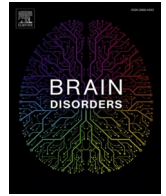


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rTMS for enhancing cognitive reserve: A case report

Chiara Di Fazio^{a,b}, Eugenio Scaliti^{c,d}, Mario Stanziano^{e,f}, Anna Nigri^e, Greta Demichelis^e,
Marco Tamietto^{a,g,h}, Sara Palermo^{a,e,h,*} 

^a Department of Psychology, University of Turin, Turin, Italy

^b International School of Advanced Studies, University of Camerino, Camerino, Italy

^c Human Science and Technologies, University of Turin, Italy

^d Department of Management "Valter Cantino", University of Turin, Italy

^e Neuroradiology Unit, Diagnostic and Technology Department, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Neurologico Carlo Besta, Milan, Italy

^f ALS Centre, "Rita Levi Montalcini" Department of Neuroscience, University of Turin, Turin, Italy

^g Department of Medical and Clinical Psychology, Tilburg University, Warandelaan 2, Tilburg, AB5037, Netherlands

^h Neuroscience Institute of Turin (NIT), Turin, Italy

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ABSTRACT

Understanding the mechanisms underlying brain ageing and age-related pathologies is crucial for addressing cognitive decline. Non-invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) have gained prominence due to their ability to modulate neurophysiological, affective and cognitive brain functions. In this case study, we present a 61-year-old woman who suffered from mood disturbances, sleep disturbances, fatigue and cognitive decline. A comprehensive neuropsychological assessment was performed to evaluate mood, cognition and quality of life. The elderly woman underwent rTMS treatment targeting the left dorsolateral prefrontal cortex (DLPFC), a region critical for executive functions and mood regulation. Significant improvements were observed in attention, processing speed, and cognitive flexibility, as evidenced by reductions in completion times on the Trail Making Test (TMT). In addition to clinical and cognitive outcomes, cortical excitability was assessed through motor-evoked potentials (MEPs) before and after the intervention. Modulation of MEPs amplitude was observed post-treatment, suggesting neurophysiological changes potentially linked to the normalization of cortical activity. Our findings suggest that rTMS may be a well-tolerated and potentially effective intervention for improving cognitive function and stabilizing mood in older adults experiencing age-related cognitive decline and mood disorders.

1. Introduction

Ageing is a natural physiological process that affects everyone. As the world's population ages rapidly, issues related to ageing have gained increasing attention, particularly the decline in cognitive function and mood disorders [1,15,21,25,45,46,63]. Ageing significantly impacts the brain, leading to notable cognitive decline and mood disorders as the population ages [29,30,41,45]. Key changes include morphological alterations like brain atrophy and enlarged ventricles, alongside functional shifts such as decreased neurotransmitter levels and altered connectivity [23,26,29,30,35]. Understanding these changes is essential, as identifying the major structural and functional transformations associated with ageing can provide insights into neurodegenerative

diseases and cognitive health [37,42]. *Cortical excitability* and *Hebbian plasticity* are key concepts in this context. Cortical excitability reflects the brain's ability to respond to stimuli and modulate neuronal activity [32]. while Hebbian plasticity refers to the ability to form and strengthen synaptic connections through learning and experience [33]. In addition to these changes, cortical excitability tends to decrease with age, which may reflect greater neural efficiency in older adults. This decline in excitability has been associated with cognitive reserve; higher cognitive reserve correlates with lower cortical excitability in cognitively unimpaired older adults [32,46].

By utilizing non-invasive brain stimulation techniques, particularly repetitive transcranial magnetic stimulation (rTMS), we explore its potential to improve cognitive functions in older adults. TMS is a non-

* Corresponding author at: Department of Psychology, University of Turin, Turin, Italy.

