Journal of Neurolinguistics 55 (2020) 100907

Contents lists available at ScienceDirect

Journal of Neurolinguistics

journal homepage: www.elsevier.com/locate/jneuroling

Can transcranial magnetic stimulation (TMS) facilitate language recovery in chronic global aphasia post-stroke? Evidence from a case study

Anastasios M. Georgiou*, Ioannis Phinikettos, Chrysa Giasafaki, Maria Kambanaros

Department of Rehabilitation Sciences, Cyprus University of Technology, Limassol, Cyprus

ARTICLE INFO

Keywords:
Transcranial magnetic stimulation (TMS)
Theta burst stimulation (TBS)
Neuronavigation
Quality of life
Case-based approach

ABSTRACT

The present study reports the findings of a 10-consecutive day neuronavigated continuous theta burst stimulation (cTBS) treatment over the right pars triangularis (pTr) for one individual with chronic global aphasia post-stroke. Baseline language and quality of life measures were collected twice prior to treatment, one day post-treatment, and then at two and 12-months follow up. Therapy was tolerated well by A.M. and no side effects were noticed during and after treatment. Results showed a trend towards improvement in expressive language in the short-term (i.e. one day post-treatment), significant improvement in spoken comprehension and moderate improvement in reading performance at follow-up (i.e. two months and one year post-treatment). Quality of life (QoL) did not significantly change as a result of the treatment. Findings from this study indicate that cTBS over the right pTr has the potential to induce recovery of aphasia across various language skills. Further research exploring individualized TMS protocols for aphasia rehabilitation post-stroke is strongly suggested with the goal that TMS can be used as a treatment modality for aphasia post-stroke in the near future.

1. Introduction

Aphasia, an acquired disorder of spoken and/or written language, is a significant aftermath of stroke. In a recent systematic review and meta-analysis, it was shown that reported post-stroke aphasia frequency varies and depends on stroke type (ischemic vs haemorrhagic) and setting (acute vs rehabilitation) (Flowers et al., 2016). Aphasia spontaneously improves during the first four weeks after the stroke event 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 skills (Brady, Kelly, Godwin, Enderby, & Campbell, 2016), 43% of patients that undergo language treatment still present with aphasia 18 months post-stroke (Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001). Hence, there is an urgent need for improved and additional treatment strategies to boost recovery of language functions after stroke in people with aphasia (PWA).

Transcranial magnetic stimulation (TMS) is a non-invasive method of brain stimulation that creates a fluxing magnetic field through electromagnetic induction, which in turn induces the generation of weak currents in underlying cortical neurons, causing them to depolarize. The frequency, intensity, and duration of the stimulation, determine TMS effects on neurons. Recently, TMS effects on motor evoked potentials (MEPs) have led to the consensus that low frequency stimulation (≤1 Hz) induces neuronal inhibition, whereas high stimulation frequencies (≥5 Hz) induce neuronal excitation (Lefaucheur et al., 2014). The assumption is

* Corresponding author. Department of Rehabilitation Sciences, Cyprus University of Technology, 15 Vragadinou Str. 3041, Limassol, Cyprus.
E-mail address: anastasios.georgiou@cut.ac.cy (A.M. Georgiou).

https://doi.org/10.1016/j.jneuroling.2020.100907
Received 17 December 2019; Received in revised form 11 March 2020; Accepted 13 March 2020

that TMS effects represent changes in synaptic efficacy (Lenz, Muller-Dalhaus & Vlachos, 2016). The delivery of multiple TMS stimuli in “trains” (i.e. repeated single magnetic pulses of the same intensity) is known as “repetitive TMS (rTMS)”.

Numerous TMS studies on neurological patients with communication impairments suggest that rTMS can facilitate language recovery in patients with post-stroke aphasia (Georgiou, Lada, & Kambanaros, 2019). Over the last few years, there is substantial evidence for positive effects of applying 1 Hz rTMS over the right homologue of Broca's area, as an adjunct to speech and language therapy (SLT), in all aphasia phases post-stroke (e.g. Haghighi, Mazdeh, Ranjbar, & Seifrabie, 2018; Hu et al., 2018; Rubi-Fessen et al., 2015). The positive effects of TMS on post-stroke aphasia rehabilitation also come from recent studies that have applied short rTMS burst protocols, such as theta burst stimulation (TBS) paradigms (e.g. Griffis, Nenert, Allendorfer, & Szaflarski, 2016; Vuksanovic et al., 2015). The basic TBS pattern, 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). Continuous TBS (cTBS) is a TBS paradigm, applied in the present study, that delivers the basic TBS pattern in a continuous, uninterrupted train lasting for a total of 40 s (i.e. 200 bursts with a total 600 pulses) inducing neuronal inhibition (see Georgiou, Konstantinou, Phinikettos, & Kambanaros, 2019).

