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ORIGINAL RESEARCH

Repetitive transcranial magnetic stimulation for the treatment of cognitive impairment in frontotemporal dementia: an open-label pilot study

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Background: Frontotemporal dementia (FTD) is one of the most frequent dementia types in patients under 65 years of age. Currently, no therapy can effectively improve the cognitive deficits associated with FTD. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method of inducing brain plasticity with therapeutic potential in neurodegenerative diseases. The purpose of this study was to evaluate the effect of rTMS on cognitive, behavioral, and emotional function in FTD.

Methods: Nine patients (seven women, four men, mean age 61.7±10.1 years) with the behavioral variant of FTD, one with nonfluent/agrammatic variant primary progressive aphasia, and one with progressive nonfluent aphasia (subtypes of FTD) underwent 10 daily sessions of 10 Hz rTMS over the bilateral dorsolateral prefrontal cortex. Cognitive and behavioral assessments were administered before and after therapy.

Results: After rTMS, the Montreal Cognitive Assessment and letter and digit cancellation test scores, as well as reading time and error number in the Stroop test improved. The caregivers' impression of the daily functioning of patients improved in the Frontal Behavioral Inventory scores. These changes were not paralleled by an improvement of mood.

Conclusion: The results indicate that rTMS may improve the cognitive performance of patients with FTD and warrant sham-controlled trials.

Keywords: frontotemporal dementia, repetitive transcranial magnetic stimulation, Montreal Cognitive Assessment

Introduction

Frontotemporal dementia (FTD) is one of the most common types of dementia among people under 65 years of age.[1] The neurodegenerative process primarily involves the frontal and temporal lobes, with various predominance. Currently, three clinical variants have been distinguished: behavioral variant frontotemporal dementia (bvFTD), nonfluent/agrammatic variant primary progressive aphasia (nfvPPA), and semantic variant-primary progressive aphasia (SV-PPA).[2] Death usually occurs 8 years after clinical onset. There is no disease-modifying treatment. Some alleviation of behavioral and other psychiatric symptoms may be achieved with selective serotonin reuptake inhibitors and with atypical antipsychotics.[3] However, there is no established therapy for cognitive deficits and none of the controlled trials conducted thus far has shown significant benefit.[4,5] Two open studies showed improvements in language function after transcranial direct current stimulation (tDCS) in nfvPPA patients.[6,7] Repetitive transcranial magnetic stimulation (rTMS) is a method used to modulate brain plasticity and is increasingly being used in the therapy of neurological and psychiatric

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disorders.[8] In this technique, trains of brief, time-varying magnetic field pulses are delivered from a coil placed over the selected cortical area, which induces an electrical field within neural tissue and repetitively excites neurons. Systematic stimulation over subsequent days is capable of changing the activity of the stimulated brain area and induces clinical effects that last for weeks or months.[9] In the area of disorders associated with dementia, such as Alzheimer's disease (AD) or dementia with Lewy bodies, rTMS has shown promising results in alleviating neuropsychiatric symptoms and improving cognitive deficits.[9] The aim of the present study was to assess whether rTMS could also have therapeutic potential in the population of patients suffering from FTD.

Materials and methods

Study design and subjects

This was an open-label study involving 2 weeks of rTMS. The study was performed according to the Declaration of Helsinki of 1975 for Human Research and the protocol was approved by the Bioethics Committee of the Jagiellonian University (permission number 122.6120.178.2015). All subjects gave their written informed consent prior to inclusion.

