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Case Report

The Positive Effect of Long-Term Repetitive Transcranial Magnetic Stimulation Therapy for Mild Cognitive Impairment: Three Case Studies

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Abstract:

***Background*:** Mild Cognitive Impairment [MCI] is a transition stage between normal aging and dementia. It seems to be useful to treat MCI before the onset of early dementia, though no pharmacological treatment is recommended [1]. These case studies aimed to assess the efficacy of long-term repetitive Transcranial Magnetic Stimulation [rTMS] treatment on cognition, and clinical changes, in elderly MCI patients.

***Methods*:** Three patients with MCI were treated by rTMS with different parameters of stimulation, targeting the Dorsolateral Prefrontal Cortex for three, six or twelve months. Cognition, depressive symptoms and overall clinical change were assessed before and after rTMS.

***Results*:** After treatment, all three MCI patients improved their cognition and overall clinical state. The three patients had no significant depressive symptoms at any time.

***Conclusions*:** Our results highlight the cognitive and clinical benefits of long-term rTMS treatment in MCI patients, without side effects. This cognitive improvement is regardless of

any antidepressive effects. These promising results must be confirmed in randomised double-blind studies in order to optimise rTMS parameters.

Keywords
Repetitive transcranial magnetic stimulation; mild cognitive impairment; cognition; cognitive decline; neuropsychology; non-invasive brain stimulation

1. Introduction

Mild Cognitive Impairment (MCI) represents a transitional state between normal aging and dementia. MCI patients have subjective and objective cognitive impairments that are significantly abnormal for their age and education level, but not enough for a diagnosis of dementia [2]. MCI affects 3% to 19% of adults older than 65 [3]. Compared to older adults without cognitive impairments, patients with MCI may have difficulties to perform complex, cognitively demanding daily activities, such as doing two things at the same time or coping with unfamiliar situations [4]. These impairments have an impact on their autonomy, though no pharmacological treatment is recommended for MCI [1, 5].

Furthermore, MCI patients have an increased risk of developing dementia: 46% develop dementia within 3 years, whereas only 3.3% of elderly patients without cognitive impairment develop dementia [6]. There is evidence to suggest that interventions are more effective when applied early in the development of dementia [7]. Thus, MCI could be a key period for providing interventions such as Transcranial Magnetic Stimulation.

Transcranial Magnetic Stimulation (TMS) is a non-invasive and painless technique, which delivers electromagnetic pulses that reach the cerebral cortex through the scalp. Repetitive TMS (rTMS) induces long-lasting neurophysiological changes, and may generate changes in brain activity in local as well as distant connected areas [8, 9]. Thus, rTMS induces cerebral plasticity [10, 11]. Authors have also demonstrated that cerebral plasticity is linked with less marked cognitive decline [12, 13]. Repetitive TMS treatment is a useful tool to modulate brain plasticity. Consequently, rTMS could enhance cognition in individuals with MCI, and delay the apparition of severe cognitive impairments that mark the onset of dementia.

Recently, studies have reported the effects of different rTMS parameters on cognition. Cotelli et al. (2012) stimulated the left Inferior Parietal Lobule of an elderly MCI patient at 20Hz for 10 sessions over two weeks. After treatment, the patient had enhanced memory capacity. This improvement was still significant 20 weeks after the end of the treatment [14]. A sample of two elderly MCI patients, and eight patients with mild dementia, showed a significant improvement in attention and psychomotor speed after one rTMS session at 10 Hz applied over the right inferior frontal gyrus [15]. A significant improvement in a non-verbal recognition memory task was also observed in eight elderly MCI patients following one rTMS session at 1Hz over the right Dorsolateral Prefrontal Cortex [DLPFC] compared with sham rTMS [16].

Double-blind randomized controlled studies also showed that active rTMS compared to a placebo significantly improved the cognitive performance of MCI patients. Sole-Padulles et al. (2006) showed that elderly adults with memory impairment and memory complaints, who received one rTMS session at 5Hz over the left DLPFC, improved their memory capacity in an

associative memory task compared to a placebo group [17]. Drumond Marra et al., (2015) stimulated the left DLPFC at 10 Hz over ten consecutive days. This rTMS treatment improved MCI memory abilities compared to the placebo group and was sustained for at least 1 month. High frequency rTMS over the left DLPFC significantly enhances cognitive functioning in MCI patients [18]. These parameters are used in studies to treat patients with Alzheimer's disease [AD] and have also shown efficacy on AD patients' cognitive functioning [19]. Some researchers used low frequency rTMS over the right DLPFC, rather than high frequency, because of its short session duration and low intensity rTMS pattern. This produced the same efficacy [20, 21]. In MCI patients, one study used low rTMS frequency over the right DLPFC and demonstrated that these patients showed greater memory capacity after the rTMS treatment [16].

Despite different rTMS parameters, all of these studies showed cognitive enhancements in elderly patients with cognitive impairments, and these improvements may be maintained after the end of the treatment [14, 18]. Thus, rTMS seems to be a promising tool to prevent cognitive decline, and slow the onset of dementia. However, the duration of the treatment in these studies was limited to a maximum of two weeks.

