Κύπρος** **Email: nikos.konstantinou@cut.ac.cy**
Υπεύθυνη Προγράμματος	**Δρ. Μαρία Καμπανάρου, Αναπληρώτρια Καθηγήτρια** **Τεχνολογικό Πανεπιστήμιο Κύπρου** **Τμήμα Επιστημών Αποκατάστασης** **Λεμεσός, Κύπρος** **Email: maria.kambanaros@cut.ac.cy**
Επιχορήγηση	•

Γιατί γίνεται η έρευνα;

Η επικοινωνία είναι η σημαντικότερη ικανότητα που έχει ο άνθρωπος. Η ικανότητά μας αυτή είναι σημαντική για την επαφή μας με άλλους ανθρώπους. Επίσης, η επικοινωνία, μας προσφέρει καλή ποιότητα ζωής. Ένα εγκεφαλικό επεισόδιο μπορεί να προκαλέσει από ήπια έως πολύ σοβαρά προβλήματα επικοινωνίας.

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ για συμμετοχή σε πρόγραμμα έρευνας (Τα έντυπα αποτελούνται συνολικά από 13 σελίδες)
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Θα θέλαμε να σας προσκαλέσουμε να συμμετάσχετε στο παρόν ερευνητικό πρόγραμμα. Ο σκοπός αυτού του ερευνητικού προγράμματος είναι η μελέτη και κατανόηση των πιθανών θετικών επιπτώσεων του Διακρανιακού Μαγνητικού Ερεθισμού στη νευρολογική αποκατάσταση επίκτητων γλωσσικών ελλειμμάτων (Αφασία) μετά από εγκεφαλικό επεισόδιο.

Τα αποτελέσματα αυτής της έρευνας πιθανόν να συμβάλουν στη βελτίωση της αξιολόγησης και θεραπευτικής παρέμβασης ασθενών με διάφορα νευρολογικά προβλήματα (π.χ. εγκεφαλικό επεισόδιο).

Η συμμετοχή σας στην έρευνα είναι εθελοντική και θα πρέπει να συμμετάσχετε μόνο εάν και εφόσον εσείς το επιθυμείτε. Ακόμα και αν αποφασίσετε να συμμετάσχετε στην έρευνα, μπορείτε να αποχωρήσετε ανά πάσα στιγμή χωρίς επιπτώσεις.

Πριν αποφασίσετε αν θέλετε να πάρετε μέρος στην έρευνα αυτή, είναι σημαντικό να διαβάσετε τις παρακάτω πληροφορίες προσεκτικά και να τις συζητήσετε με όποιο άλλο άτομο επιθυμείτε. Επίσης, μπορείτε να απευθυνθείτε σε μας για οποιαδήποτε απορία έχετε ή και για περαιτέρω πληροφορίες.

Επίθετο:	.....	Όνομα:	.....
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Γιατί επιλέχθηκα να συμμετάσχω στην έρευνα;

- Είμαι 18 – 75 ετών.
- Είμαι δεξιόχειρας (θα σας κάνουμε κάποιες ερωτήσεις για να το διαπιστώσουμε).
- Η μητρική μου γλώσσα είναι τα Ελληνικά.
- Έχω πάθει 1 μόνο εγκεφαλικό στη ζωή μου στο αριστερό ημισφαίριο (το οποίο έχει διαγνωστεί με αξονική ή μαγνητική τομογραφία εγκεφάλου).
- Το εγκεφαλικό το έπαθα τουλάχιστον πριν 6 ολόκληρους μήνες.
- Το εγκεφαλικό μού προκάλεσε κάποια αναπηρία.
- Έχω πρόβλημα στην έκφραση του λόγου.
- Το πρόβλημά μου στην έκφραση του λόγου είναι ήπιο ή μέτριο ή σοβαρό.
- Δεν έχω σοβαρό πρόβλημα στην κατανόηση του λόγου.
- Θέλω να βελτιωθεί η κατάστασή μου.
- Μου έχουν δοθεί σαφείς προφορικές και γραπτές οδηγίες.
- Η κατάσταση της υγείας μου είναι σταθερή.
- Αν έχω ιστορικό με επιληπτικές κρίσεις, πρέπει αυτές να είναι ρυθμισμένες με φαρμακευτική αγωγή και μην έχω πάθει επιληπτική κρίση για τουλάχιστον 2 χρόνια.
- Η φυσική μου κατάσταση, μου επιτρέπει να συμμετάσχω στην έρευνα.
- Δεν έχω νοητική υστέρηση.
- Δεν έχω Άνοια ή κάποια άλλη νευρολογική ασθένεια εκτός του εγκεφαλικού.
- Δεν είμαι χρήστης ναρκωτικών ουσιών.
- Ο γιατρός που με παρακολουθεί συστηματικά επιβεβαιώνει ότι μπορώ να συμμετάσχω στην έρευνα.

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ για συμμετοχή σε πρόγραμμα έρευνας

(Τα έντυπα αποτελούνται συνολικά από 13 σελίδες)

Σύντομος Τίτλος του Προγράμματος στο οποίο καλείστε να συμμετάσχετε
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Δεν πρέπει να συμμετάσχω στην έρευνα αν:

1. Τα Ελληνικά δεν είναι η μητρική μου γλώσσα.
2. Έχω πάθει περισσότερα από 1 εγκεφαλικά επεισόδια στο αριστερό ημισφαίριο.
3. Έχω μεταλλικά αντικείμενα στο λαιμό, στο μάτι ή στα μάτια μου, στο αυτί ή στα αυτιά μου, στον εγκέφαλό μου ή στην καρδιά μου.
4. Έχω ηλεκτρόδια στον εγκέφαλο μου.
5. Έχω θραύσματα από σφαίρα στον λαιμό ή στο κεφάλι μου.
6. Έχω τατουάζ στο πρόσωπο με μεταλλικό υλικό ή υλικό που είναι ευαίσθητο σε μαγνήτη.
7. Έχω άλλα μεταλλικά αντικείμενα στην καρδιά, στον λαιμό ή στον εγκέφαλό μου.
8. Έχω σοβαρές δερματικές βλάβες στο κεφάλι.
9. Έχω μη ελεγχόμενες επιληπτικές κρίσεις.
10. Έχω κάποια άλλη νευρολογική πάθηση που επηρεάζει την κίνηση μου και την αισθητικότητά μου (για παράδειγμα, όγκος στον εγκέφαλο).
11. Έχω σοβαρά προβλήματα στην κατανόηση του λόγου, που μπορούν να επηρεάσουν την κατανόηση του παρόντος κειμένου και των οδηγιών για την έρευνα.
12. Έχω σοβαρό πρόβλημα όρασης ή/και ακοής που δεν μου επιτρέπει τη συμμετοχή μου στην έρευνα.
13. Είχα γνωστικές διαταραχές πριν από το εγκεφαλικό (π.χ. διαταραχές μνήμης, διαταραχές επικοινωνίας)
14. Έχω ψυχιατρική διαταραχή, εκτός από κατάθλιψη
15. Έχω εκφυλιστική (προοδευτική) νευρολογική διαταραχή (για παράδειγμα Άνοια, νόσο του Πάρκινσον, Σκλήρυνση κατά Πλάκας).
16. Έχω σοβαρό ή πρόσφατο πρόβλημα με την καρδιά μου.
17. Πάσχω από κάποια σοβαρή ασθένεια (π.χ. νόσο των νεφρών ή του συκωτιού)
18. Παίρνω φάρμακα που έχουν επιδράσεις στον εγκέφαλο, εκτός από αντικαταθλιπτικά.
19. Χρειάζομαι παρηγορητική φροντίδα.