The aim of this research was to investigate any changes in language performance using cTBS as a stand-alone treatment in a patient with chronic global aphasia post-stroke.

2. Case report

2.1. Ethics statement

Permission was sought from the Cyprus National Bioethics Committee (CNBC) to conduct the intended research. The study was performed in accordance with the principles of the Helsinki Declaration and the Medical Research Involving Human Subjects Act (WMO). A written informed consent was obtained by the participant and her carer.

2.2. Case summary

The participant (A.M.) 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 had not received any treatment for two years before enrolling in the present study. Table 1 presents the background demographics of the A.M. and Fig. 1 illustrates her brain MRI revealing diffuse cortical and subcortical lesions of the left frontal, temporal and parietal cortices.

A.M. met the following inclusion criteria: (1) she was native a speaker 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) she 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, Panagea, Papathanasopoulos, & Kastellakis, 2013); (5) chronological age was no greater than 75 years. 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 dysarthria affecting intelligibility; (6) auditory or visual deficits and; (7) cognitive disorders known before the stroke.

2.3. Language measures

2.3.1. The Boston Diagnostic Aphasia Examination-shortened version (BDAE-SF)

This tool (Messinis et al., 2013) was used for baseline, post-treatment and follow-up assessment of language skills The battery includes evaluation of language comprehension, expressive language, reading and writing. The tool has satisfactory psychometric properties (Messinis, Panagea, Papathanasopoulos, & Kastellakis, 2013). For the purposes of the present study, written language was not assessed.

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

The Peabody Picture Vocabulary Test–Revised (PPVT-R) is a measure that assesses receptive vocabulary at the word level (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. A.M. was asked to point to the picture out of four that matches the word said by the examiner.

2.4. Problem solving skills measure

2.4.1. Raven's Coloured Progressive Matrices (RCPM)

The Raven's Coloured Progressive Matrices (RCPM) (Raven, Raven, & Court, 1998) consists of 36 items in three sets of 12 and is a non-verbal intelligence test, representative of general intellectual capacity. The test was used to assess problem solving skills. 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-

Table 1
Demographic and clinical characteristics of A.M.

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
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

Key: F: female; SLT: speech and language therapy.

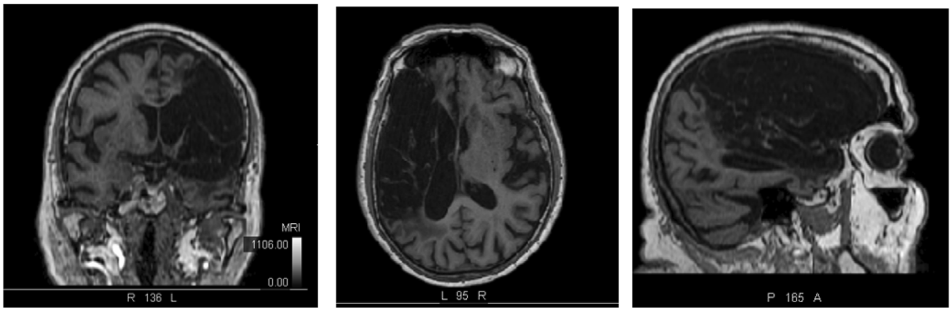

Fig. 1. Brain MRI of A.M. one week before therapy initiation. Left picture: coronal view. Middle picture: axial view. Right picture: sagittal view.

retest reliability appears to be weak for intervals longer than one year (e.g., Kazlauskaite & Lynn, 2002; Raven & Raven, 2003). In this study the maximum interval was 2 months.

2.5. Quality of life measure

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

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 A.M. 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.

2.6. Continuous theta burst stimulation (cTBS)

The assessment of resting motor threshold (RMT) was performed using surface electromyography (EMG) in which leads were placed over the first dorsal interosseous (FDI) muscle of the left hand of A.M. The 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. After obtaining RMTs, the participant underwent cTBS at 80% of her individual RMT, using Magstim Rapid2® (Magstim Co., Wales, UK) connected to a 70 mm 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 A.M. to locate the optimal coil position (Fig. 1). The participant received inhibitory rTMS (cTBS) to the pars triangularis (Tr) of the right inferior frontal gyrus (homologous BA45) following the protocol suggested by Huang, Edwards, Rounis, Bhatia, and Rothwell (2005). Particularly, a 40 s train of uninterrupted TBS was given (600 pulses in total).