Through three clinical cases, we aimed to evaluate the impact of rTMS on overall cognitive functioning and the overall clinical state, as well as its tolerance in MCI patients for periods ranging from three months to one year.

2. Case Descriptions

Three MCI patients, two females and a male (mean age: 69 years (±6.65 SD); 8 years of education (±3.05 SD)), fulfilled the criteria of MCI [2]. MCI patients were diagnosed by experienced neurologists who addressed patients to TMS treatment. They were offered compassionate active open rTMS treatment.

2.1 Clinical and Cognitive Assessments

The primary outcome was based on the Montreal Cognitive Assessment (MoCA) [22]. The MoCA assesses overall cognitive functioning, with a maximum score of 30 points. It has a higher sensitivity compared to the Mini-Mental State Examination (MMSE) for detecting and evaluating cognitive changes in MCI impairment [22].

The secondary outcome included the Clinical Global Impression (CGI) that assess the severity of the disease [23] to observe clinical changes, and the Hamilton Rating Scale for Depression (HDRS), [24] to assess depressive symptoms.

2.2 RTMS Parameters

The rTMS treatment (Magstim Super Rapid, Inomed) was delivered using a figure-eight-shaped coil. The target region was localized using a neuronavigation system (Brainsight) The DLPFC was determined as the middle part of middle frontal gyrus by the method used by [25]. For each patient, the resting motor threshold (MT) was defined as the minimum TMS intensity sufficient to produce a visible response in the abductor pollicis brevis muscle with at least five out of 10 TMS pulses [26]. Every patient received rTMS treatment over three months, and two patients received additional rTMS maintenance treatment after this period. This maintenance consisted of fewer

rTMS sessions compared to the first three months of treatment. All three patients had only one rTMS session per day, according to their availabilities. During the first month, the patients had rTMS sessions between 2 and 4 times a week. During the second and the third month, the patients had between one and two rTMS sessions a week, except for Ms C. who was unavailable in the second month. Starting from the fourth month, Mr. G had one rTMS session every 15 days. Ms. C. had rTMS sessions from M9 to M12: between 3 and 4 times a week during M9 and M10, then between 1 and 3 times a week during M11 and M12. The rTMS parameters, which were different for each patient, are described in **Table 1**.

Table 1 rTMS parameters for each MCI patient

Patient	Target	Frequencies	% motor threshold	Number of trains	Duration of trains (seconds)	Inter-train intervals (seconds)	Treatment duration (months)
Ms. A	Left DLPFC	10Hz	110	6	60	30	3
Mr. B	Right DLPFC	1 Hz	120	6	60	30	6
Ms. C	Left DLPFC	burst: 50hz	80	20	10	8	12

3. Case Study n1: Ms. A.

3.1 Method

At the time of treatment, Ms. A was a 62 year-old woman, with nine years of education. She had had an alcohol abuse for ten years and had been suffering from memory deficit, insomnia, weight loss, and listlessness. When she began rTMS therapy she was taking seroplex, and rivotril. She received 31 rTMS sessions over three months. This treatment was delivered over the left DLPFC at 10Hz and 110% of motor threshold. Clinical and cognitive assessments were conducted at baseline and after three months (M3).

3.2 Results

The cognitive test (MoCA) result improved after three months of rTMS treatment. HDRS and CGI scores decreased after rTMS treatment from baseline to M3 (**Table 2**).

4. Case Study n2: Mr. B.

4.1 Method

At the time of treatment, Mr. B. was a 73 year-old divorcee, with 11 years of education. He had had a feeling of unease since his retirement that had been amplified after a fire in his building. He was anxious and complained about his memory and he had been suffering from memory deficit for two years. He had already received EMDR therapy and Cognitive remediation therapy, with no

success. Therefore, we offered him rTMS therapy. He was not in medication when he began rTMS therapy. He received 35 rTMS sessions over six months. He received 27 sessions during the first three months, and eight sessions during the rTMS maintenance treatment. Repetitive TMS was delivered over the right DLPFC at 1Hz, and 110% of motor threshold.

Clinical and cognitive assessments were conducted at baseline, M3 and M6.

4.2 Results

The cognitive test (MoCA) result increased from baseline to M3, then stabilized from M3 to M6. HDRS and CGI scores decreased from baseline to M3, then have a slight increase between M3 to M6 (**Table 2**).

5. Case Study n3: Ms. C.

5.1 Method

At the time of rTMS treatment, Ms. C. was a 74 year-old woman, with five years of education. For two years before rTMS treatment, Ms. C had been suffering from attentional deficit, memory deficit and memory complaints, with symptoms of anxiety and depression. Her memory deficit increased during stressful situations. She was taking Cymbalta and was using an Exelon patch when she began rTMS treatment. She received 12 months of rTMS treatment. She received 22 sessions during the first three months, and 66 rTMS maintenance sessions from M3 to M12. Repetitive TMS was delivered over the left DLPFC with Theta Burst Stimulation with intermittent trains (iTBS) (burst: 50 Hz, 80% motor threshold). This is a shorter duration, lower intensity rTMS pattern, which is more comfortable for patients.