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

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Τί θα μου συμβεί αν συμμετάσχω στην έρευνα;

Αν αποφασίσετε να συμμετάσχετε στην έρευνα θα συμβούν αυτά που ακολουθούν.

1. Λήψη Ιστορικού & Χορήγηση Ερωτηματολογίων

Θα έρθει σε επαφή μαζί σας ένας από τους ερευνητές (Λογοπαθολόγος). Στην πρώτη συνάντηση με τον Λογοπαθολόγο, θα σας ζητηθεί να δώσετε ένα λεπτομερές ιστορικό, το οποίο θα περιλαμβάνει δημογραφικά στοιχεία, ιατρικό ιστορικό, την τρέχουσα κατάσταση της υγείας σας, τη χρήση φαρμάκων, την εκπαίδευση και την επαγγελματική σας απασχόληση. Η συνάντηση αυτή θα διαρκέσει περίπου 15 λεπτά.

2. Γλωσσική Αξιολόγηση – Γνωστική Αξιολόγηση – Αξιολόγηση Ποιότητας Ζωής

Για να έχουμε μια πιο ολοκληρωμένη εικόνα των γλωσσικών και γνωστικών σας δεξιοτήτων, καθώς και για το πώς αξιολογείτε την ποιότητα ζωής σας, θα σας ζητηθεί να αξιολογηθείτε από Λογοπαθολόγο. Η αξιολόγηση των γλωσσικών και γνωστικών σας δεξιοτήτων θα γίνει 2 φορές πριν την έναρξη της θεραπείας (12 μέρες πριν και 1 μέρα πριν τη θεραπεία), αμέσως μετά το πέρας του θεραπευτικού προγράμματος, καθώς και 2 μήνες μετά την ολοκλήρωση του προγράμματος. Η αξιολόγηση της ποιότητας ζωής σας θα γίνει 1 μέρα πριν και 2 μήνες μετά τη θεραπεία. Κάθε συνάντηση θα διαρκέσει περίπου 1 ώρα και 30 λεπτά.Τα εργαλεία που θα χρησιμοποιηθούν είναι 7:

1. Στο πρώτο εργαλείο θα σας ζητηθεί να δείξετε κάποιες εικόνες.
2. Στο δεύτερο εργαλείο θα σας ζητηθεί να δείξετε κάποιες άλλες εικόνες.
3. Στο τρίτο εργαλείο θα σας ζητηθεί να

- ✓ Να απαντήσετε σε διάφορες ερωτήσεις καθημερινής φύσης.
- ✓ Να κάνετε μία ελεύθερη συζήτηση με τον εξεταστή.
- ✓ Να περιγράψετε κάποιες εικόνες.
- ✓ Να ακούσετε κάποιες λέξεις και να δείξετε αυτές τις λέξεις σε εικόνες που θα σας δοθούν.
- ✓ Να επαναλάβετε κάποιες λέξεις και προτάσεις.
- ✓ Να κάνετε ανάγνωση.

4. Στο 4^{ο} εργαλείο θα σας ζητηθεί να κατονομάσετε κάποιες εικόνες.
5. Στο 5^{ο} εργαλείο θα σας ζητηθεί να περιγράψετε μία εικόνα
6. Στο 6^{ο} εργαλείο θα σας ζητηθεί να απαντήσετε μονολεκτικά σε κάποιες ερωτήσεις.
7. Στο 7^{ο} εργαλείο θα σας ζητηθεί να σχεδιάσετε κάτι.

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

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Όλες οι αξιολογήσεις θα γίνουν από Λογοπαθολόγο ο οποίος είναι εγγεγραμμένος στον Σύνδεσμο Λογοπαθολόγων Κύπρου. Όλες οι αξιολογήσεις θα γίνουν είτε στο σπίτι σας, είτε στην «ΚΛΙΝΙΚΗ ΑΠΟΚΑΤΑΣΤΑΣΗΣ του ΤΕΠΑΚ». Αυτό θα το συναποφασίσετε με τον Λογοπαθολόγο. Οι αξιολογήσεις αυτές δεν ενέχουν κινδύνους για τη ζωή σας.

Οι αξιολογήσεις είναι πολύ χρήσιμες γιατί τα αποτελέσματά τους θα μας δείξουν αν η θεραπεία με τον Διακρανιακό Μαγνητικό Ερεθισμό μπορεί να βελτιώσει τα προβλήματα επικοινωνίας που αντιμετωπίζετε. Συγκεκριμένα:

- Η πρώτη και η δεύτερη αξιολόγηση (αξιολογήσεις πριν τη θεραπεία) θα αναδείξουν το είδος των προβλημάτων επικοινωνίας που αντιμετωπίζετε, καθώς και τη σοβαρότητα αυτών των προβλημάτων.

-Η τρίτη αξιολόγηση (1 μέρα μετά την ολοκλήρωση του προγράμματος) θα δείξει αν υπάρχει βελτίωση στα προβλήματα επικοινωνίας σας **αμέσως** μετά την ολοκλήρωση του θεραπευτικού προγράμματος.

-Η τρίτη αξιολόγηση (2 μήνες μετά το τέλος της θεραπείας) θα δείξει αν υπάρχει βελτίωση των επικοινωνιακών σας προβλημάτων **σε βάθος χρόνου**. Δηλαδή θα δείξει αν η θεραπεία είναι αποτελεσματική για τουλάχιστον 2 μήνες.