The study included patients with all variants of FTD. They met the criteria for probable bvFTD[10] or for the clinical diagnosis of nfvPPA or SV-PPA.[11] The criteria for probable bvFTD included the presence of three out of six neuropsychological features: disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality, and dysexecutive neuropsychological profile, as well as radiological abnormalities in the frontal and/or anterior temporal lobes, which, depending on technique, should indicate atrophy, hypoperfusion, or hypometabolism. The clinical diagnosis of nfvPPA required the presence of agrammatism or speech apraxia and two out of three other features: impaired comprehension of complex sentences, spared single-word comprehension, and spared object knowledge. The criteria for the clinical diagnosis of SV-PPA included impaired confrontation, naming and single-word comprehension, and the presence of three of the following features: impaired object knowledge, surface dyslexia or dysgraphia, spared repetition, and spared speech production. To be included, patients with nfvPPA and SV-PPA were required additionally to show generalized cognitive decline reflected by an abnormal score on the Montreal Cognitive Assessment (MoCA). A further inclusion criterion was an age between 40 and 80 years. Also required was the presence of a caregiver who was responsible for the patient's adherence to therapy and capable of assessing potential changes in the patient's daily function. Neuroimaging was carried out no earlier than 2 years prior to inclusion. Exclusion criteria included neuropsychiatric symptoms or cognitive deficits suggestive of pathology other than frontotemporal lobar degeneration, treatment with memantine or other procognitive agents, and the presence of contraindications to rTMS as listed by the Safety of TMS Consensus Group of the International Federation of Clinical Neurophysiology (IFCN).[12]

We recruited 11 patients (seven women and four men) with a mean age of 61.7±10.1 years. Nine of them were diagnosed with bvFTD, one with nfvPPA, and one with SV-PPA. Three patients were mildly depressive (baseline Hamilton Depression Rating Scale [HDRS] 8–16) and one was severely depressive (HDRS≥24). The demographic and clinical data of the investigated group are summarized in Table 1.

Table 1 Demographic and clinical data of the recruited patients

Gender	Age (years)	Education (years)	Diagnosis	Disease duration (years)	MoCA at baseline	HDRS at baseline
M	58	17	bvFTD	2	23	4
F	53	17	bvFTD	5	21	24
F	64	17	bvFTD	5	20	13
F	72	21	bvFTD	2	18	0
M	68	17	bvFTD	1	23	5
M	43	13	bvFTD	3	25	14
F	64	12	bvFTD	2	12	13
M	65	17	bvFTD	6	26	0
F	70	13	nfvPPA	2	9	4
F	48	14	SV-PPA	1	17	0
F	74	10	bvFTD	7	18	0
Mean (n=7 F)	61.7	15.3		3.3	19.3	7
SD (n=4 M)	10.1	3.1		2.1	5.3	7.9

Abbreviations: M, male; F, female; MoCA, Montreal Cognitive Assessment; HDRS, Hamilton Depression Rating Scale; bvFTD, behavioral variant of frontotemporal dementia; nfvPPA, nonfluent/agrammatic variant primary progressive aphasia; SD, standard deviation; SV-PPA, semantic variant-primary progressive aphasia.

Intervention

rTMS at a frequency of 10 Hz was delivered over the bilateral dorsolateral prefrontal cortex (DLPFC), defined as a point 7 cm anterior to the hotspot area for the left and right abductor digiti minimi (ADM). The hotspot was determined as an area on the scalp where the magnetic stimuli could produce the greatest motor evoked potentials (MEPs) from ADM. Stimulation intensity was 90% of the resting motor threshold (RMT) or, if the patient could not fully relax the hand musculature, 90% of the active motor threshold (AMT). RMT and AMT were determined according to the relative frequency method, described by the IFCN.[13] According to this, RMT is the lowest intensity of magnetic field capable of evoking MEPs of amplitude ≥50 μV after at least five of 10 stimuli in the hotspot and from the relaxed muscle. For AMT, the amplitude required is ≥200 μV and the muscle is slightly contracted. The whole intervention included 10 sessions, delivered in one session per day, on 10 consecutive working days. In every session, 1,500 pulses were delivered to each DLPFC (in total 3,000 pulses per session) divided into 20 trains, each containing 75 pulses, separated by 25 s intervals. Stimulation was done with a double 70-mm air-cooled figure-of-eight coil with a peak magnetic field of 0.93 T and with the Magstim Rapid^2 stimulator (Magstim Company, Whitland, UK). Medication for neuropsychiatric symptoms remained unchanged several weeks before and during the intervention.