2.7. Procedures

A certified speech and language pathologist with 12 years clinical experience blind to the study (i.e., she did not know whether or not the participant would receive real TMS treatment) carried out the cognitive and language assessment and QoL measurement (baseline, post-treatment, follow up). A second speech and language pathologist analysed the data (cognitive, linguistic and QoL). A.M. underwent a brain MRI scan during the week prior to treatment and; underwent language and cognitive testing 12 days and again one day prior to treatment and QoL assessment one day before treatment. Then, she received a 10-consecutive day cTBS treatment; underwent language and cognitive testing again one day after, two months and one year post treatment and; underwent QoL assessment two months and one year post treatment (see Table 2). Due to moderate comprehension deficits A.M. exhibited, proxy (sister) ratings were used to evaluate QoL. Post termination of the treatment period (10 consecutive days), A.M. was asked not to participate in any formal aphasia rehabilitation program for at least two months and if possible for 12 months in total. Nonetheless, she was urged to actively engage in conversations with her carers. Such activities were not monitored by the researchers. To ensure treatment fidelity, we monitored and measured how well the treatment protocol was implemented using the Template for Intervention Description and Replication (TIDieR) 12 item checklist and guide (Hoffmann et al., 2014).

3. Statistical analysis

Weighted Statistics (WEST) and in particular the procedures "West-Trend" and "West-ROC" (one tailed) as suggested by Howard,

Table 2
Experimental timeline.

Pre rTMS sessions	rTMS sessions (10 consecutive days)	Post rTMS sessions
• brain MRI • Language testing • Cognitive testing • QoL assessment	50 Hz neuronavigated cTBS at 80% RMT applied at right pTr	• Language testing • Cognitive testing • QoL assessment
Time (relative to start of treatment)		
– 12 & – 1 days (baseline 1 & 2)	0 days (rTMS therapy)	+1 day, + 2 months & 1 year (post rTMS)

Note: A.M. underwent a brain MRI scan during the week prior to treatment; language and cognitive testing 12 days and again one day prior to treatment and QoL assessment one day before treatment. Then, she received a 10-consecutive day rTMS treatment; underwent language and cognitive testing again one day, two months and one year post treatment and; underwent QoL assessment two months and one year post treatment.

Best, and Nickels (2015) were applied. Such statistical procedures are suitable for studies with small sample sizes and heterogeneous participants. The level of performance prior to treatment is established 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 or the short versus the long-term periods. Weighted statistics were used to analyze data from the Greek BDAE-SF; the PPVT-R and the RCPM. Results from the SAQOL-39g assessment were reported and no statistical analysis was performed.

4. Results

Results showed a trend towards improvement in expressive language in the short-term (i.e. one day post-treatment), significant improvement in language comprehension and moderate improvement in reading performance at follow-up (i.e. two and 12-months post-treatment). Quality of life (QoL) did not significantly change as a result of the treatment. Performance on language and cognitive measures are reported in Table 3 and rated quality of life scores are reported in Table 4.

4.1. Short-term effects (i.e. one day post-treatment) of cTBS (pre TMS 1 – pre TMS 2 – post TMS) using WEST

A.M. did not show an overall improvement in comprehension ($t(63) = 0.44$, $p = .32$), problem solving skills, naming and reading. However, she showed moderate improvement in expressive language ($t(25) = 1.79$, $p = .04$), but the improvement was not higher in the treated (i.e. TMS period) versus the untreated period (i.e. baseline periods) ($t(25) = 0.90$, $p = .19$). Results for the short-term effects of cTBS are shown in Fig. 2.

4.2. Long-term effects (i.e. two months post-treatment) of cTBS (pre TMS 2 – post TMS – follow-up 1) using WEST

A.M. did not show an overall improvement in expressive language ($t(25) = 0.57$, $p = .28$), problem solving skills and naming. However, she showed significant improvement in comprehension ($t(63) = 3.66$, $p < .001$) and moderate improvement in reading ($t(28) = 1.79$, $p = .04$) and this improvement was greater during the first follow-up period (i.e. two months post-TMS) compared to short-term (i.e. one day post-TMS) 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 Fig. 2.