Clinical and cognitive assessments were conducted at baseline, M3, M6 and M12. Two MoCA results were obtained via the conversion table for MMSE to MoCA [27].

5.2 Results

The cognitive (MoCA) result showed an improvement from baseline to M6, and a decline between M6 and M12. HDRS scores showed a mood improvement until M6, which stabilized until M12. CGI scores showed an enhancement in the patient's overall clinical state from baseline to M3, then stabilization from M3 to M12 (**Table 2**)

5.3 General Results

For each patient, cognitive results improved after 3 months of rTMS treatment, and for two patients this improvement went on until 6 months. Furthermore, clinical results showed an absence of major depressive episodes at baseline, during and after treatment. Likewise, the CGI results decreased from baseline to M3, and then, for two patients, scores were stabilized, showing a general enhancement of the patients' clinical state. Good compliance and no side effects were observed after rTMS treatment: neither trembling nor headaches were reported.

Table 2 Clinical and cognitive scores for each patient

		Baseline	M3	M6	M12
Ms. A.	Moca	22	26	-	-
	HDRS	10	2	-	-
	CGI	4	2	-	-
Mr. B	Moca	28	30	30	-
	HDRS	5	1	3	-
	CGI	4	1	2	-
Ms. C.	Moca	15	19	22	18
	HDRS	9	7	5	5
	CGI	5	3	3	3

6. Discussion

The aim of this study was to evaluate the long-term application of rTMS to the DLPFC on cognitive functions and clinical state in patients with MCI, using different rTMS stimulation parameters. These case studies are the first to use rTMS treatment to improve the cognitive and clinical abilities in MCI patients over a long period of time. After three months, six months or one year of rTMS stimulation compared to baseline, all three patients improved their cognitive abilities. These preliminary results could emphasize that rTMS over the DLPFC could help in enhance or maintain clinical and cognitive states in MCI patients, therefore slow the progression of the potential neurodegenerative disease. Authors have already suggested that rTMS stimulation over the DLPFC improved cognitive performance in different diseases such as depression [28], in healthy participants [29, 30] and also among elderly participants with MCI [16, 18]. This can be explained by the involvement of the Prefrontal Cortex [PFC] in several cognitive functions such as working memory, executive functions, and control of cognition [31-33]. Furthermore, the PFC is a key area connected to several other brain areas [34, 35]. It is still unclear how rTMS is involved in cognitive enhancement [29]. Although interpretation of rTMS effects on the brain raises some difficulties, rTMS has already been shown to increase functional connectivity between different brain areas, correlated to cognitive enhancement [36, 37]. Thus, rTMS could modulate the neural connections between regions which can support cognitive functions.

MCI patients' clinical results showed an absence of major depressive episodes at baseline and after rTMS treatment. The three patients had no significant depressive symptoms at any time. Consequently, the cognitive improvement is regardless of any antidepressive effects. On the other hand, the onset of depressive symptoms in later life can be an early manifestation of dementia [38]. Depressive symptoms can be a sign of the clinical and cognitive evolution of MCI patients. Furthermore, the overall clinical state improved for all three patients.

Despite these interesting results, these case studies have a number of limitations. Firstly, we need more neuropsychological evaluations to observe precisely which aspects of cognitive performance are improved, and how long the effects last after the end of the rTMS treatment. Secondly, different stimulation parameters were used for each patient, thus it is unclear which are the most appropriate. Finally, to confirm the effectiveness of long-term rTMS treatment on MCI

patients, it will be essential to investigate this non-pharmacological intervention through randomized double-blind studies in a larger sample of MCI patients.

7. Conclusions

These three case studies showed the benefit of long-term rTMS treatment on MCI patients. Repetitive TMS applied over the DLPFC, with three different parameters, improved MCI cognitive and clinical results, which were maintained over a long period of time without any serious side effects. Another new area that seems to be promising in rTMS treatment for MCI and AD patients is the precuneus, which is a key area for memory deficiency [39, 40].

A recent randomized, double-blind, sham-controlled clinical trial was conducted to assess the effect of high rTMS frequency on the precuneus in AD patients. The study showed significant efficacy of rTMS on memory function [41]. Future studies could stimulate this specific brain area in MCI patients to counteract potential memory decline.

Furthermore, several studies showed that rTMS associated with cognitive training generates symptomatology improvement in both AD and MCI patients [42-44]. The modulation of neuron activity by rTMS associated with cognitive training seems to have a synergetic effect that produces a greater impact compared to cognitive training alone.

Currently, no treatments are known to stop the progression from MCI to dementia. Nevertheless, rTMS seems to be a preventing tool that can slow the progression of cognitive and clinical disorders in MCI patients. These promising clinical and cognitive results must be confirmed in different studies in order to optimize the parameters of rTMS in MCI patients.

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Author Contributions

N. Bouaziz and P. Schenin-King Andrianisaina made rTMS sessions; C. Isaac, S. Braha-Zeitoun did clinical and cognitive assessments; D. Januel and F. Durand analyzed data and written the article; D. Januel and C. Isaac made corrections the entire manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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