E-mail address: sara.palermo@unito.it (S. Palermo).

invasive technique which employs electric currents through a coil to generate magnetic fields that penetrate the scalp and skull, modulating neuronal activity in targeted brain regions [9,53–55,61]. By targeting specific regions of the brain, TMS modulates neuronal activity and allows researchers to study how temporary disturbances in brain function affect cognitive processing [8,22,36,49,58,62]. rTMS has proven to be a valuable tool for improving cognitive function in healthy adults [66]. In particular, rTMS has been studied for its effects on cognitive functions such as decision-making, working memory, attention, and cognitive control [5,57,60,69]. The left dorsolateral prefrontal cortex (DLPFC) has received considerable attention in rTMS applications due to its crucial role in executive functions and working memory, both of which are often impaired in age-related cognitive decline. By influencing the DLPFC, may reduce over-activation in neuronal networks, including the default mode network (DMN), which can lead to structural changes in white and grey matter [19,65]. In addition to the direct modulation of neuronal activity, non-invasive brain stimulation techniques such as rTMS can also influence cognitive functions by modulating neurochemical factors. Thus, investigation of such neurochemical correlates, including the potential role of neuropeptides such as orexin-A, may provide a more comprehensive understanding of the mechanisms underlying rTMS-induced cognitive improvements, particularly in areas such as attention and executive functions, which are often targeted by rTMS interventions in cognitive decline [43]. Moreover, rTMS has the potential to enhance neuronal plasticity, which typically diminishes with age due to hypermyelination and neuronal connection degeneration [4,5]. In view of this, rTMS is a promising non-invasive method for improving cognitive function and promoting brain plasticity, especially in the context of age-related changes [2].

This case report presents a novel treatment aimed at enhancing cognitive reserve through prolonged longitudinal intervention. For the first time, we document the temporal relationship between pre-treatment and post-treatment cognitive changes, highlighting the effectiveness of this approach. In addition to assessing cognitive changes, we aim to explore alterations in cortical excitability throughout the intervention period. Understanding these changes is crucial, as they may provide insights into the underlying neural mechanisms that contribute to cognitive reserve and overall cognitive health.

2. Case presentation

We describe the case of GO, a 61-year-old woman from Messina (Italy) who has recently moved house. She had previously retired after working as a secretary for 50 years and became a widow about ten years

ago, which led to her first move to Turin (Italy) to be closer to her daughter. After her recent move, GO began to suffer from somatoform symptoms, feelings of insecurity and mental exhaustion. When she consulted a doctor, she reported that she had been suffering from mood swings and difficulty falling asleep for the past two months. These symptoms significantly affected her daily life and led to increasing physical fatigue and a noticeable deterioration in attention and memory function. It is also important to note that GO suffers from hyperthyroidism, which could contribute to her reported fatigue. Although she describes herself as taciturn and rather reserved, she is socially engaged through volunteer work and her involvement with the University of the Third Age in Turin. The recent move appears to be a significant event that coincides with the onset of the difficulties she reports.

GO was analysed at baseline (T0) and 12 weeks (T12) after rTMS treatment. To ensure that potential changes were due to the rTMS intervention, GO did not change her lifestyle or undergo any other type of treatment during the treatment period.

In the first session, health-related quality of life, motivation for treatment and then behavioural status were assessed using neuropsychogeriatric batteries. Then the neuropsychological assessment was performed. (Table 1).

Mood disturbances were assessed using specific scales: The Beck Anxiety Inventory (BAI: [7]), a self-report scale measuring the severity of anxiety symptoms, and the Beck Depression Inventory - Version II (BDI-II: [6]), designed to assess the severity of depression, including symptoms such as hopelessness and irritability.

The subjects' level of health-related quality of life was assessed using the 5-level EuroQol-5 dimension (EQ-5D-5L: [24,64]), a standardized tool that evaluates five dimensions of health status, and the Fatigue Assessment Scale (FAS: [20]), which measures physical and mental fatigue.

The global cognitive assessment included the following: the Addenbrooke's Cognitive Examination-Revised (ACE-R: [40]), which also allows for scoring of the Mini-Mental State Examination (MMSE: [27]). The Trail Making Test - Parts A and B - (TMT: [3,52]) was used to assess the patient's cognitive processing speed, attention and executive functions. Parallel versions were used for the test-retest [3]. Additional indices, delta and ratio, were calculated to assess patients' cognitive flexibility and task-switching abilities.

