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Brain stimulation improves associative memory in an individual with amnestic mild cognitive impairment

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In patients with cognitive deficits, brain stimulation has been shown to restore cognition (Miniussi et al., 2008, *Brain Stimulation, 1*, 326). The aim of this study was to assess whether repetitive Transcranial Magnetic Stimulation (rTMS) could improve memory performance in an individual with amnestic Mild Cognitive Impairment (aMCI). Stimulation of the left parietal cortex increased accuracy in an association memory task, and this improvement was still significant 24 weeks after stimulation began. These findings indicate that rTMS to the left parietal cortex improved memory performance in aMCI.

Keywords: Neurorehabilitation; Parietal cortex; Face–name association; MCI; Brain stimulation.

Recently, in patients with neurological disease, several studies have reported enhanced performance on specific cognitive tasks following non-invasive brain stimulation (e.g., repetitive Transcranial Magnetic Stimulation, rTMS) to specific cortical areas (see Miniussi et al., 2008).

Episodic memory encoding and retrieval processes have been linked to different networks; lesion and functional imaging studies have indicated that episodic memory involves a widespread network of brain structures, including the prefrontal cortex (PFC) and the posterior parietal cortex (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). In elderly subjects, successful memory encoding and retrieval is associated with activation of the left inferior parietal lobules (IPL) and the anterior hippocampus (Kircher et al., 2008).

In healthy participants, rTMS studies have confirmed the role of the PFC during encoding and retrieval of verbal or non-verbal material (Rossi et al., 2001; Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003). However, regarding rTMS studies in posterior brain areas, the mechanism has not yet been elucidated. Previous studies have demonstrated the involvement of parietal areas, which is in contrast to rTMS studies. In particular, Rossi et al. (2006) found that the activity of the intraparietal sulci, unlike that of the dorsolateral prefrontal cortex (DLPFC), are not causally involved in the encoding and retrieval of visual scenes; however, by combining functional Magnetic Resonance Imaging (fMRI) and rTMS, Manenti, Tettamanti, Cotelli, Miniussi, and Cappa (2010) provided the first evidence for the causal role of

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not only prefrontal but also parietal cortices during word retrieval.

Furthermore, Sole-Padulles et al. (2006) demonstrated a beneficial role of high-frequency rTMS in associative memory among elderly subjects with memory deficits and low performance on neuropsychological memory tests. The study combined rTMS and fMRI and showed a selective behavioral improvement in a face–name association memory task following an off-line stimulation. Moreover, this improvement was associated with the recruitment of the right PFC and bilateral posterior cortices.

Mild Cognitive Impairment (MCI) is widely used to define the disorder in individuals who have subjective cognitive deficits, objective memory impairments, or other cognitive deficits, without impairments in daily activities (Petersen et al., 1999).

Despite the clinical impact, there is no published evidence that rTMS can induce improvements in patients with selective memory impairment. Previous imaging and rTMS studies have shown the involvement of the DLPFC and the parietal cortex during memory processes, suggesting that, in patients with memory deficits, stimulation of these areas could induce improvements in memory. The aim of this study was to assess whether rTMS applied to the left parietal cortex, could induce improvements in memory performance in an individual with amnestic Mild Cognitive Impairment (aMCI).

CASE REPORT

A 61-year-old man, with 18 years of education, was referred for memory complaints. He was diagnosed with aMCI (MMSE: 27), according to clinical criteria (Petersen et al., 1999).

His evaluation included formal neuropsychological testing (Table 1), a physician interview, and a neurological examination. The patient had his first clinic visit 18 months prior to enrolling in the present study. During this period, he was examined regularly every 6 months. A physician (O.Z.) completed a medical history and conducted general physical, neurological, and psychiatric examinations. The patient had no history of neurological or psychiatric disorders, alcohol abuse, psychosis, major depression (Hamilton Depression Rating Scale = 4), or sleep disturbances. There was no indication of dementia, according to the clinical interview with the patient and his caregiver (Clinical Dementia Rating, CDR = 0.5). The diagnosis of aMCI was confirmed at the follow-up visits, and the patient had been steadily treated with Rivastigmine Patch (9.5 mg/day) for the previous 12 months. The patient did not take any other medication.