4.3. Long-term effects (i.e. one year post-treatment) of cTBS (post TMS – follow-up 1 – follow-up 2) using WEST

A.M. did not improve after expressive language ($t(25) = 0.76$, $p = .75$), cognition and naming. However, she showed significant improvement, after the post TMS period, in comprehension ($t(63) = 2.80$, $p = .003$) and moderate improvement in reading ($t(28) = 2.11$, $p = .02$). Results for the long-term effects of cTBS are shown in Fig. 2.

Table 3
Language and Cognitive outcomes at post-treatment and follow-up compared to baseline for A.M.

Item	Baseline 1 scores	Baseline 1 scores	Post TMS scores	Follow up 1 scores	Follow up 2 scores
Problem solving skills	7/36	8/36	8/36	8/36	7/36
Auditory comprehension	12/64	13/64	13/64	26/64	24/64
Expressive language (Boston naming test – excluded)	0.5/33	0.5/33	2/33	1/33	1/33
Boston naming test – Accuracy	1/15	0/15	1/15	0/15	1/15
Reading skills	2/33	2/33	2/33	5/33	6/33

Table 4
Quality of life for A.M. at pre-treatment (baseline) and at 2 months and 12 months follow-up using the SAQOL-39g.

Item (max score: 5)	Baseline measure	2 months follow-up	12 months follow-up
SAQOL – 39g Mean score	2.05	2.18	2.12
Physical score	2.38	2.44	2.25
Communicate score	1.57	1.72	1.85
Psychosocial score	2.20	2.38	2.25

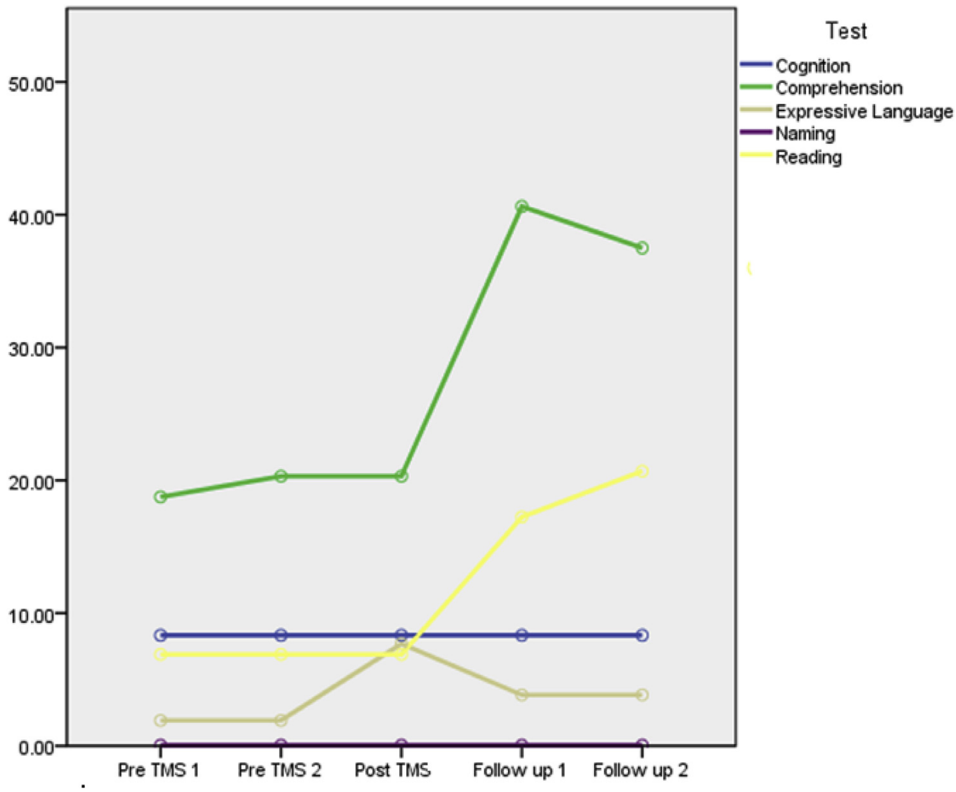

Fig. 2. Short-term (one day post-TMS) and long-term effects (two months and one year) of cTBS on cognitive and language performance for A.M. The Y axis depicts relative values to demonstrate the magnitude of variation, if any, between assessments for each domain.

5. General discussion

This study set to explore whether cTBS as a stand-alone treatment (i.e. without any behavioural language treatment) has the potential to improve language abilities in the chronic stage of aphasia in one severely affected individual. Overall, severely affected patients with global post-stroke aphasia are predominantly excluded from TMS studies. However, these people constitute a group with distinctive needs as their functional communication is severely affected. In numbers, almost 20% of stroke survivors never regain the level of language functioning they had prior to stroke (Gottesman & Hillis, 2010).