Before starting treatment with rTMS, a thorough assessment was performed by the treating physician (MS). This assessment included a detailed review of the patient's medical history (both recent and past), clinical condition and any contraindications to treatment.

A follow-up evaluation was conducted after 6 months (T36) to assess

Table 1

Results of the neuropsychological assessment at the start of treatment (T0) and at follow-up (T12 and T36). Where there are cut-off values, these are given in normal statistical direction. Abnormal values are shown in bold. The changes between baseline and follow-up are shown as a difference analysis. The positive effect of the treatment on the individual clinical parameter is indicated by an arrow pointing upwards. Legend: *ACE-R*: Addenbrooke's Cognitive Examination Revised; *BAI*: Beck Anxiety Inventory; *BDI II*: Beck Depression Inventory version II; *CRiq*: Cognitive Reserve Index; *EQ-5D-5L*: 5-level EuroQol-5 Dimension; *FAS*: Fatigue Assessment Scale; *MMSE*: Mini Mental State Examination; *TMT*: Trail Making Test.

	T0	T12	T12-t0 (Δ)	T36	T36-t0 (Δ)	rTMs effect
Quality of Life Assessment						
EQ-5D-5 L profile	11,111	11,223	11,121	11,121		↑
EQ-5D-5 L index	1	0.794	0.953	0.953	+0.159	↑
Perceived Health						
FAS GLOBAL	< 21	50	60	90	+40	↑
Mental		25	19	20	-5	↑
Physical		8	8	6	-2	
		17	11	14	-3	
Mood Assessment						
BDI-II	≤ 13	18	11	5	-13	↑
BAI	≤ 7	22	12	6	-16	↑
Cognitive Assessment						
CRiq	> 84	112	-	112	=	↑
MMSE	≥ 23.8	25.2	27.7	27.2	+ 2	↑
ACE-R	> 79	93	97	97	+ 4	↑
TMT A	≤ 87.32	29.83	22.67	20.77	- 9.06	↑
TMT B	≤ 269.14	47.96	43.94	40.90	- 7.06	

the long-term durability of the effects on both the neuropsychological and neurophysiological profiles.

To further evaluate the effects of rTMS, cortical excitability was assessed through motor-evoked potentials (MEPs). This allowed us to explore neurophysiological changes potentially linked to enhanced intracortical inhibition and normalization of cortical activity, which are mechanisms associated with improved cognitive and affective outcomes.

2.1. Cortical excitability

Cortical excitability was assessed after the rTMS treatment through MEPs. Single-pulse TMS (spTMS) was applied to the left motor cortex (M1) using a figure-of-eight coil (Magstim EGI) to induce a monophasic posterior-anterior current. The M1 stimulation site was determined as the location of maximal activation of the right first dorsal interosseous (FDI) muscle. MEPs were recorded using surface electromyography (EMG) electrodes placed over the FDI, and a Biopac MP-160 (Biopac, Goleta, CA, USA) electromyograph was used to acquire EMG signals (band-pass filter: 30–500 Hz; sampling rate: 2 kHz). EMG data were filtered (low-pass, 20 Hz) and analyzed offline using a custom MATLAB script (MathWorks).

Additionally, the resting motor threshold (rMT) was defined as the minimum stimulator intensity that elicited MEPs of at least 50 mV amplitude in 5 out of 10 trials. MEPs were recorded at 120 % of rMT, and the peak-to-peak amplitudes were averaged to quantify cortico-motor excitability [48,53]. This assessment followed consensus guidelines endorsed by the International Federation of Clinical Neurophysiology (IFCN) for the safe application of TMS [53,55].

2.2. rTMS protocol

The treatment protocol involved three weekly sessions conducted on alternate days, for a total of 12 weeks of treatment, to assess the cumulative effects of rTMS on the GO's symptoms and overall quality of life.