Outcome measures

Before and after rTMS, patients underwent assessment with the Clinical Global Impression-Improvement,[14] the 21-item HDRS,[15] and the Geriatric Depression Scale (GDS).[16] Frontal deficits were investigated with the Frontal Assessment Battery (FAB),[17] a test which consists of six subsets related to the mental processes of conceptualization and abstract reasoning, mental flexibility, motor programming and executive control of action, resistance to interference, self-regulation, inhibitory control, and environmental autonomy. The performance in each subset was rated between 0 and 3. The final result is the summation of the subscores of the subsets, with lower scores indicating more severe frontal deficits.

Overall cognitive performance was assessed with the Polish version of the MoCA.[18] The MoCA is a test originally developed to detect mild cognitive impairment, which was later adopted to evaluate cognitive impairment in early AD,[19] Parkinson's disease,[20] and other diseases. The test features 30 points, which collectively assess performance in seven cognitive domains: visuospatial/executive, naming, attention, language, abstraction, delayed recall, and orientation. A lower summarized score indicates worse cognitive performance and the cut-off indicating cognitive impairment is <26.[18]

Further assessment included the Stroop Color – Word Test, which consists of three stages. First, patients read the names of colors written in black ink as quickly as possible; second, they name the colors of printed rectangles. Finally, patients are required to read a list of the names of colors from the first stage, but written in incongruent ink colors. The time taken to perform these tasks is scored along with the number of errors.[21]

Patients also underwent the Letter Cancellation Test (LCT) and the Digit Cancellation Test (D-CAT), two tools used to assess sustained attention. The LCT consists of a page with 170 letters of the Latin alphabet printed randomly, with even spaces between letters. The subjects are instructed to cross out the letters E and R as quickly as they can. The final result takes into consideration the number of correctly crossed-out letters, the number of incorrectly crossed-out letters, and the time taken to complete the test.[22] In D-CAT, subjects should cancel the digits 2 and 8 among one to nine randomly printed digits. The evaluation is similar to the LCT.[23]

Finally, the subjects performed the Verbal Fluency Test.[24] In the first part of this test, they were given 60 s to say as many words beginning with the letter S or F as they could. In the second part, the same amount of time was given to say the names of as many animals or fruits as possible.

The caregiver's impression of patient function was rated with the Polish version of the Frontal Behavioral Inventory (FBI).[25] The FBI evaluates frontal behavioral deficits via an interview with the caregiver and consists of 24 items grouped in two subscales. The first of these subscales measures negative symptoms and the second disinhibition symptoms. Items are rated from 0 to 3, where 3 implies a more severe behavioral disorder. Baseline and posttreatment measurements were performed on the days of the first and last sessions, respectively.

Statistics

Measurements taken before and after rTMS were compared using the two-tailed Wilcoxon signed-rank test. Considering our interest in the outcome of all cognitive domains that may be affected in FTD, and our intention to avoid excessive type II errors in this small and explorative study, we decided not to employ a correction for multiple comparisons. Calculations were made with the Statistica data analysis software system, version 12.0 (StatSoft, 2008; Palo Alto, CA, USA). The significance level was set to $p<0.05$.

Results

A few patients complained of pain during rTMS at the site of stimulation, which resolved by the second or third session. One patient (female, 64 years of age) suffered from mild, diffused headache, persisting for 2–3 months after rTMS, which she attributed to the stimulation. There were no other side effects. Mean motor threshold (AMT in one patient and RMT in the rest), averaged for both hemispheres, was 73%±17%. FBI was not performed in one patient (female, 64 years of age).