Όλα τα δεδομένα που θα συλλεχθούν θα φυλαχθούν σε ειδικό χώρο του Τμήματος Επιστημών Αποκατάστασης του Τεχνολογικού Πανεπιστημίου Κύπρου υπό την καθοδήγηση της Δρ. Μαρίας Καμπανάρου. Πρόσβαση στα δεδομένα θα έχουν μόνο οι ερευνητές της συγκεκριμένης έρευνας :

-Αναστάσιος Μ. Γεωργίου
-Νίκος Κωνσταντίνου
-Καμπανάρου Μαρία

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ για συμμετοχή σε πρόγραμμα έρευνας (Τα έντυπα αποτελούνται συνολικά από 13 σελίδες)
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3. Μαγνητική Τομογραφία Εγκεφάλου

Θα σας ζητηθεί να επισκεφθείτε το Διαγνωστικό Κέντρο «Πρόγνωσις» στην πόλη της Λάρνακας για τη συλλογή μαγνητικής τομογραφίας του εγκεφάλου σας. Στο διαγνωστικό κέντρο θα σας ζητηθεί να ξαπλώσετε για περίπου 30 λεπτά στο κρεβάτι του μαγνητικού τομογράφου (MRI) για συλλογή εικόνων της δομής και της λειτουργίας του εγκεφάλου σας. Θα σας ζητηθεί να επισκεφθείτε το διαγνωστικό κέντρο μία φορά πριν την έναρξη της θεραπευτικής παρέμβασης, μία φορά αμέσως μετά την ολοκλήρωση της (10 μέρες μετά την πρώτη συλλογή) και ακόμη μία φορά ακόμα, 2 μηνές μετά.

Οι εικόνες του εγκεφάλου σας θα φυλαχθούν στο Τμήμα Επιστημών Αποκατάστασης του Τεχνολογικού Πανεπιστημίου Κύπρου υπό την καθοδήγηση της Δρ. Μαρίας Καμπανάρου. Ο σκοπός για τον οποίο θα γίνει η συλλογή εικόνων εγκεφάλου είναι η ανίχνευση πιθανών διαφορών στη δομή και στη λειτουργία του εγκεφάλου σας λόγω της θεραπείας. Ως εκ τούτου, οι εικόνες αυτές δεν μπορούν να χρησιμοποιηθούν για διαγνωστικούς ή άλλους κλινικούς σκοπούς παρά μόνο για σκοπούς μελέτης πιθανών αλλαγών της δομής (π.χ. μεγέθους) και της λειτουργίας του εγκεφάλου σας, λόγω της συγκεκριμένης θεραπευτικής παρέμβασης.

Η τεχνική της μαγνητικής τομογραφίας (MRI) είναι μια από τις πιο προηγμένες και κατατοπιστικές διαγνωστικές διαδικασίες που είναι διαθέσιμες σήμερα. Το MRI είναι μια μέθοδος απόκτησης εικόνων των δομών που βρίσκονται στο εσωτερικό του σώματός σας, χρησιμοποιώντας έναν μεγάλο μαγνήτη και ραδιοκύματα. Δε χρησιμοποιούταν ακτίνες Χ ή ακτινοβολία για τη λήψη των εικόνων. Ως διαδικασία, είναι εντελώς ανώδυνη και δεν υπάρχουν γνωστές βλαβερές παρενέργειες της από τη χρήση της. Αυτό που απατείται είναι να παραμείνετε ακίνητη/ος πάνω στο κρεβάτι ενώ είσαστε μέσα στον μαγνητικό τομογράφο. Ενώ ο τομογράφος θα δημιουργεί τις εικόνες του εγκεφάλου σας, θα ακούτε κάποια βουητά και δυνατούς ήχους. Αυτό είναι μέρος της κανονικής λειτουργίας του τομογράφου και δεν πρέπει να σας ανησυχεί.

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

Λόγω της χρήσης ραδιοκυμάτων από τον μαγνητικό τομογράφο, άτομα με καρδιακό βηματοδότη, κλιπ ανευρύσματος εγκεφάλου, καθώς και μεταλλικά εμφυτεύματα ή άλλες ηλεκτρικές συσκευές στο σώμα τους, δε θα πρέπει να εισέρχονται στο δωμάτιο του μαγνητικού τομογράφου. Είναι σημαντικό να ενημερώσετε τους ερευνητές στο Έντυπο Ελέγχου Ασφαλείας Μαγνητικού Τομογράφου αν έχετε οποιαδήποτε από αυτές τις μεταλλικές συσκευές στο σώμα σας. Επίσης, δεδομένου ότι οι επιπτώσεις της μαγνητικής τομογραφίας στο έμβρυο είναι άγνωστες, παρακαλείστε να ενημερώσετε τους ερευνητές στο της παρούσας έρευνας εάν είστε έγκυος ή νομίζετε ότι μπορεί να είστε έγκυος.

4. Θεραπευτική Παρέμβαση με Διακρανιακό Μαγνητικό Ερεθισμό

Το θεραπευτικό πρόγραμμα θα λάβει χώρα στην «ΚΛΙΝΙΚΗ ΑΠΟΚΑΤΑΣΤΑΣΗΣ του ΤΕΠΑΚ». Θα σας ζητηθεί να συμμετάσχετε σε 10 συνεχόμενες ημερήσιες συνεδρίες οι οποίες θα περιλαμβάνουν ερεθισμό του φλοιού του εγκεφάλου σας (του εξωτερικού τμήματος του εγκεφάλου σας) με τη χρήση ΔΜΕ. Κάθε συνεδρία θα έχει διάρκεια περίπου 25 λεπτά. Κατά τη διάρκεια της θεραπείας, εσείς θα είσαστε ξαπλωμένος/η σε μια οδοντιατρική καρέκλα. Η θεραπεία θα αφορά τον ερεθισμό συγκεκριμένων περιοχών του εγκεφάλου σας, με μια σειρά από μαγνητικούς παλμούς που παράγονται από ένα μονωμένο πηνίο το οποίο θα τοποθετήσουμε στο τριχωτό της κεφαλής σας. Αυτοί οι μαγνητικοί παλμοί ταξιδεύουν μέσω του τριχωτού της κεφαλής και του κρανίου σας προκαλώντας ηλεκτρικό ρεύμα μικρής έντασης στον φλοιό του εγκεφάλου σας.

Είναι σημαντικό να γνωρίζετε ότι οι μαγνητικοί παλμοί μπορεί να προκαλέσουν μια μικρή αίσθηση ελαφρού χτυπήματος πάνω στο τριχωτό της κεφαλής σας. Αυτή η αίσθηση συνήθως δεν είναι δυσάρεστη αλλά μερικές φορές μπορεί να προκαλέσει μια ενοχλητική αίσθηση. Είναι σημαντικό να γνωρίζετε πως μπορείτε ανά πάσα στιγμή να ζητήσετε να σταματήσει η διαδικασία και να αποχωρήσετε χωρίς να δικαιολογηθείτε και με καμία συνέπεια.