He was selected for this study based on the following criteria (Sarazin et al., 2007): (i) a subjective memory complaint assessed by the Everyday Memory Questionnaire (Sunderland, 1984); (ii) an objective memory impairment assessed by specific neuropsychological memory tests; (iii) preservation of general cognitive functioning assessed by general neuropsychological tests; (iv) a normal Instrumental Activities of Daily Living (IADL) score (Lawton & Brody, 1969); and (v) the absence of the diagnostic criteria for dementia (American Psychiatric Association, 1987). A structural brain MRI excluded the presence of cerebrovascular disease and white matter lesions.

An experienced neuropsychologist (M.C.) administered and evaluated a comprehensive diagnostic set of memory tests. The cognitive assessment included tests to screen for dementia (Mini Mental State Examination) and neuropsychological tests to assess non-verbal reasoning (Raven Colored Progressive Matrices), language comprehension (Token Test), verbal fluency (phonemic and semantic), memory (Story recall; Auditory-Verbal Learning Test, immediate and delayed recall; Rey-Osterrieth Complex Figure, recall; Digit Span; Spatial Span; Serial Position Curve), apraxia and visuo-spatial abilities (De Renzi Imitation Test; Rey-Osterrieth Complex Figure, Copy), and attention and executive functions (Trail-Making Test A and B; Wisconsin Card Sorting Test). All of the tests were administered and scored according to the standard procedures (Lezak, Howieson, & Loring, 2004). The cognitive assessment was divided into two parts, a standard evaluation and an experimental evaluation, and both were administered at baseline (before the rTMS treatment), shortly after the rTMS treatment (2 weeks), and 24 weeks after the baseline. The results of the baseline cognitive assessment are reported in Table 1.

For the experimental evaluation, we used an unfamiliar face–name association task (FNAT) composed of an encoding and a retrieval phase. During the encoding phase, the patient was shown a grey-scale picture of a face on a monitor followed by a proper name. During the retrieval phase, the patient was shown a face with two proper names

TABLE 1
Patient's performance on general standard neuropsychological tests

	Adjusted score baseline	*Adjusted score after rTMS (2 weeks)*	*Adjusted score at follow up (24 weeks)*	*Cut-offs*
Screening for dementia				
MMSE	24.5/30	25.5/30	24.6/30	24
Non-verbal reasoning				
Raven Colored Progressive Matrices	33/36	34/36	33/36	>17.5
Memory				
Story recall	12	14/28	13/28	>7.5
Auditory-Verbal Learning Test, immediate recall	33.8/75	30.8/75	31.8/75	>28.52
Auditory-Verbal Learning Test, delayed recall	**3.6/15***	5.4/15	**3.6/15***	>4.68
Rey-Osterrieth Complex Figure, Recall	**9.3/36***	**8.3/36***	**6.8/36***	>9.46
Spatial Span	5.8	5.8	5.8	>3.50
Digit Span	7.5	5.5	5.5	>3.75
Serial position curve				
Primacy effect	**4***	8	8	>4.5
Recency effect	20	22	23	>7.5
First item	1.25	4.25	0.25	>0
Language				
Token Test	30.5/36	32.5/36	31.5/36	>26.25
Fluency, phonemic	56	48	44	>16.0
Fluency, semantic	52	63	59	>24.0
Praxia				
Rey-Osterrieth Complex Figure, Copy	33.5/36	36/36	33.5/36	>28.88
De Renzi Imitation test, dx	71/72	71/72	72/72	>62.0
De Renzi Imitation test, sx	67/72	68/72	71/72	>62.0
Executive funcion				
Trail-Making Test A	18	13	13	<93.0
Trail-Making Test B	69	53	52	<282.0
Trail-Making Test B–A	45	34	33	186
Wisconsin Card sorting test, Global score	23.8/128	14.8/128	20.8/128	<90.60
Wisconsin Card sorting test, Perseverative Responses	11.2	9.2	6	<42.70
Wisconsin Card sorting test, Non-perseverative Errors	4.6	5.6	5	<30.0
Wisconsin Card sorting test, Failure to mantain set	1	0	0	<4.0

Age- and education-adjusted scores are reported. *denotes scores below cut-off.