After rTMS, there was improvement in the total score of MoCA as well as in the domains of visuospatial abilities and abstraction. In the D-CAT and LCT, there were fewer omissions; the time was shortened in the latter. In both tests, the number of commission errors could not be statistically compared owing to the low number of degrees of freedom. This was also the case for the number of errors in the Stroop reading test; however, in this test, performance time was shortened. In Stroop Color naming, the number of errors was reduced and the FBI score was reduced. Other tests and questionnaires showed no changes. The detailed data of measurements acquired before and after rTMS are presented in Table 2. Two patients with mild depression improved to normal status in terms of HDRS score. A third patient with mild depression remained with the same diagnosis (a change in HDRS from 13 to 12 points). One patient with severe depression showed a reduction in HDRS, allowing us to classify him as mildly depressive (a change from 24 to 12 points). Two patients (both women, aged 72 and 48 years) showed an increase in HDRS score after rTMS, one from 0 to 2 and the other from 0 to 4. GDS was abnormal in three cases showing mild depression (10–19 points). Five patients improved, two remained unchanged, and four deteriorated after rTMS.

Owing to the high prevalence of patients with bvFTD, calculations were repeated after the exclusion of two patients with nfvPPA and SV-PPA. This post hoc analysis showed an increase in MoCA total score (20.7±4.3 vs 22.4±5.2, T=3, p=0.036) and in the domain of visuospatial abilities (3.0±1.3 vs 3.8±1.1, T=0, p=0.043). There were fewer omissions in LCT (6.0±7.3 vs 2.4±2.9, T=3, p=0.021). In the Stroop test, the time for color naming and for interference shortened (36.7±16.1 vs 33.4±12.8 s, T=4, p=0.049951 and 91.9±59.2 vs 86.7±57.1 s, T=1, p=0.017, respectively). Scores on the FBI also decreased (32.8±14.5 vs 25.1±13.5 s, T=0, p=0.012). Other measurements showed no changes.

Table 2 Results of particular tests before and after rTMS

Test	Before rTMS		After rTMS		T	p-value
	Mean	SD	Mean	SD		
CGI-I	4.0	1.7	2.8	0.6	3	0.934
Domains of MoCA	2.8	1.3	3.6	1.1	0	0.018*
visuospatial/executive						
Naming	2.4	1.0	2.4	0.9	5	1.000
Attention	4.0	2.4	4.0	1.8	18	1.000
Language	1.5	1.1	1.9	1.3	0	0.109
Abstraction	1.0	0.8	1.5	0.7	0	0.043*
Delayed recall	1.9	2.0	2.0	2.0	6	0.686
Orientation	5.5	1.2	5.5	1.2	1.5	1.000
MoCA total score	19.3	5.3	21.1	5.8	3	0.013*
D-CAT						
Time	88.6	20.7	85.1	19.4	22	0.328
Omissions	6.1	4.0	4.7	3.7	7.5	0.023*
LCT						
Time	79.4	13.1	73.8	13.3	9	0.033*
Omissions	7.8	7.7	3.9	4.3	3	0.008*
Stroop reading time	27.4	8.6	25.7	8.5	8	0.047*
Stroop color naming time	43.2	21.5	43.7	28.3	20.5	0.476
Errors	3.1	4.2	1.1	2.0	0	0.028*
Stroop interference time	97.1	58.2	113.8	79.1	11	0.093
Errors	7.5	11.7	5.0	6.2	5	0.069
FAB	12.1	4.5	13.2	4.1	10	0.074
VFT						
Formal fluency	7.5	5.3	9.3	6.1	4	0.091
Semantic fluency	11.5	7.1	12.0	6.1	24.5	0.450
GDS	4.8	4.2	4.8	4.1	22.5	1.000
HDRS	7.0	7.9	3.8	4.3	8	0.161
FBI	33.6	13.4	26.2	12.3	0	0.005*

Note: *Significant difference ($p<0.05$).