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

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Όπως υποδηλώνει το όνομα, ο ΔΜΕ χρησιμοποιεί μαγνητικά πεδία. Ως εκ τούτου, μπορεί να προβεί επιβλαβής σε άτομα που έχουν μεταλλικά ή ηλεκτρονικά εμφυτεύματα στο σώμα τους. Παρακαλείστε να ενημερώσετε τους ερευνητές σημειώνοντας τις απαντήσεις σας στο Έντυπο Ελέγχου Ασφαλείας, σε περίπτωση που έχετε κάποιο από αυτά. Επίσης, δεδομένου ότι οι επιπτώσεις της ΔΜΕ στο έμβρυο είναι άγνωστες, σας συμβουλεύουμε να μην λάβετε μέρος στο πείραμα εάν είστε έγκυος ή νομίζετε πως υπάρχει περίπτωση να είσαστε έγκυος. Επίσης, σας συμβουλεύουμε να μην λάβετε μέρος, αν έχετε πιει αλκοόλ τις τελευταίες 24 ώρες, αν έχετε χρησιμοποιήσει ναρκωτικά κατά τον τελευταίο μήνα ή εάν δεν είχατε έναν καλό ύπνο το βράδυ πριν από το πείραμα.

Υπάρχουν παρενέργειες από τις θεραπείες;

Παρέχοντας μια συνεχή σειρά μαγνητικών ερεθισμάτων με τη χρήση ΔΜΕ σε σύντομο χρονικό διάστημα, υπάρχει πολύ μικρός κίνδυνος για συγκεκριμένες παρενέργειες. Σύμφωνα με την επιστημονική βιβλιογραφία δεν υπάρχει καμία μακροπρόθεσμη παρενέργεια μετά τη χρήση του ΔΜΕ. Παρόλο που οι πιθανές παρενέργειες είναι ήπιες και σπάνιες, εμείς θα είμαστε πολύ προσεκτικοί κατά τη διεξαγωγή της έρευνας. Δηλαδή, στην έρευνα θα συμμετάσχουν άτομα για τα οποία υπολογίζεται ότι η πιθανότητα εμφάνισης κάποιας παρενέργειας είναι **πολύ χαμηλή έως μηδαμινή.** Επίσης, όλοι οι ερευνητές είναι εκπαιδευμένοι και κάτοχοι διπλώματος Πρώτων Βοηθειών.

Διεθνώς έχουν αναφερθεί οι εξής παρενέργειες (μετά από χρήση ΔΜΕ σε υγιείς και ασθενείς συμμετέχοντες):
-επιληπτική κρίση
-ήπια παροδική ευφορία
-ήπιος παροδικός πονοκέφαλος
-ήπιος παροδικός πόνος σε δόντια
-παροδικό μούδιασμα ή κοκκίνισμα στην περιοχή όπου ακουμπούν τα μηχανήματα
-ήπια παροδική ενόχληση στα αυτιά λόγω θορύβου του μηχανήματος – για την αντιμετώπιση του θορύβου κάποιοι ασθενείς φοράνε ωτοασπίδες κατά τη διάρκεια της θεραπείας. Εμείς θα χρησιμοποιήσουμε ωτοασπίδες σε όσους συμμετέχοντες κριθεί απαραίτητο.

Είναι σημαντικό να γνωρίζετε ότι η ΔΜΕ έχει χρησιμοποιηθεί με ασφάλεια τα τελευταία περίπου 30 χρόνια σε χιλιάδες άτομα σε όλο τον κόσμο.

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

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Θα ωφεληθώ από την έρευνα;

Δεν είστε υποχρεωμένος/η να συμμετάσχετε στην έρευνα και η συμμετοχή σας σε αυτήν την μελέτη δεν σας εγγυάται άμεσα ιατρικά οφέλη αλλά ούτε και τα αποκλείει. Υπάρχουν διεθνείς μελέτες που λένε ότι υπάρχουν οφέλη με τη θεραπεία με ΔΜΕ για προβλήματα επικοινωνίας μετά από εγκεφαλικό επεισόδιο. Συγκεκριμένα, υπάρχει πιθανότητα να βελτιωθεί η επικοινωνία σας μετά από την ολοκλήρωση της θεραπείας. Πολλές διεθνείς έρευνες υποστηρίζουν ότι η αποτελεσματικότητα της θεραπείας είναι εμφανής για τουλάχιστον 2 μήνες μετά την ολοκλήρωσή της. Υπάρχουν και μελέτες με πιο ασαφή αποτελέμστα αναφορικά με τη βελτίωση καθώς και τη χρονική διάρκεια της βελτίωσης.

Οι πληροφορίες από αυτήν την έρευνα μπορεί στο μέλλον να βοηθήσουν άλλους συνανθρώπους μας που αντιμετωπίζουν παρόμοια προβλήματα με σας. Έτσι, τα αποτελέσματα της παρούσας έρευνας αναμένεται να συμβάλουν στην επιστημονική γνώση σχετικά με την νευρολογική αποκατάσταση προβλημάτων επικοινωνίας σε ασθενείς που έχουν πάθει εγκεφαλικό επεισόδιο.

Πότε θα τελειώσει η διαδικασία της έρευνας;

Η έρευνα θα τελειώσει αφού σας αξιολογήσει ο Λογοπαθολόγος 2 μήνες μετά τη θεραπεία σας.

Αν θελήσετε να σταματήσετε τη θεραπεία οποιαδήποτε στιγμή, είσαστε ελεύθερος/η σταματήσετε. Η απόφασή αυτή είναι σεβαστή από τους ερευνητές και δεν επηρεάζει σε καμία περίπτωση τη σχέση σας μαζί τους και την ποιότητα της θεραπείας που θα λάβετε.

Τί θα συμβεί μετά;

Θα γίνει ανάλυση αποτελεσμάτων από τους ερευνητές.

Τί θα γίνει με τα αποτελέσματα της έρευνας;

Μία έκθεση της έρευνας θα υποβληθεί για δημοσίευση και τα αποτελέσματα της έρευνας μπορεί επίσης να χρησιμοποιηθούν για εκπαιδευτικούς ή άλλους ερευνητικούς σκοπούς. **Όμως, τα ατομικά σας στοιχεία δε θα δημοσιευτούν.**

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ για συμμετοχή σε πρόγραμμα έρευνας (Τα έντυπα αποτελούνται συνολικά από 13 σελίδες)
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Ποιος θα έχει πρόσβαση στα αποτελέσματα;

Όλες οι πληροφορίες που θα συλλεχθούν θα παραμείνουν αυστηρώς εμπιστευτικές και μόνο οι ερευνητές θα έχουν πρόσβαση στις πληροφορίες.

Από την αρχή της έρευνας σε καθέναν από τους συμμετέχοντες θα αντιστοιχεί ένας αριθμός ο οποίος θα χρησιμοποιείται σε όλα τα μετέπειτα αποθηκευμένα αρχεία.