(i.e., the correct name and another previously presented name), and the patient had to associate the correct name to the face. During the encoding, the participant was required to respond if a male or female face was presented and to encode the face–name association. During the retrieval, the patient was required to associate one of the two presented proper names to the face, as was presented during the encoding.

The FNAT was used to assess the patient's associative memory. Each stimulus consisted of a grey-scale face associated with a proper name. Faces were downloaded from an electronic dataset on the web and processed by Adobe Photoshop 5.0 (http://www.adobe.com). The unfamiliar faces were photographs of people unknown to the patient. A set of 50 unfamiliar faces was identified (25 males, 25 females). These pictures were scaled to 210 × 263 pixels and presented on a computer screen (subtending a visual angle of 3.15° × 4°). With respect to names, a set of 50 (25 males, 25 females) unfamiliar proper names were generated and randomly

assigned to the unfamiliar faces. Both the encoding and the retrieval phases were comprised of two training trials followed by three separate blocks of 16 trials, with each presented in a random order. Gender of the stimuli were counterbalanced and randomized across blocks. Responses were collected via a response-box, and the stimuli remained on the screen until the response was made. Finally, to exclude any learning effects resulting from its repeated execution, the task was conducted twice at baseline (i.e., baseline 1 and baseline 2) before rTMS treatment.

In addition, the same task was administered to 22 normal control (NC) subjects comparable in age and education (age: 64 ± 4; education: 13 ± 4) to investigate both the experimental performance and the learning abilities of a healthy aging group. The evaluation in the NC group was performed with the same timing as that used for the patient (i.e., baseline 1, baseline 2, and 2 weeks), with the exception of the 24-week evaluation. The protocol was approved by the Ethics Committee of IRCCS Fatebenefratelli, Brescia, Italy.

rTMS PROCEDURE

Based on previous rTMS and neuroimaging studies of episodic memory, we defined the DLPFCs and IPL as potential target areas for rTMS treatment (Cabeza et al., 2008; Manenti et al., 2010; Rossi et al., 2006; Sandrini et al., 2003).

To determine the location of a target area for the off-line rTMS treatment, we initially conducted two on-line rTMS experimental sessions during which each of the named areas, DLPFC and IPL, was stimulated individually.

We localized the left and right DLPFC and IPLs using the SofTaxic Evolution navigator system (www.emsmedical.net).

Prior to rTMS application, the motor threshold was defined as the lowest stimulation intensity over the primary motor cortex that resulted in a contraction in the contralateral hand, of at least 50%, in 10 consecutive stimulations (42% of the maximum stimulator output in our patient).

Two on-line rTMS tests (i.e., during FNAT) were performed: one for the DLPFCs and one for the IPLs. On-line rTMS was applied while the patient was performing the retrieval phase of the FNAT. We proposed that the stimulation of one of these areas during the execution of the FNAT could modify performance (i.e., accuracy). Each on-line rTMS test included three blocks corresponding to three stimulation types (left, right and sham stimulation; 20 Hz for 500 ms, from the trial onset, at 100% of the motor threshold). We found that only stimulation of the left IPL improved accuracy in the FNAT ($p = .04$) compared to sham.

Subsequently, the patient received daily rTMS treatments, 5 days a week for 2 weeks (25 minutes per day), to the left IPL (Talairach coordinates –44, –51, 43). A rapid magnetic stimulator and a figure-eight, double 70 mm, cooled coil (www.magstim.com) were used for rTMS administration. Fifty trains of high-frequency (20 Hz) rTMS were delivered for 2 seconds with an interstimulus interval of 28 seconds (40 stimuli/train, 50 trains, 2000 pulses/session, five sessions/week, 2 weeks). The stimulation intensity was set to 100% of the motor threshold. These parameters are consistent with the safety recommendations for rTMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009), and the patient reported no adverse effects.