The participant in the present study was had severe chronic global aphasia post-stroke resulting from diffuse lesions in the frontal, parietal and temporal (middle and superior gyri) lobes, insula and basal ganglia. She had undergone long-term (20 months) SLT in the past and discontinued it two years before enrolment in the present study. The present findings indicate that she manifested a trend towards improvement in expressive language in the short-term, significant improvement in comprehension and moderate improvement in reading skills in the long-term (i.e. two and 12 months post-TBS).

In the past, other groups of researchers (e.g. Barwood et al., 2013) have also 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). Our results corroborate such findings. Crucially, based on findings from Barwood et al. (2013) and on reports from other studies (e.g. Martin et al., 2009; Seniow et al., 2013; Waldowski, Seniów, Leśniak, Iwański, & Członkowska, 2012), language improvements induced by inhibitory rTMS may occur over a period of many months. This is also true for our case study, as A.M. manifested long-term language improvements. Notably, the significant language improvement observed in the participant of our study corroborates findings of the study of 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 severely affected patients with aphasia benefited from treatment. Such findings suggest that individuals with severe aphasia are good responders to TMS.

As for the use of TBS in aphasia rehabilitation post-stroke, there are a number of studies that provide evidence for its efficacy. Recently, intermittent TBS (iTBS) was applied in eight individuals with chronic aphasia post-stroke for five consecutive days over the course of two weeks over residual language areas in or near the left inferior frontal gyrus (IFG) identified through fMRI (Griffis et al., 2016). One week after treatment, the researchers observed during covert verb generation increases in left IFG activation, decreases in right IFG activation, reduced right to left IFG connectivity and improvements in verbal fluency. In a second study, cTBS was applied for 15 daily sessions over Broca's homologue of the right hemisphere and immediately after, iTBS was applied over Broca's area of the left hemisphere in an individual with chronic aphasia post-stroke (Vuksanovic et al., 2015). The findings revealed improvement in several language functions, most notably in propositional speech, semantic fluency, short-term verbal memory, and verbal learning. A randomised, sham-controlled, crossover trial, by Kindler et al. (2012) applied cTBS over the right Broca's homologue in 18 patients with aphasia in different stages (acute vs. chronic) post-stroke. The cTBS protocol applied included 801 pulses delivered in 267 bursts and each burst contained 3 pulses at 30Hz, repeated with an interburst interval of 100 ms. The total duration of a train was 44 s. Naming performance was significantly better, and naming latency was significantly shorter after real cTBS compared to the sham condition. The results of our case study lend support to the findings of the recent TBS aphasia treatment literature, that the faster TBS compared to traditional TMS protocols, have the potential to drive language gains in people with chronic aphasia post-stroke.

Notwithstanding the robust evidence supporting that focal TMS and other noninvasive brain stimulation techniques (NIBS) boost aphasia rehabilitation, the neural mechanisms by which such techniques exert their positive effects on language are still unravelled (Harvey et al., 2017). Some possible mechanisms, however, have been suggested so far especially for improvement in naming abilities post-rTMS in aphasia. It has been suggested that hyperactivity of neurons in the right pTr resulting from reduced interhemispheric disinhibition from the damaged dominant left hemisphere to homotopic regions in the nondominant hemisphere may excessively suppress the right pars opercularis (pOp) via their share U-fibers (short association fibers), possibly hindering recovery (Naeser et al., 2010). The observation that modulating the right pTr also leads to i) significant improvement in language domains other than naming such as comprehension in this study and others (e.g. Haghighi et al., 2018; Hu et al., 2018; Rubi-Fessen et al., 2015) and ii) trends towards improvement in comprehension and writing in other studies (e.g. Thiel et al., 2013); shows that even though TMS is applied to a very specific brain area (i.e. pTr), in reality it modulates activity in wider networks and thus promotes recovery of several language domains. Indeed, there is evidence that disinhibition of neurons in the right pTr with rTMS may lead to less inhibition of the right pOp via U-fibers leading to secondary modulation of areas of the right hemisphere connected to the pOp (e.g. right ventral premotor cortex, horizontal mid-portion of the arcuate fasciculus and superior longitudinal fasciculus) (Naeser et al., 2010). In addition, there are studies (e.g. Heiss et al., 2013; Thiel et al., 2013) that 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 noted in global aphasia scores.