Αφού ολοκληρωθεί η έρευνα, τα έντυπα αρχεία θα φυλαχθούν σε ένα ντουλάπι για 5 χρόνια. Μετά από 5 χρόνια όλα τα δεδομένα θα καταστραφούν. Πρόσβαση στα δεδομένα θα έχουν μόνο οι κύριοι ερευνητές.

Θα πληρωθώ για να συμμετάσχω στην έρευνα;

Όχι.

Η έρευνα έχει εγκριθεί από κάποιον οργανισμό;

Η έρευνα αυτή έχει αξιολογηθεί και έχει εγκριθεί από την Εθνική Επιτροπή Βιοηθικής Κύπρου, με αριθμό: ΕΕΒΚ/ΕΠ/2017/37

Άλλες σημαντικές πληροφορίες:

-Εάν επιθυμείτε να συμμετάσχετε, μπορείτε να αποχωρήσετε από την έρευνα ανά πάσα στιγμή χωρίς καμία επίπτωση.
-Εάν επιθυμείτε να συμμετάσχετε θα πρέπει να σταματήσετε **τη λογοθεραπεία, την εργοθεραπεία και τη φυσικοθεραπεία μέχρι την ολοκλήρωση του προγράμματος (περίπου 3 μήνες).**
-Το συγκεκριμένο Έντυπο Συγκατάθεσης και το Έντυπο Ελέγχου Ασφαλείας που θα πρέπει να συμπληρώσετε, έχουν ελεγχθεί και εγκριθεί από την Κυπριακή Εθνική Επιτροπή Βιοηθικής.
-Εάν επιθυμείτε να εκφράσετε με οποιονδήποτε τρόπο ανώνυμα ή επώνυμα τα σχόλια ή παράπονά σας για τη συγκεκριμένη έρευνα μπορείτε να επικοινωνήσετε με την εξής ανεξάρτητη αρχή:

Δρ. Χαράλαμπος Χρυσοστόμου
Προϊστάμενος Υπηρεσίας Έρευνας και Διεθνούς Συνεργασίας
Τεχνολογικό Πανεπιστήμιο Κύπρου
Τηλέφωνο: +357 25 002562
Ηλεκτρονικό ταχυδρομείο (email): c.chrisostomou@cut.ac.cy

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία	

Appendix 8

Guiding Questions for Selecting Outcome Measures (Coster, 2013)

Greek BDAE-SF: Boston Diagnostic Aphasia Examination-Short Form; PPVT-F: Peabody Picture Vocabulary Test–Revised, GOAT: Greek Object and Action Test; MAIN: Multilingual Assessment Instrument for Narrative; Raven's Test; SAQOl-39: Stroke and Aphasia Quality of Life Scale-39 item (SAQOL-39)

	Tools					
What: Specification of the construct	**Greek BDA-SF**	**PPVT-R**	**GOAT**	**MAIN**	**Raven's Test**	**SAQOL-39g**
1. Is there a well-specified explanatory model showing how the intervention links to the outcome of interest?	Yes	Yes	Yes	Yes	No	No
2. Have the most relevant dimensions or aspects of the outcome been specified clearly?	Yes	Yes	Yes	Yes	Yes	Yes
How: Rationale for selecting the measure	**Greek BDA-SF**	**PPVT-R**	**GOAT**	**MAIN**	**Raven's Test**	**SAQOL-39g**
1. Does the measurement construct of the instrument match the study's target outcome (as specified by the model)?	Yes	Yes	Yes	Yes	Yes	No
2. Does the instrument address the relevant domains of greatest importance?	Yes	Yes	Yes	Yes	Yes	No
3. Do the items sample the domain at the desired or appropriate level of specificity?	Yes	Yes	Yes	Yes	Yes	Yes/No
4. Are the items well suited to the characteristics of the population (i.e., are they free from bias)?	Yes	Yes	Yes	Yes	Yes	Yes

5. Does the measurement dimension reflect the type of change expected from the intervention?	Yes	Yes	Yes	Yes	Yes	No
6. Do points on the scale match the degrees of variation expected in the sample?	Yes	Yes	Yes	Yes	Yes	Yes
7. Are item and scale wording appropriate (i.e., meaningful, understandable) for this population?	Yes	Yes	Yes	Yes	Yes	Yes/No
8. Does evidence exist that the measure is sensitive to degrees of change expected in this population?	Yes	Yes	Yes	Yes	Yes	Yes
9. Does evidence exist supporting the ability of the measure to identify meaningful change?	Yes	Yes	Yes	Yes	Yes	Yes
Who: Determination of the most appropriate source of outcome information	**Greek BDA-SF**	**PPVT-R**	**GOAT**	**MAIN**	**Raven's Test**	**SAQOL-39g**
1. Do the potential providers of outcome information (e.g., professional, caregiver) match the qualifications criteria of the instrument being considered?	Yes	Yes	Yes	Yes	Yes	Yes
2. If someone other than a professional will be the respondent, is it probable that the respondent will be able to complete the assessment (i.e., has the necessary sensory, literacy, cognitive, physical, and communication abilities?)	Yes	Yes	Yes	Yes	Yes	Yer/No
3. Can the measure be adapted if needed to accommodate functional limitations of the respondent?	No	No	No	No	No	Yes
4. Will the identified respondents be available throughout the study period (i.e., for all measurement points)?	Yes	Yes	Yes	Yes	Yes	Yes
When: Determination of when outcomes should be measured	**Greek BDA-SF**	**PPVT-R**	**GOAT**	**MAIN**	**Raven's Test**	**SAQOL-39g**
1. Does the length of time between assessments match the time period over which this instrument is likely to show effects?	Yes	Yes	Yes	Yes	Yes	Yes

2. Can the measure be administered as often as required by the study design?	Yes	Yes	Yes	Yes	Yes	Yes

Appendix 9

Speech & Language History Form

Παρακαλώ συμπληρώστε το ακόλουθο ερωτηματολόγιο:

ΒΙΟΓΡΑΦΙΚΑ ΣΤΟΙΧΕΙΑ:

Όνομα: _____ **Επίθετο**: _____
Διεύθυνση: _____
Επαρχία: _____
Τηλέφωνο: _____ Κινητό_____
Email:_____

Ημερομηνία Γεννήσεως: _____Ηλικία: _____
Τόπος γεννήσεως:
_____

Μορφωτικό επίπεδο (Δημοτικό, Γυμνάσιο, Λύκειο, Ανωτάτη Σχολή κλπ):_____
Επάγγελμα:
_____
_____
Μητρική γλώσσα: _____ Άλλες γλώσσες:
_____

Παραπέμπεται από:
_____

Λόγος παραπομπής:
_____

ΙΑΤΡΙΚΟ ΙΣΤΟΡΙΚΟ:

Ιατρική Διάγνωση και **ημερομηνία επεισοδίου**:
_____
_____
_____

Σημειώστε ό,τι αφορά:		
o Καρδιακή ανακοπή	o Καρκίνος	o Νοητική Υστέρηση
o Αρρυθμίες καρδίας	o Καρκίνος κεφαλής/λαιμού	o Σχιστία υπερώας
o Υπέρταση	o Έρπη ζωστήρα	o Χρόνια κρυολογήματα
o Διαβήτης	o Βρογχίτιδα	o Παράλυση ή πάρεση προσωπικού νεύρου
o Αγγειακό εγκεφαλικό επεισόδιο (ΑΕΕ)	o Χρόνια Αποφρακτική Πνευμονοπάθεια (ΧΑΠ)	o Ψυχολογικά θέματα/θέματα ψυχικής υγείας
o Χρόνια λαρυγγίτιδα	o Ιγμορίτιδα	o Πολλαπλή Σκλήρυνση
o Γαστρο-οισοφαγική παλινδρόμηση (ΓΟΠ)	o Φυματίωση	o Νόσος του Huntington's ή του Parkinson's
o Ωτίτιδες	o Πνευμονία	o Θέματα φώνησης ή αλλαγές φώνησης
o Μηνιγγίτιδα	o Άσθμα	o Πολύποδες ή φωνητικά οζίδια
o Επιληπτικές κρίσεις - σπασμοί	o Πάθηση Θυρεοειδούς	o Αλλεργίες
o Κρανιοεγκεφαλική Κάκωση (ΚΕΚ)	o Αρθρίτιδα	o Εγκεφαλική παράλυση
o Νευρολογική πάθηση	o Βαρηκοΐα / Κώφωση	o Νόσος του Alzheimer's
o Γενετική Άνοια	o Αυτισμός	o Γενετικό Σύνδρομο

Υπάρχουν άλλα προβλήματα πέραν όσων αναφέρονται πιο πάνω;

_____

_____

_____

<u>ΝΕΥΡΟΛΟΓΙΚΗ ΕΞΕΤΑΣΗ</u>: Εξετάσεις που έχουν γίνει στον ασθενή: (σημειώστε με ✓ ότι αρμόζει)

- Αξονική Τομογραφία – Διάγνωση / Αποτελέσματα:

  _____

  _____

- Μαγνητική Τομογραφία - Διάγνωση / Αποτελέσματα:
  _____
  _____
- Ηλεκτροεγκεφαλογράφημα – Διάγνωση / Αποτελέσματα:
  _____
  _____
- Αγγειογραφία – Διάγνωση / Αποτελέσματα:
  _____
  _____
- Άλλες Εξετάσεις:
  _____
  _____
  _____
  _____

Νευρολογική Διάγνωση:

_____
_____
_____

Πληροφορίες για τυχόν **εγχειρίσεις** που έγιναν:

_____
_____
_____
_____

Ακολουθεί κάποια **φαρμακευτική αγωγή; Ναι___ Όχι___** , εάν **Ναι**, παρακαλώ σημειώστε όνομα και δοσολογία φαρμάκου:

- _____
- _____
- _____
- _____
- _____
- _____
- _____

Κινητικές Δυσκολίες: (σημειώστε με ✓ ότι αρμόζει)

Ημιπληγία - Δεξιά ___ Αριστερά ___

Διπληγία – Άνω άκρα ___ Κάτω άκρα ___

Τετραπληγία, είδος

_____

Τίποτα από τα παραπάνω

Χρησιμοποιεί κάποιο από τα ακόλουθα βοηθήματα;
- Τροχοκάθισμα
- Βοήθημα βάδισης (π.χ. walking frame (πι), rollator)
- Μπαστούνι
- Άλλο βοήθημα _____
- Δε χρησιμοποιεί

Μπορεί να ανεβοκατεβαίνει σκαλιά ή σκάλες; **Ναι_____ Όχι_____**

- Δεξιόχειρας Αριστερόχειρας
  - Επικρατέστερο χέρι για την πλειοψηφία της οικογένειας: _____

ΙΣΤΟΡΙΚΟ ΛΟΓΟΥ / ΟΜΙΛΙΑΣ (σημειώστε με ✓ στην στήλη που αρμόζει)

Σύμπτωμα	Ποτέ	Κάποτε	Συχνά
Δυσκολία έκφρασης σκέψεων			
Δυσκολία να γίνει κατανοητός από άλλους			
Δυσκολία να καταλάβει τι του λένε οι άλλοι			
Δυσκολία Προσανατολισμού/Μνήμης			
Δυσκολία στην Επίλυση προβλημάτων			
Δυσκολία στην Εστίαση /Προσοχή			
Δυσκολίες Ανάγνωσης/Γραφής			
Δυσκολία στην Εξεύρεση Λέξεων			
Δυσκολία να παραμείνει σε ένα θέμα κατά τη διάρκεια συζήτησης			
Δυσκολία στη ροή της ομιλίας (τραυλισμός)			
Δυσκολία στο να ακολουθά οδηγίες			
Στοματοπροσωπικές αδυναμίες (αδυναμία, δυσκολία συντονισμού γλώσσας, μαγούλων, χειλιών, κλπ.)			
Δυσκολίες φώνησης			
Δυσκολία κατάποσης			

- Παρουσιάζει πρόβλημα κατάποσης; **Ναι_____ Όχι_____**
- Σημειώστε ό,τι αρμόζει:
  - Τρέφεται από το στόμα
  - Τρέφεται με ρινογαστρικό σωλήνα
  - Τρέφεται με γαστροστομία

- Τρόπος παρούσας επικοινωνίας:
  - Προφορικά
  - Νοήματα / χειρονομίες
  - Γραφή
  - Εναλλακτικός τρόπος επικοινωνίας (π.χ. ηλεκτρονική συσκευή)
  - Άλλο _____

- Άλλες δυσκολίες από τις προαναφερθέντες:
  _____
  _____
  _____

Άλλα θέματα:

- Παρουσιάζει προβλήματα όρασης; **Ναι ___ Όχι ___**, εάν **Ναι**, πότε άρχισαν;
  _____
  _____
- Φορεί γυαλιά; **Ναι ___ Όχι ___**

- Εάν έχει βαρηκοΐα, φέρει ακουστικό βοήθημα; **Ναι ___ Όχι ___**, εάν **Ναι**, σε ποιο αυτί; _____

- Φοράει τεχνητή οδοντοστοιχία; **Ναι ___ Όχι ___**, εάν **Ναι**, παρακαλώ περιγράψτε
  _____
  _____
- Υπάρχει κάποιος άλλος στην οικογένεια με παρόμοια ή τα ίδια προβλήματα; Εξηγήστε
  _____
  _____
  _____