RESULTS

For the two baseline evaluations (baseline 1 and 2; Figure 1), the patient's performance did not change; therefore, no learning repetition effects were present for the FNAT ($\chi^2 < 1$, df = 1, $p > .05$). In contrast, for the NC group, the repetition of the task resulted in an improvement in performance, $F(2, 42) = 39$, $p < .001$. Post-hoc analyses (Bonferroni) revealed that the NC group's performance during the second (2 days after baseline 1) and the third (2 weeks after) repetitions were higher than the performance

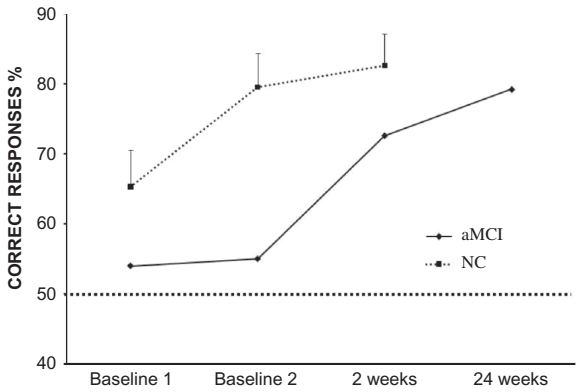

Figure 1. Percentage of correct responses (%) in a face–name association task (FNAT) over several sessions. aMCI, amnestic mild cognitive impairment patient; NC, normal control group. Error bars represent the standard errors of only one side. The dotted line indicates chance performance.

during the first presentation (baseline 1; $p < .001$); there was no difference between the second and third repetitions (baseline 2 vs. 2 weeks; $p > .05$).

Regarding the rTMS treatment, the patient's performance on the FNAT was compared, using the non-parametric χ^2 statistical test (Figure 1), to the four time points: baseline (pre-treatment; mean between the first two repetitions of the task, baseline 1 and 2), 2 weeks (post-treatment) and at the follow-up (24 weeks after baseline). The analysis showed a significant improvement in the patient's performance on the FNAT after 2 weeks of rTMS (73%) with respect to baseline (54%) ($\chi^2 = 6.99$, $df = 1$, $p < .001$, Yates correction). The improvement was still significant 24 weeks after treatment (79%) as compared to baseline ($\chi^2 = 13$, $df = 1$, $p < .001$). The performance at 24 weeks was not different from the score obtained at 2 weeks ($p > .05$), suggesting that the increased performance observed at 2 weeks was stable until follow-up.

Compared with the NC group, the patient did not show an improvement in performance resulting from the repetition of the task (no difference between the first two repetitions baseline 1 vs. 2), but the patient did demonstrate an increased performance after rTMS treatment. The direct comparison between the patient's performance and the performance of the healthy subjects revealed a significant difference at baseline, $t(21) = 5.1$, $p < .001$, at the second repetition, $t(21) = 11.6$, $p < .001$, and after 2 weeks, $t(21) = 5.0$, $p < .001$, while the patient's performance after 24 weeks was not different from the NC group after 2 weeks, $t(21) = 1.9$, $p > .05$.

In the baseline neuropsychological standard evaluation, the patient had scores below cut-off on some memory tasks: delayed recall of Auditory-Verbal Learning Test, recall of Rey-Osterrieth Complex Figure and Primacy effect of Serial Position Curve task. Two weeks after rTMS treatment onset, we observed an improvement on the delayed recall of Auditory-Verbal Learning Test and the Primacy effect of Serial Position Curve task. However, only the improvement in the Primacy effect of Serial Position Curve task persisted 24 weeks after treatment. Primacy is strongly correlated to the consolidation of long-term memory. The patient's improvement in this task suggests an increase in the ability to encode verbal items to memory, which parallels the improvement on FNAT.

DISCUSSION

The goal of this study was to assess whether application of high-frequency rTMS to the left IPL for 25 minutes a day, 5 days a week, for 2 weeks would lead to significant increases in memory performance in an individual with aMCI.

