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Neuronavigated theta burst stimulation for chronic aphasia: two exploratory case studies

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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-month 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 quality of life 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, non-invasive brain stimulation protocol on improvement of language abilities post-stroke need further exploration.

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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 (Dickey et al., 2010; Heiss & Thiel, 2016). 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 and 30 years (Cyprus WHO, 2017). 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, 2010), 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, Kelly, Godwin, Enderby, & Campbell, 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 press*). 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-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 and 4 Hz of rTMS to inhibit increased activation of the homologous BA45 and others have targeted right superior temporal areas (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; Thiel et al., 2006; Weiduschat et al., 2011). 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. Naeser et al., 2012; Rubi-Fessen et al., 2015; Seniow et al., 2013). 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; Kindler et al., 2012; Vuksanovic et al., 2015). 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, Edwards, Rounis, Bhatia, and Rothwell (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 in 18 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 30 Hz, 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 stand-alone 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.

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, Panagea, Papathanasopoulos, & Kastellakis, 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.

Table 1. Demographic and clinical characteristics of the participants.

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 – two times per week – 45 min of SLT	15 days before enrolment
2	F	39	12	25	LMCA	Global	Severe	10 months – two times per week – 45 min of SLT	15 days before enrolment

Note: LMCA = Left Middle Cerebral Artery; PWA = people with aphasia; SLT = speech-language therapy

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, automatized 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 protocol (QPA)

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 Protocol (QPA) (Saffran, Berndt, & Schwartz, 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 Varkanitsa, 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-39)

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, Christaki, Chelas, Efstratiadou, & Hilari, 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 50 μ V 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 70 mm 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.

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.

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.

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

Item	Participant 1				Participant 2			
	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 (<i>SD</i> = 1.02)	14/32	17/32	17.5/32	31.91/32 (<i>SD</i> = .28)
Expressive language (Boston naming test – excluded)	19/35	25/435	21/35	32.45/33 (<i>SD</i> = 1.00)	11/48	7/48	9/48	33/33 (<i>SD</i> = .000)
Boston naming test – Accuracy	10/15	10/15	10/15	14.76/15 (<i>SD</i> = .622)	2/15	1/15	1/15	15/15 (<i>SD</i> = .000)

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

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

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

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

Item (max score: 5)	Participant 1		Participant 2	
	Baseline measure	3 months post TMS (follow up)	Baseline measure	3 months post TMS (follow up)
SAQOL – 39 g 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

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](#).

Discussion

In this explorative study, two participants were recruited to pilot whether cTBS as a stand-alone 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 for 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 (Naeser et al., 2005; Rubi-Fessen et al., 2015; Weiduschat et al., 2011) and trends toward improvements in specific groups of patients with aphasia (Seniow et al., 2013, Waldowski, Seniów, Bilik, & Członkowska, 2009) 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 (≤ 1 Hz) related induced inhibition and high frequencies (≥ 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, Candia, Folkers, Schedlowski, & Schönbacher, 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, Hamilton, Norise, Turkeltaub, and Coslett (2011) 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 Varkanitsa (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 in the present study 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 has 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 non-invasive brain stimulation methods need to be explored and established.

Statement of interest

The authors report no conflict of interest.

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