- Παρουσιάζει προβλήματα με τον ύπνο; **Ναι ___ Όχι ___**

- Κάπνισμα και αλκοόλ:
  _____

Για περιπτώσεις επίκτητων νευρολογικών διαταραχών (π.χ. αγγειακά εγκεφαλικά επεισόδια, κρανιοεγκεφαλικές κακώσεις, κλπ) παρακαλώ σημειώστε:

- Προβλήματα υγείας πριν την εγκεφαλική βλάβη:
  _____
  _____
  _____
  _____

- Προβλήματα λόγου και ομιλίας πριν την βλάβη, παρακαλώ αναφέρατε:
  _____
  _____
  _____

  Παρακολουθείτο από κάποιον ειδικό; **Ναι** ___ **Όχι** ___ , εάν **Ναι**, παρακαλώ αναφέρατε τη χρονική διάρκεια και τα αποτελέσματα της παρέμβασης:
  _____
  _____
  _____
  _____
  _____

  Γενική Συμπεριφορά Ασθενή:
  - Πριν την εγκεφαλική βλάβη :_____
  - Μετά την εγκεφαλική βλάβη:_____
  - Γενικές παρατηρήσεις:
    _____
    _____
    _____

ΟΙΚΟΓΕΝΕΙΑΚΟ/ ΚΟΙΝΩΝΙΚΟ ΙΣΤΟΡΙΚΟ

- Οικογενειακή κατάσταση:
  - Άγαμος/η
  - Χωρισμένος/η
  - Παντρεμένος/η
  - χήρος/χήρα
- Όνομα Συζύγου:
  _____
- Τόπος παρούσης διαμονής:
  _____

- Παιδιά :

ΟΝΟΜΑΤΑ	ΗΛΙΚΙΕΣ

  - Τωρινή επαγγελματική απασχόληση:
    _____

  - Συνεχίζετε να εργάζεστε; Ναι___ Όχι___, εάν Ναι,
    - Τίτλος εργασίας:
      _____
    - Εργοδότης:
      _____

  - Ακολουθεί ένα εβδομαδιαίο πρόγραμμα θεραπειών ή/και δραστηριοτήτων όπως :
    _____
    _____
    _____
    _____
    _____
    _____

  - Αγαπημένες ασχολίες (χόμπι) :
    _____
    _____
    _____

Παρακαλώ σημειώστε οποιεσδήποτε άλλες πληροφορίες οι οποίες πιστεύετε ότι θα είναι χρήσιμες:
_____
_____
_____
_____
_____
_____
_____

Το ερωτηματολόγιο αυτό συμπληρώθηκε από :

Όνομα : _____ (σχέση με το άτομο: _____)

Υπογραφή : _____

Ημερομηνία : _____

Για πανεπιστημιακή χρήση μόνο: Όνομα Λογοπαθολόγου: _____

Appendix 10

Face Sheet

Φύλλο Πληροφοριών

(Οι κάτωθι πληροφορίες είναι εμπιστευτικές και δε θα κοινοποιηθούν)

Για καθεμιά από τις παρακάτω ερωτήσεις, παρακαλώ ***κυκλώστε*** *την απάντηση/απαντήσεις που σας ταιριάζουν καλύτερα. Στις* ***ερωτήσεις 2 & 3*** *συμπληρώστε τις κατάλληλες απαντήσεις.*

1. **Φύλο:** Άρρεν Θήλυ

2. **Ημερομηνία Γέννησης:**

3. **Χρόνια Εκπαίδευσης:**

4. **Το 1^{ο} εγκεφαλικό το έπαθα:**
Α) 1-6 μήνες πριν
Β) 7-11 μήνες πριν
Γ) 12-23 μήνες πριν
Δ) 2 χρόνια πριν
Ε) 3-5 χρόνια πριν
ΣΤ) 6-8 χρόνια πριν
Ζ) περισσότερο από 9 χρόνια πριν

5. **Το τελευταίο εγκεφαλικό το έπαθα:**
Α) Έπαθα μόνο 1 εγκεφαλικό στη ζωή μου
Β) 1-6 μήνες πριν
Γ) 7-11 μήνες πριν
Δ) 12-23 μήνες πριν
Ε) 2 χρόνια πριν
ΣΤ) 3-5 χρόνια πριν
Ζ) 6-8 χρόνια πριν
Η) περισσότερο από 9 χρόνια πριν

6. **Λογοθεραπεία έκανα για:**
1-11 μήνες 1-2 χρόνια 3-5 χρόνια άνω των 6 χρόνων
Δεν έκανα ποτέ λογοθεραπεία Κάνω ακόμα Λογοθεραπεία

7. **Τελευταία φορά έπαθα επιληπτική κρίση πριν από:**
1-11 μήνες 1-2 χρόνια 3-5 χρόνια άνω των 6 χρόνων
Δεν έπαθα ποτέ επιληπτική κρίση Παθαίνω ακόμα επιληπτικές κρίσεις

8. Τελευταία φορά πήρα αγωγή για επιληψία πριν από:

1-11 μήνες 1-2 χρόνια 3-5 χρόνια άνω των 6 χρόνων

Παίρνω ακόμα αγωγή για την επιληψία

Δεν πήρα ποτέ αγωγή για επιληψία

Δηλώνω ότι οι πληροφορίες που δίνονται στο παρόν είναι αληθείς και ορθές.

Ημερομηνία:

Ονοματεπώνυμο:

Υπογραφή:

Appendix 11

Screening for TMS eligibility

ΕΝΤΥΠΟ ΑΝΙΧΝΕΥΤΙΚΟΥ ΕΛΕΓΧΟΥ ΓΙΑ ΔΙΑΚΡΑΝΙΑΚΟ ΜΑΓΝΗΤΙΚΟ ΕΡΕΘΙΣΜΟ (ΔΜΕ)

Παρακάτω είναι ένα ερωτηματολόγιο που χρησιμοποιείται για να καθορίσει αν οι πιθανοί συμμετέχοντες είναι κατάλληλοι για ΔΜΕ.

ΠΑΡΑΚΑΛΩ ΣΥΜΠΛΗΡΩΣΤΕ ΤΟ ΠΑΡΑΚΑΤΩ ΕΝΤΥΠΟ:

Δημογραφικά Στοιχεία

Ημερ. γέννησης: .....
Τόπος γέννησης: .....
Μητρική/ές γλώσσα/ες: Ελληνική Άλλη
(ονομάστε την άλλη γλώσσα) .....

Μόρφωση: Δημοτικό / Γυμνάσιο / Λύκειο / Κολλέγιο / Πανεπιστήμιο / Μεταπτυχιακό / Διδακτορικό
Άλλο: .....
Επάγγελμα: .....
Διεύθυνση: .....
.....
Τηλ. επικοινωνίας: .....