The stimulation setup consisted of an STM 9000 magnetic stimulator (ATES MEDICA Device, Verona, Italy) for the rTMS protocol. To determine the intensity for rTMS, the rMT of GO was assessed at the beginning of each treatment session, following standard protocols [53,55]. During the treatment period, the mean rMT was at 76 % of the maximum stimulator output (MSO), with a standard deviation of ± 2 . The left dorsolateral prefrontal cortex (DLPFC) was chosen as the stimulation site. The stimulation intensity was set to 120 % of rMT and the stimulation frequency was 10 Hz. Each training session consisted of 800 stimulation pulses, for a total of 20 trains, and the interval between each train was 50 s. Each session lasted approximately 17 min [47,56,72].

During all sessions, the left DLPFC was targeted using image-guided neuronavigation. The position of the coil was determined on the GO scalp using the SofTactic Navigator System (Electro Medical Systems). A Polaris Vicra digitiser (Northern Digital) was used to digitise the landmarks of the skull (nasion, inion and 2 preauricular points) to obtain a uniform representation of the scalp. A customised estimated magnetic resonance image (MRI) was generated by a 3D warping procedure in which a high-resolution MRI template was matched to the participant's scalp model and craniometric points. This method ensures a global localisation accuracy of approximately 5 mm. The stimulation site was identified based on previous functional MRI (fMRI) and TMS studies in Talairach space. The MNI coordinates were converted to Talairach space using GingerALE 2.3.1. The left DLPFC was localised at coordinates $x = -50$, $y = 30$, $z = 36$, derived from mean coordinates obtained in a previous study that targeted this region for cognitive control and working memory tasks [59,73]. The mean coordinates \pm standard deviation of the cortical target region of the left DLPFC corresponded to the lateral part of Brodmann area 9 ($x = -48 \pm 3$, $y = 27 \pm 5$, $z = 37 \pm 2$).

The identified left DLPFC scalp site was marked with a pen on the

head of GO to guide coil placement. The SofTactic system then automatically estimated the individual Talairach coordinates corresponding to the projection of the targeted scalp site onto the surface of the stereotactic template created in the MRI. These estimated coordinates indicate the most superficial cortical location where the TMS effects are expected to be strongest (Fig. 1a). For the post-treatment assessment, GO was presented with the TMS Secondary Effects Questionnaire (TMSens_Q: [28].), a standardised instrument to assess the side effects of TMS treatment, with scores ranging from 0 (no discomfort) to 4 (severe discomfort). All sessions were carried out in accordance with the described methodology (Fig. 1b).

2.3. Main findings

Regarding compliance with rTMS treatment, GO reported mild side effects in the TMSens_Q questionnaire only after the first three sessions. In particular, she experienced mild scalp discomfort and headaches (rating 1 / 4).

Importantly, the patient's neuropsychological test results improved significantly from baseline (T0) to follow-up (T12). The EQ-5D-5 L index increased by 0.159, indicating a general improvement in health-related quality of life. Perceived health improved by 10 points, while the FAS decreased by 6 points, reflecting a significant reduction in perceived fatigue. The BDI-II decreased by 7 points, indicating a slight improvement in mood, which although still altered, became subclinical. In addition, the BAI score decreased by 10 points. Cognitive assessments also showed positive changes, with the ACE-R score increasing by 5 points and the MMSE score increasing by 2.5 points. TMT scores showed significant improvements after rTMS treatment. Part A showed a decrease of 7.16 s, indicating improved cognitive processing speed and attention. Part B also showed a reduction of 4.02 s, indicating improved cognitive flexibility and executive function. A modified *t*-test for individual versus control sample was used to compare the performance of GO with that of a control sample matched for gender, age and education [$N = 10$; age = 60.9 ± 1.52 years; education = 14 ± 3.16 years] [16,17]. The procedure was applied to the behavioural dimensions and the cognitive dimensions, for which a more precise interpretative