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; T, test value; CGI-I, Clinical Global Impression-Improvement; MoCA, Montreal Cognitive Assessment; D-CAT, Digit Cancellation Test; LCT, Letter Cancellation Test; FAB, Frontal Assessment Battery; VFT, Verbal Fluency Test; GDS, Geriatric Depression Scale; HDRS, Hamilton Depression Rating Scale; FBI, Frontal Behavioral Inventory.

Discussion

To the best of our knowledge, this is the first report to investigate the efficacy of rTMS in improving the cognitive and neuropsychiatric symptoms of FTD. Two previous case reports described an improvement in the language function of patients with PPA; however, these did not disclose whether the syndrome was related to FTD.[26,27] Moreover, our study appears to be one of the first studies to report cognitive improvement in FTD. Apart from the previously mentioned studies with tDCS,[6,7] there was only one other study, in which oxytocin improved social, but no other aspects of cognition.[28] In this light, the improvements achieved in the significant part of tests used in our study may be seen as outstanding compared to previously published results. The MoCA improvement of nearly 2 points is similar to that seen in one randomized controlled trial for rTMS in AD,[29] which showed a significant difference compared to a placebo. On the other hand, there was less improvement than in another study of AD patients, in which the level of improvement was 4.21±2.46 points.[30] In the previous study,

however, the stimulation (1 Hz to the right DLPFC) included 20 sessions, which is twice as many as the number used in our present study. The observed improvement appears not to differ from other trials of rTMS in dementia in terms of cognitive function which responded to therapy. Most studies have reported improvement in scales measuring general cognitive status and in many other functions, of which some, such as attention and memory, also showed improvement in our group.[9] It remains unclear whether the effect of rTMS on cognition in dementia results from an influence on the underlying neurodegenerative process or from the nonspecific enhancement of frontal activity. Several studies have reported improvements in various cognitive functions after rTMS, or other noninvasive brain stimulation techniques, applied to frontal areas in healthy individuals, which would allow us to attribute the beneficial effects observed in patients to nonspecific neuroenhancement.[31] On the other hand, the results are different in other diseases where cognitive impairment is linked to symptoms: in schizophrenia no effect of rTMS on cognition was found,[32] and in depression, it was modest and limited to specific functions of psychomotor speed, visual scanning, and set-shifting ability.[33]

Considering the possibility that our results may have been influenced by a learning effect, we carried out a review of the appropriate literature. In healthy older volunteers, a learning effect was described for the Stroop test over an interval of 5.7 days between two subsequent tests,[34] which is significantly shorter than in our study. The MoCA performed after 60 min,[35] or after 1 month,[36] did not show a significant learning effect in healthy individuals. Similarly, placebo groups in other studies investigating the efficacy of rTMS in dementias did not show an improvement on either MoCA[29,30] or Stroop.[37] Thus, in our opinion, the learning effect is unlikely to explain the obtained results, although it needs to be definitely excluded using a sham comparator.

Another concern may have arisen from the lack of correction for multiple comparisons; as a consequence, some of the significant differences among our results may have occurred by chance. However, we would like to highlight that while the number of tests performed on the whole group (24) generally increases the risk of false rejection of the null hypothesis, the number of significant differences detected (nine) makes it improbable that all of these differences are accidental and do not reflect the association between intervention and improvement. We did not take into account the repetition of the analysis on the sample limited to bvFTD as the tests performed on nearly the same data were unlikely to increase the chance of additional, significant differences. In our opinion, using a correction in such an exploratory and small study would increase the risk of type II errors too much. This lack of correction may have influenced our results in respect of the number of cognitive domains that responded to therapy, but was very unlikely to have affected our main conclusion that rTMS may have potential in the therapy of cognitive impairment in patients with FTD.