_____ _____
Υπογραφή Συμμετέχοντα Ημερομηνία

_____ _____
Υπογραφή Μάρτυρα Ημερομηνία

ΟΝΟΜΑ ΑΣΘΕΝΟΥΣ ή/και ΕΘΕΛΟΝΤΗ:
Παρακαλώ σημειώστε ό,τι ισχύει:

Νευρολογική ή Ψυχιατρική διαταραχή	ΝΑΙ	ΟΧΙ
Τραύμα στο κεφάλι	ΝΑΙ	ΟΧΙ
Εγκεφαλικό επεισόδιο	ΝΑΙ	ΟΧΙ
Χειρουργική επέμβαση στον εγκέφαλο	ΝΑΙ	ΟΧΙ
Μέταλλο ή μεταλλικά ρινίσματα στο κρανίο ή στα μάτια	ΝΑΙ	ΟΧΙ
Εγκεφαλική βλάβη	ΝΑΙ	ΟΧΙ
Βηματοδότη	ΝΑΙ	ΟΧΙ
Ιστορικό με σπασμούς ή/και επιληπτικές κρίσεις	ΝΑΙ	ΟΧΙ
Οικογενειακό ιστορικό επεισοδίων επιληψίας	ΝΑΙ	ΟΧΙ
Εμφυτευμένες ηλεκτρονικές συσκευές (π.χ. κοχλιακό εμφύτευμα)	ΝΑΙ	ΟΧΙ
Ενδοκρανιακές γραμμές	ΝΑΙ	ΟΧΙ
Σκλήρυνση κατά Πλάκας	ΝΑΙ	ΟΧΙ
Κατάθλιψη	ΝΑΙ	ΟΧΙ
Θεραπεία με Αντικαταθλιπτικά (π.χ. Αμιτρυπτιλήνη, Αλοπεριδόλη)	ΝΑΙ	ΟΧΙ
Εμφυτευμένη αντλία παροχής φαρμακευτικής αγωγής	ΝΑΙ	ΟΧΙ
Ενδοκρανιακή πάθηση	ΝΑΙ	ΟΧΙ
Αλφισμός (λευκοπάθεια)	ΝΑΙ	ΟΧΙ
Έντονο άγχος/ανησυχία	ΝΑΙ	ΟΧΙ
Κυοφορούσα αυτή την περίοδο	ΝΑΙ	ΟΧΙ
Χρόνιοι πονοκέφαλοι	ΝΑΙ	ΟΧΙ
Συχνές τάσεις λιποθυμίας	ΝΑΙ	ΟΧΙ
Έχετε πιει αλκοόλ τις τελευταίες 24 ώρες;	ΝΑΙ	ΟΧΙ
Έχετε κάνει χρήση ναρκωτικών ουσιών τον τελευταίο μήνα;	ΝΑΙ	ΟΧΙ
Είχατε ικανοποιητικό βραδινό ύπνο το βράδυ πριν το πείραμα;	ΝΑΙ	ΟΧΙ

Δηλώνω υπεύθυνα ότι όλες οι πληροφορίες που παρέχονται στο παρόν έντυπο ελέγχου ΔΜΕ είναι αληθείς και πλήρεις από κάθε άποψη.

_____ _____

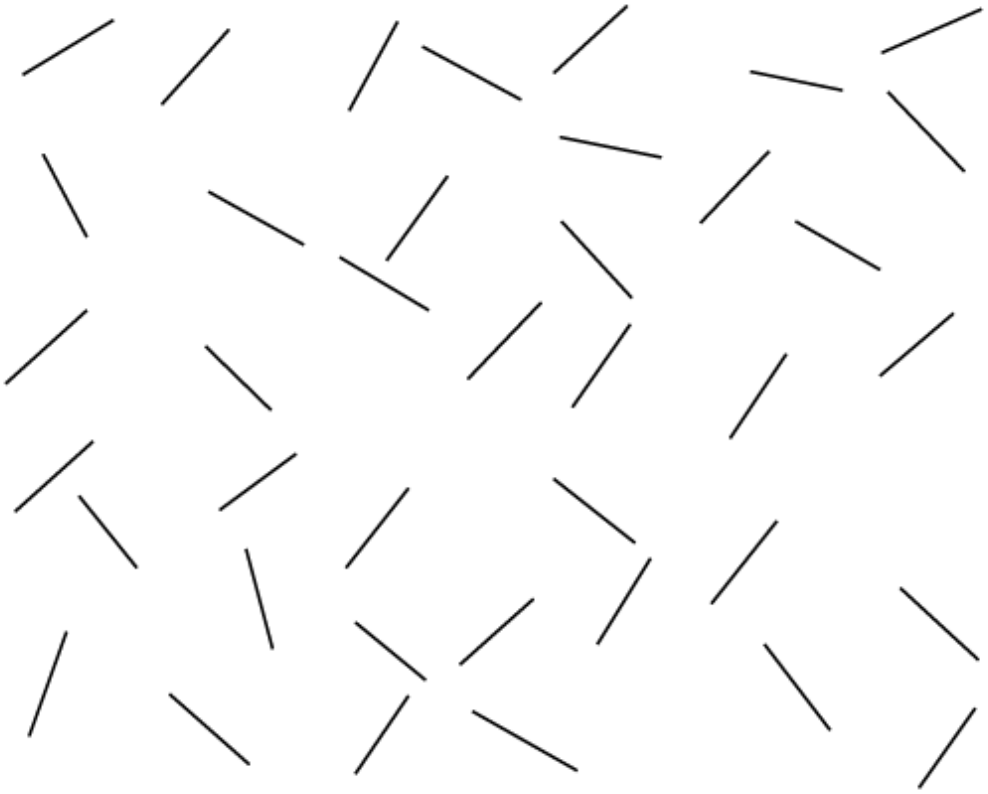
Υπογραφή Συμμετέχοντα Ημερομηνία

_____ _____

Υπογραφή Μάρτυρα Ημερομηνία

Appendix 12

Hemispatial Neglect Test



Appendix 13

Handedness Inventory

Ερωτηματολόγιο για την Δειοχειρία – Αριστεροχειρία (Σύντομη Έκδοση)

Ημερομηνία: _____ Φύλο: _____

Παρακαλώ να μας υποδείξετε ποιο χέρι χρησιμοποιούσατε για τις παρακάτω δραστηριότητες ή αντικείμενα πριν το εγκεφαλικό:

	Πάντα δεξί	**Συνήθως δεξί**	**Και τα δύο**	**Συνήθως αριστερό**	**Πάντα αριστερό**
Γραφή					
Πέταγμα Throwing					
Οδοντόβουρτσα Toothbrush					
Κουτάλι					