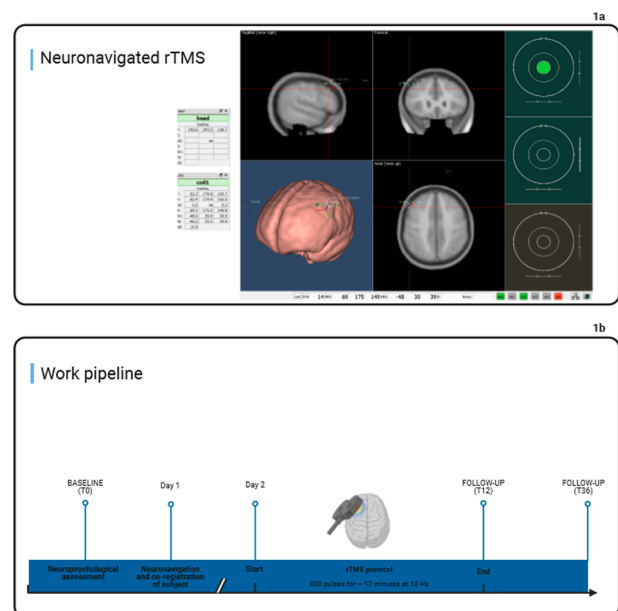


Fig. 1. a) Neuronavigation-guided TMS targeting GO's left DLPFC; b) Work pipeline for the 12-week rTMS treatment program, consisting of three weekly sessions conducted on alternate days, for a total of 36 sessions. Assessments were conducted after 12 weeks and at a 6-month follow-up to evaluate long-term effects.

consideration of the improvement was required (Table 2).

A modulation in MEPs amplitude was observed showing different peak-to-peak amplitude values pre (Mean \pm SE: 3.9 ± 0.03) and post-treatment (1.4 ± 0.05). Follow-up measurements at 6 months (Mean \pm SE: 0.97 ± 0.11) suggest that this modulation was maintained over time (Fig. 2).

Overall, these results indicate an improvement in cognitive function, which, together with the reduction in fatigue and stabilisation of mood, culminates in an improved quality of life, as shown by the EQ-5D-5 L index.

3. Discussion

Overall, our results suggest an enhancement in general cognitive functions, combined with a reduction in fatigue and a stabilisation of mood, culminating in an improved quality of life. The cognitive enhancements observed in our case report align with the current literature on the efficacy of repetitive transcranial magnetic stimulation [60,68]. In particular, targeted rTMS treatment of the DLPFC correlates directly with improved performance on the Trail Making Test, emphasising the efficacy of this intervention in improving specific cognitive domains. Overall, the positive changes in TMT scores point to the beneficial impact of rTMS on brain function and its potential to attenuate age-related cognitive decline [18,44,57,67].

The observed modulation of MEP amplitude—suggesting enhanced intracortical inhibition and potential normalization of cortical activity—could reflect a shift toward a more efficient neural state. Intracortical inhibition is essential for maintaining balance in the brain's excitatory and inhibitory networks, and it often declines with age [34, 51]. rTMS, particularly high-frequency stimulation, could have enhanced this inhibition, potentially leading to improved cognitive control and emotional regulation. This enhancement of intracortical inhibition may help the brain recalibrate its responses to stimuli, thereby improving function in both cognitive and emotional domains. Moreover, this modulation could signify a process of neuroplastic reorganization in which the brain, even in the elderly, demonstrates an ability to "rewire" itself in response to external stimulation: rTMS may stimulate the brain's intrinsic capacity for adaptive plasticity, helping it overcome the degenerative processes typically associated with aging, such as the weakening of synaptic connections and reduced efficiency in

neural networks. This reawakening of the brain's neuroplasticity could be pivotal in delaying the onset of cognitive decline and enhancing cognitive resilience against age-related impairments.