Previous neuroimaging evidence suggests that, in elderly subjects, successful memory encoding and retrieval is associated with activation of the left IPL and the anterior hippocampus (Kircher et al., 2008). The present study provides direct evidence for a putative role of the left IPL in associative memory and its enhancement by rTMS. Similarly, using imaging data, Sole-Padulles et al. (2006) have shown that elderly adults who received DLPFC rTMS temporarily improved their performance in an association memory task by activating the prefrontal and posterior areas.

In this vein, it has also been suggested that the recruitment of a larger neural network in older participants (Dennis & Cabeza, 2010), as well as in Alzheimer's patients, might reflect attempts to compensate for functional loss (Backman et al., 1999). Although the mechanisms involved in enhancing memory formation from rTMS are still speculative, rTMS might interact with the brain to maintain or strengthen the neural connections between regions. The present findings may reflect rTMS-induced neuromodulation, which promotes a long-term rearrangement of synaptic connections within a precise network. Comparing the patient with the NC group, which showed learning after the first repetition, allowed us to exclude the hypothesis that the patient's improvement was due to task repetition and therefore practice effects. The present results are consistent with previous studies, which have shown that neuromodulation of a specific behaviourally-activated network produces an increase in cortical efficacy when performing a cognitive task.

Several studies have suggested that rhythmic transcranial stimulation can enhance cognitive performance (Miniussi et al., 2008). A possible mechanism might be that the modulation of cortical activity through the use of rhythmic stimulation may re-adjust pathological patterns of brain activity, which provides an opportunity to induce new, improved activity patterns with an enhancement of the affected functional networks (Thut & Miniussi, 2009).

The preliminary results presented here highlight the therapeutic potential of the induction of long-term neuromodulation using brain stimulation in the treatment of aMCI. Our patient showed a stable aMCI diagnosis over 24 weeks, and until the patient was studied, he did not show any other cognitive or psychiatric disorder. We found that the improvement due to rTMS treatment was specific to the associative memory task. In addition, immediately after 2 weeks of rTMS treatment, we observed an improvement in performing neuropsychological tasks that assess long-term memory.

The major limitation in our study was the use of a single case and the lack of a placebo condition. However, several factors suggest that the cognitive improvement observed in our study cannot be solely accounted for by task practice effects. First, it seems unlikely that the magnitude of improvement found in this study is solely due to a task practice effect. We also show the absence of any rTMS effects on language, apraxia, visuo–spatial abilities, and executive functions, suggesting the specificity of the result, and the repetition learning effects cannot be explained by the present data. Furthermore, normal control subjects, who did not receive real rTMS treatment, did not show any significant improvement in FNAT task when tested after the third evaluation. We cannot exclude, however, that the absence of any additional improvement on the FNAT is due to the high performance obtained rapidly by the control group.

We acknowledge that these are preliminary findings, and present data cannot entirely rule out the practice effect, therefore future studies should use parallel versions of the same neuropsychological assessments to evaluate cognitive performance pre- and post-stimulation. However, if confirmed in larger samples, using a randomized, blinded design (e.g., real vs. placebo rTMS), these results could highlight the potential role of transcranial brain stimulation in modulating and facilitating memory performances in individuals with aMCI.

As to the long-term effects, we identified an improvement in the formation of associative memories 20 weeks after the end of rTMS treatment (24 weeks from the baseline). To date, this is the first study that has shown a long-lasting cognitive role of rTMS treatment in aMCI patients. A recent study described a long-lasting (12 weeks post-treatment) improvement on sentence comprehension tasks after rTMS in Alzheimer's disease patients (Cotelli et al., 2011), but no studies have investigated rTMS effects in aMCI. These findings may reflect a rTMS-induced modulation of short- and/or long-range cortical synaptic efficacy and connectivity that potentiates the functional network, which leads to more effective processing. This neuromodulation could explain the long-lasting effects even if the mechanism behind these changes remains poorly understood.

The possibility of using brain stimulation as a tool to promote neuroplasticity is promising, not only for advancing our understanding of brain plasticity mechanisms but also for designing new neurorehabilitation strategies.

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