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). 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. 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). However, there have been two randomised controlled trials (RCTs) (i.e. Barwood et al., 2013; Medina et al., 2012) that also 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), 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. 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).

Last but not least, as stroke affects health related QoL (Towfighi & Saver, 2011), in the present study the QoL of A.M. was assessed using proxy ratings as she struggled to respond to the SAQOL-39g questions because of comprehension deficits. Previous research on proxy assessments of QoL in stroke survivors indicates that proxy raters tend to report more QoL problems than patients themselves (Carod-Artal, Coral, Trizotto, & Moreira, 2009; Pinkney, Gayle, Mitchell-fearon, & Mullings, 2017; 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, Christaki, Chelas, Efstratiadou, & Hilari, 2012). In the current study, the findings indicated that the QoL did not significantly change as a result of the treatment.

A major strength of this study is that the patient underwent two baseline measurements to rule out training effects and, that she was followed up to one year post-TMS to assess the long-term effects of treatment. It was shown that improvement in comprehension and reading were sustained up to one year post-treatment revealing the potential TBS has to drive longitudinal changes in language performance without SLT. However, a major weakness is that there was no control (sham) condition. While the use of multiple baselines was applied to lessen concerns that the observed effects might be due to random variation in subject performance, the fact that the subject was likely fully aware of their treatment status, leaves this study very open to likely placebo effects. Another limitation of this study is 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.

6. Conclusion

Findings from this study indicate that cTBS over the right pTr has the potential, despite its short duration, to drive long-term changes in language performance in various language skills in individuals suffering from chronic global aphasia post-stroke. Crucially, 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.

Funding

This work was co-funded by the European Regional Development Fund and the Republic of Cyprus through the Research and Innovation Foundation (Project: EXCELLENCE/1216/0517).

CRediT authorship contribution statement

Anastasios M. Georgiou: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing - review & editing. **Ioannis Phinikettos:** Formal analysis, Methodology, Software. **Chrysa Giasafaki:** Formal analysis, Validation. **Maria Kambanaros:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of competing interest

No potential conflict of interest was reported by the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroling.2020.100907.

References

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

Brady, M. C., Kelly, H., Godwin, J., Enderby, P., & Campbell, P. (2012). Speech and language therapy for aphasia following stroke. *Cochrane Database of Systematic Reviews, 6*, CD000425.

Brady, M. C., Kelly, H., Godwin, J., Enderby, P., & Campbell, P. (2016). Speech and language therapy for aphasia following stroke. *Cochrane Database of Systematic Reviews, 6*, CD000425.

Breitenstein, C., Grewe, T., Flöel, A., Ziegler, W., Springer, L., Martus, P., et al. (2017). Intensive speech and language therapy in patients with chronic aphasia after stroke: A randomised, open-label, blind-endpoint, controlled trial in a health care setting. *The Lancet, 389*(10078), 1528–1538.

Carod-Artal, F. J., Coral, L. F., Trizotto, D. S., & Moreira, C. M. (2009). Self- and proxy-report agreement on the stroke impact scale. *Stroke, 40*, 3308–3315.

Cattell, R. B. (1940). A culture-free intelligence test, I. *Journal of Educational Psychology, 31*, 176–199.

Cattell, R. B., & Cattell, A. K. S. (1963). *Culture fair intelligence test.* Champaign, IL: Institute for Personality and Ability Testing.

Coslett, H. B. (2016). Noninvasive brain stimulation in aphasia therapy: Lessons from TMS and tDCS. In G. Hickok, & S. L. Small (Eds.). *Neurobiology of language* (pp. 1035–1054). London, UK: Elsevier Inc.

Dunn, L. M., & Dunn, L. M. (1981). *Peabody picture vocabulary test-revised.* Circle Pines, MN: American Guidance Service.

Efstratiadou, E. A., Chelas, E. N., Ignatiou, M., Christaki, V., Papathanasiou, I., & Hilari, K. (2012). Quality of life after stroke: Evaluation of the Greek SAQOL-39g. *Folia Phoniatrica et Logopaedica, 64*(4), 179–186.

Flowers, H. L., Skoretz, S. A., Silver, F. L., Rochon, E., Fang, J., Flamand-Roze, C., et al. (2016). Poststroke aphasia frequency, recovery, and outcomes: A systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation, 97*(12), 2188–2201.

Georgiou, A., Konstantinou, N., Phinikettos, I., & Kambanaros, M. (2019). Neuronavigated theta burst stimulation for chronic aphasia: Two exploratory case studies. *Clinical Linguistics and Phonetics, 33*(6), 532–546.