This study represents the first longitudinal investigation into a population undergoing normative physiological aging, which adds a significant strength to our findings. However, it is important to acknowledge certain limitations. As this is the first longitudinal study examining the impact of rTMS on healthy elderly individuals, the necessity for follow-up studies is paramount. Long-term data are required to ascertain the durability of cognitive enhancements and mood improvements observed in our case report. Without extended follow-up, it remains unclear whether the benefits of rTMS are sustained over time or if they diminish after treatment cessation. Furthermore, our findings are based on a single case study, which limits the generalizability of the results to a broader population of older adults. Larger sample sizes in future studies will be crucial for validating our findings and ensuring that they are representative of the aging population as a whole. Additionally, individual differences in response to rTMS treatment may influence outcomes, as factors such as baseline cognitive function, mood status, and comorbidities could affect the efficacy of rTMS. This highlights the need for personalized treatment protocols. Further research should also consider the effects of individual variability in neuroplastic responses. For example, cortical excitability at baseline, as measured by MEPs, might predict the extent to which rTMS can modulate neuronal activity and improve cognitive function, especially given the observed correlation between higher cognitive reserve and lower cortical excitability in older adults [22,32,33,46]. While the influence of the neurochemical milieu was not directly investigated in the current study, age-related changes in neurotransmitter concentrations and the balance between excitatory and inhibitory mechanisms likely play an important role in the brain's capacity for plasticity and its response to rTMS. Future studies could explore how these individual neurobiological factors, including the potential for Hebbian plasticity, contribute to the heterogeneity of treatment outcomes and enable the development of customised rTMS protocols.

We are pioneering a tailored treatment aimed at enhancing cognitive reserve in healthy elderly individuals, marking a novel approach in this field. Meta-analyses show that rTMS significantly improves global cognitive function in patients with mild cognitive impairment and early Alzheimer's disease. In particular, high-frequency rTMS protocols (10 Hz) applied to the left DLPFC over 20 or more sessions show significant cognitive improvements [13,71]. Our study suggests improvements in the areas of attention, memory and executive functions, which are consistent with the cognitive areas typically affected by rTMS treatment. rTMS also shows promising results in the treatment of depressive symptoms, especially in cases that do not respond to pharmacological interventions [38,60,71]. The left DLPFC, our target area, plays a crucial role in mood regulation, and its modulation correlates with an improvement in depressive symptoms. The mood improvement reported by our subject is consistent with these results.

Moreover, neuromodulation may play a vital role in preventing of frailty in the elderly by promoting Hebbian plasticity [38]. This fundamental mechanism of synaptic strength and neural network adaptation is essential for cognitive resilience and functional recovery [11,33]. By improving synaptic efficiency and connectivity in key regions of the brain, rTMS can promote the brain's natural ability to reorganise and repair, preventing or delaying the onset of frailty [10,14]. This neuromodulatory approach not only improves cognitive functions, but also promotes overall brain health, which may lead to better functional outcomes and quality of life in the ageing population [57].

Our case study aligns with broader research that highlights the favorable safety profile of rTMS [31,39,50,70]. Most reported side effects, such as occasional mild headaches or scalp discomfort, are transient and manageable without specialised treatment. Importantly, the non-invasive nature of rTMS makes it a convenient and accessible treatment option for older patients who may be at higher risk of

Table 2

Neuropsychological assessment for GO and the normal controls. Two-tailed probability ≤ 0.05 . The results indicate that cognitive and behavioral abnormalities (T0) tends towards normality (T12) and stabilises over time (T36). The trend was better in GO compared to healthy controls who had never undergone rTMS treatment, suggesting that the treatment might be effective in promoting brain and cognitive reserve.

		GO's scores	Normal controls' scores (Mean \pm SD)	t-value	p
T0	BDI-II	18	5.2 ± 2.89	4.211	0.002
	BAI	22	4.8 ± 1.75	9.365	0.000
	MMSE	25.2	26.88 ± 0.63	-2.527	0.032
	ACE-R	93	95.3 ± 1.82	-1.199	0.261
	TMT A	29.83	30.42 ± 5.30	-0.106	0.918
	TMT B	47.96	43.42 ± 3.12	0.158	0.878
T12	BDI-II	11	5.1 ± 2.60	2.164	0.059
	BAI	12	4.9 ± 1.28	5.289	0.001
	MMSE	27.7	26.88 ± 0.63	1.241	0.246
	ACE-R	97	95.5 ± 1.84	0.777	0.457
	TMT A	22.67	29.91 ± 6.76	-1.198	0.261
	TMT B	43.94	42.206 ± 2.55	0.648	0.533
T36	BDI-II	5	4.8 ± 2.09	0.091	0.930
	BAI	6	5.1 ± 0.99	0.867	0.409
	MMSE	27.2	26.88 ± 0.633	0.482	0.641
	ACE-R	97	96.4 ± 1.42	0.400	0.698
	TMT A	20.77	26.83 ± 3.27	-1.767	0.111
	TMT B	40.90	41.069 ± 3.06	-0.053	0.959