Contrary to expectations, cognitive improvement was not followed by an antidepressive effect. This result may have been due to the relatively low rate of patients with abnormal HDRS. On the other hand, the study by Schaller et al,[38] describing improvements of mood in healthy individuals after rTMS, led us to expect a reduction in HDRS and GDS in our patients. We speculate that greater awareness of the disease, which may occur along with cognitive improvement, could account for the lack of an antidepressive effect. Another reason may lie in our rTMS protocol, which involved high-frequency stimulation of the right DLPFC, which, in turn, may account for the deterioration in the mood of several participants. One previous case report reported that high-frequency stimulation over the right DLPFC induced an increase in the Montgomery–Åsberg Depression Rating Scale from 7 to 21 points.[39] Such a stimulation protocol was also tried to alleviate bipolar mania, with some studies reporting a significant effect.[40,41] In terms of other results, the reduction in FBI score may positively influence the caregiver's quality of life, which is often severely affected, resulting in significant changes to social and family life.[42] To the best of our knowledge, only two previous studies have reported a reduction in FBI score after intervention.[28,43]

The explanation of our results relies on several, only partially verified hypotheses pertaining to how rTMS may influence cerebral function. At the cellular level, repetitive neural excitation changes synaptic and plasmalemmal excitability and upregulates growth factors.[44] In animal models, previous research has shown that rTMS affects the mRNA transcript of particular genes in neural cell cultures.[45] Cellular changes thus lead to the modification of excitability and metabolic activity of targeted cortical areas as well as inducing synaptic plasticity.[8] We chose the prefrontal areas as the target of stimulation because previous studies showed that these areas are behaviorally involved in a variety of cognitive operations, including working and episodic memory, inhibition, monitoring, strategic organization, and planning.[46] Moreover, previous data indicate that stimulation over the DLPFC can improve language function,[47] attention, memory, and other cognitive functions in healthy volunteers.[48] Finally, we investigated other rTMS studies on patients with dementias involving frontal areas and related cognitive deficits. In these previous studies, rTMS was most commonly delivered over

the bilateral DLPFC.[9] Similarly, our relatively weak stimulation intensity was based on previous experience and on the premise that cognitively and behaviorally impaired patients could not adhere to stronger pulses, which, in some cases, may induce mild to moderate pain.[12] Despite our concerns, the adherence to and attitude toward therapy were very good among our patients and caregivers, and only mild pain was reported. In our opinion, future studies on dementias could attempt suprathreshold stimulation, which is often used in other conditions, such as depression.[8]

In the present study, we investigated patients with all subtypes of FTD. The large proportion of patients with bvFTD allowed a post hoc analysis of this subgroup, which showed similar effects to those for all patients.

Limitations

We are aware of the preliminary character of this study, which lacks a placebo arm and follow-up. Moreover, determination of the stimulation point in relation to the motor hotspot, instead of using one of the available neuronavigation systems, could have caused minor deviation from the actual DLPFC. Finally, the inclusion of patients with concomitant depression could have confounded the results toward a reduction of cognitive enhancement, as previous data showed very limited effects on cognition among depressive patients.[33]

Conclusion

rTMS is safe and well tolerated in FTD patients. The outcomes of this study indicate that this technique may improve cognitive performance in this group of patients. The results of the FBI further suggest that rTMS may also improve daytime functioning, with potential benefit for caregivers. The data obtained in this study warrant randomized controlled trials on this subject.

Disclosure

In March 2016, Jakub Antczak received gratification of the equivalent of 183 USD (700 Polish Zloty - PLN) for a TMS teaching course sponsored by Elmiko Medical Sp. z o.o., the Polish distributor of PowerMAG Repetitive Magnetic Stimulator (Heitec AG, Erlangen, Germany). In June 2009, he also received the reimbursement of travel costs and a participation fee to attend the Magstim TMS Summer School for similar teaching for the Polish distributor of Magstim magnetic stimulators (Ma-Je-R Sp. z o.o.). The authors report no other conflicts of interests in this work.

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