Georgiou, A. M., Lada, E., & Kambanaros, M. (2019). *Evaluating the quality of conduct of systematic reviews on the application of transcranial magnetic stimulation (TMS) for aphasia rehabilitation post-stroke.* Aphasiologyhttps://doi.org/10.1080/02687038.2019.1632786.

Gottesman, R. F., & Hillis, A. E. (2010). Predictors and assessment of cognitive dysfunction resulting from ischaemic stroke. *The Lancet Neurology, 9*(9), 895–905.

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.

Haghighi, M., Mazdeh, M., Ranjbar, N., & Seifrabie, M. A. (2018). Further evidence of the positive influence of repetitive transcranial magnetic stimulation on speech and language in patients with aphasia after stroke: Results from a double-blind intervention with sham condition. *Neuropsychobiology, 75*(4), 185–192.

Harvey, D. Y., Podell, J., Tukeltaub, P. E., Faseyitan, O., Coslett, B., & Hamilton, R. H. (2017). Functional reorganization of right prefrontal cortex underlies sustained naming improvements in chronic aphasia via repetitive transcranial magnetic stimulation. *Cognitive and Behavioral Neurology, 30*, 133–144.

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

Heiss, W. D., & Thiel, A. (2016). Basic principles of rTMS in aphasia treatment after stroke. In T. Platz (Ed.). *Therapeutic rTMS in neurology. Principles, evidence, and practice recommendations* (pp. 73–85). New York: Springer.

Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., et al. (2014). Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *British Medical Journal, 348*(March), 1–12.
Howard, D., Best, W., & Nickels, L. (2015). Optimising the design of intervention studies: Critiques and ways forward. *Aphasiology, 29*(5), 526–562.
Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*, 201–206.
Huang, Y.-Z., & Rothwell, J. C. (2007). Theta burst stimulation. In M. A. Marcolin, & F. Padberg (Eds.). *Transcranial magnetic stimulation for treatment of psychiatric disorders. Advances in biological psychiatry* (pp. 187–203). Basel, Switzerland: Karger.
Hu, X., Zhang, T., Rajah, G. B., Stone, C., Liu, L., He, J., et al. (2018). Effects of different frequencies of repetitive transcranial magnetic stimulation in stroke patients with non-fluent aphasia: A randomised, sham-controlled study. *Neurological Research, 40*(6), 459–465.
Ignatiou, M., Christaki, V., Chelas, E. V., Efstratiadou, E. A., & Hilari, K. (2012). Agreement between people with aphasia and their proxies on health-related quality of life after stroke, using the Greek SAQOL-39g. *Psychology, 3*(3), 686–690.
Jensen, A. R. (1980). *Bias in mental testing.* New York: Free Press.
Kartsona, A., & Hilari, K. (2007). Quality of life in aphasia: Greek adaptation of the stroke and aphasia quality of life scale-39 item (SAQOL-39). *Europa Medicophysica, 43*(1), 27–35.
Kazlauskaite, V., & Lynn, R. (2002). Two-year test-retest reliability of the coloured progressive Matrices. *Perceptual & Motor Skills, 95*, 354.
Kindler, J., Schumacher, R., Cazzoli, D., Gutbrod, K., Koenig, M., Nyffeler, T., ... Muri, M. R. (2012). Theta burst stimulation over the right Broca's homologue induces improvement of naming in aphasia patients. *Stroke, 43*(8), 2175–2179.
Laska, A. C., Hellblom, A., Murray, V., Kahan, T., & Von Arbin, M. (2001). Aphasia in acute stroke and relation to outcome. *Journal of Internal Medicine, 249*(5), 413–422.
Lefaucheur, J. P., Andre-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., ... Garcia-Larrea, L. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology, 125*(11), 2150–2156.
Lenz, M., Müller-Dahlhaus, F., & Vlachos, A. (2016). Cellular and molecular mechanisms of rTMS-induced neural plasticity. In T. Platz (Ed.). *Therapeutic rTMS in neurology* (pp. 11–22). Springer Charm.
Martin, P. I., Naeser, M. A., Ho, M., Treglia, E., Kaplan, E., Baker, E. H., et al. (2009). Research with transcranial magnetic stimulation in the treatment of aphasia. *Current Neurology and Neuroscience Reports, 9*(6), 451–458.
Medina, J., Norise, C., Faseyitan, O., Coslett, H. B., Turkeltaub, P. E., & Hamilton, R. H. (2012). Finding the right words: Transcranial magnetic stimulation improves discourse productivity in non-fluent aphasia after stroke. *Aphasiology, 26*(9), 1153–1168.
Messinis, L., Panagea, E., Papathanasopoulos, P., & Kastellakis, A. (2013). Boston diagnostic aphasia examination-short form in Greek language. *Patras: Gotsis,* 1–18.
Naeser, M. A., Martin, P. I., Treglia, E., Ho, M., Kaplan, E., Bashir, S., et al. (2010). Research with rTMS in the treatment of aphasia. *Restorative Neurology and Neuroscience, 28*(4), 511–529.
Pinkney, J. A., Gayle, F., Mitchell-fearon, K., & Mullings, J. (2017). Health-related quality of life in stroke survivors at the university hospital of the west indies. *Journal of Neurology Research, 7*(3), 46–58.
Raven, J., & Raven, J. (2003). Raven progressive Matrices. In R. Steve, & R. S. McCallum (Eds.). *Handbook of nonverbal assessment* (pp. 223–237). New York: Kluwer.
Raven, J., Raven, J. C., & Court, J. H. (1998). *Manual for raven's progressive Matrices and vocabulary scales. Section 2: The coloured progressive Matrices.* San Antonio, TX: Harcourt Assessment.
Ridding, M. C., & Ziemann, U. (2010). Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. *Journal of Physiology, 588*(13), 2291–2304.
Rohde, T. E., & Thompson, L. A. (2007). Predicting academic achievement with cognitive ability. *Intelligence, 35*, 83–92.
Rubi-Fessen, I., Hartmann, A., Huber, W., Fimm, B., Rommel, T., Thiel, A., et al. (2015). Add-on effects of repetitive transcranial magnetic stimulation on subacute aphasia therapy: Enhanced improvement of functional communication and basic linguistic skills. A randomized controlled study. *Archives of Physical Medicine and Rehabilitation, 96*(11), 1935–1944.
Rushton, J. P., Skuy, M., & Fridjhon, P. (2003). Performance on Raven's advanced progressive Matrices by african, east Indian, and white engineering students in South Africa. *Intelligence, 31*, 123–137.
Saxena, S., & Hillis, A. E. (2017). An update on medications and noninvasive brain stimulation to augment language rehabilitation in post-stroke aphasia. *Expert Review of Neurotherapeutics, 17*(11), 1091–1107.
Seniow, J., Waldowski, K., Lesniak, M., Iwanski, S., Czepiel, W., & Czlonkowska, A. (2013). Transcranial magnetic stimulation combined with speech and language training in early aphasia rehabilitation: A randomized double-blind controlled pilot study. *Topics in Stroke Rehabilitation, 20*(3), 250–261.
Simos, P. G., Sideridis, D. G., Protopapas, A., & Mouzaki, A. (2011). Psychometric evaluation of a receptive vocabulary test for Greek elementary students. *Assessment for Effective Intervention, 37*(1), 34–49.
Thiel, A., Hartmann, A., Rubi-Fessen, I., Anglade, C., Kracht, L., Weiduschat, N., et al. (2013). Effects of noninvasive brain stimulation on language networks and recovery in early poststroke aphasia. *Stroke, 44*(8), 2240–2246.
Towfighi, A., & Saver, J. L. (2011). Stroke declines from third to fourth leading cause of death in the United States historical perspective and challenges ahead. *Stroke, 42*, 2351–2355.
Vuksanovic, J., Jelic, M. B., Milanovic, S. D., Kacar, K., Konstantinovic, L., & Filipovic, S. R. (2015). Improvement of language functions in a chronic non-fluent post-stroke aphasic patient following bilateral sequential theta burst magnetic stimulation. *Neurocase, 21*(2), 244–250.
Waldowski, K., Seniów, J., Leśniak, M., Iwański, S., & Członkowska, A. (2012). Effect of low-frequency repetitive transcranial magnetic stimulation on naming abilities in early-stroke aphasic patients: A prospective, randomized, double-blind sham-controlled study. *The Scientific World Journal, 2012*, 1–8.
Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation, June 5-7, 1996. *Electroencephalography and Clinical Neurophysiology, 108*(1), 1–16.
Williams, L. S., Bakas, T., Brizendine, E., Plue, L., Tu, W., Hendrie, H., et al. (2006). How valid are family proxy assessments of stroke patients' health-related quality of Life ? *Stroke, 37*, 2081–2085.