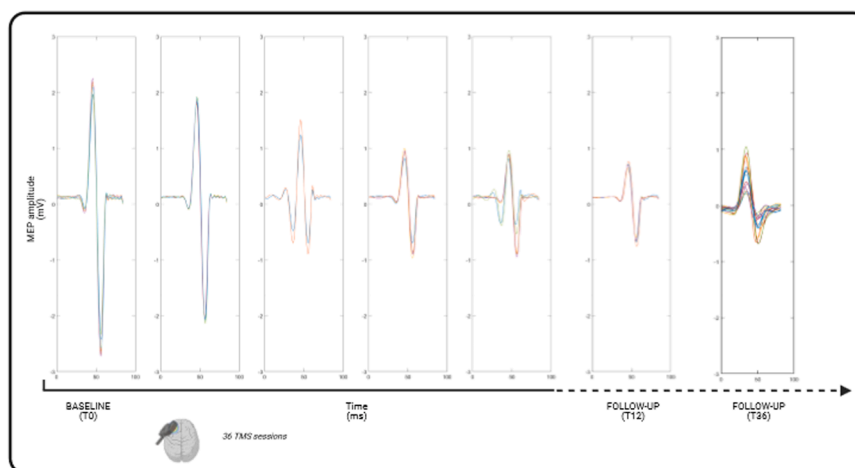


Fig. 2. Assessment of cortical excitability measured through motor evoked potentials (MEPs) at baseline, during the 12-week rTMS treatment period, following the final session, and at the 6-month follow-up.

complications from more invasive procedures. The combination of efficacy, safety and ease of administration emphasises the potential of rTMS as a valuable tool in the fight against cognitive decline and mood disorders in older adults [12,47,56,72].

In conclusion, this case study contributes to the growing body of evidence supporting rTMS as an effective non-invasive tool for improving cognitive function, stabilizing mood, and promoting neuroplasticity in older adults. The observed neurophysiological changes, including the modulation of cortical excitability, underscore the potential of rTMS to "reawaken" the aging brain, enhancing its capacity for adaptive plasticity and mitigating age-related cognitive decline. However, further research is required to optimize rTMS treatment protocols, investigate long-term effects, and explore its potential as a preventive measure for frailty and cognitive decline in the aging population.

Informed patient consent

The author(s) should confirm that written informed consent has been obtained from the involved patient(s) or if appropriate from the parent, guardian, power of attorney of the involved patient(s); and, they have given approval for this information to be published in this case report (series).

Please refer to Elsevier's policy regarding written patient consent requirements: <https://www.elsevier.com/about/policies-and-standards/patient-consent>

Complete written informed consent was obtained from the patient for the publication of this study and accompanying images.

Data statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics approval

The study was approved by Bioethical Committee of the University of Torino, Prot n. 209,329 of 08/04/2024 (2024-UNTOCLE-0209,329), and was conducted in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the individual and from healthy controls for the publication of any potentially identifiable images or data included in the article.

CRedit authorship contribution statement

Chiara Di Fazio: Writing – review & editing, Writing – original draft,

Methodology, Investigation, Data curation. **Eugenio Scaliti:** Writing – review & editing, Formal analysis. **Mario Stanziano:** Writing – review & editing, Data curation. **Anna Nigri:** Writing – review & editing, Data curation. **Greta Demichelis:** Writing – review & editing, Data curation. **Marco Tamietto:** Writing – review & editing. **Sara Palermo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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