Brain Stimulation 13 (2020) 1655–1664

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Enhancing cognitive training effects in Alzheimer's disease: rTMS as an add-on treatment

Chiara Bagattini [a, *], Mara Zanni [b], Federica Barocco [b], Paolo Caffarra [c], Debora Brignani [a], Carlo Miniussi [d], Carlo Alberto Defanti [b]

[a] Cognitive Neuroscience Section, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, 25125, Brescia, Italy
[b] Fondazione Europea Ricerca Biomedica, Ospedale Sant'Isidoro, 24069, Trescore Balneario, Bergamo, Italy
[c] Department of Medicine and Surgery, Section of Neuroscience, University of Parma, 43126, Parma, Italy
[d] Center for Mind/Brain Sciences- CIMeC, University of Trento, 38068, Rovereto, Italy

ARTICLE INFO

Article history:
Received 30 December 2019
Received in revised form
8 August 2020
Accepted 22 September 2020
Available online 28 September 2020

Keywords:
rTMS treatment
Alzheimer's disease
Mild cognitive impairment
Cognitive training
Add-on effect
Face-name associative memory

ABSTRACT

The treatment of Alzheimer's disease (AD) in the field of non-pharmacological interventions is a challenging issue, given the limited benefits of the available drugs. Cognitive training (CT) represents a commonly recommended strategy in AD. Recently, repetitive transcranial magnetic stimulation (rTMS) has gained increasing attention as a promising therapeutic tool for the treatment of AD, given its ability of enhancing neuroplasticity. In the present randomized, double-blind, sham-controlled study, we aimed at investigating the add-on effect of a high frequency rTMS protocol applied over the left dorsolateral prefrontal cortex (DLPFC) combined with a face-name associative memory CT in the continuum of AD pathology. Fifty patients from a very early to a moderate phase of dementia were randomly assigned to one of two groups: CT plus real rTMS or CT plus placebo rTMS. The results showed that the improvement in the trained associative memory induced with rTMS was superior to that obtained with CT alone. Interestingly, the extent of the additional improvement was affected by disease severity and levels of education, with less impaired and more educated patients showing a greater benefit. When testing for generalization to non-trained cognitive functions, results indicated that patients in CT-real group showed also a greater improvement in visuospatial reasoning than those in the CT-sham group. Interestingly, this improvement persisted over 12 weeks after treatment beginning.

The present study provides important hints on the promising therapeutic use of rTMS in AD.

Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders characterized by progressive decline in cognition, behaviour and activities of daily living. AD severity may be considered along a biological and clinical continuum ranging from a very early preclinical stage to the final overt dementia phase with multi-domain cognitive and functional impairments. Mild cognitive impairment (MCI) syndrome occurs between these stages and represents the point of transition from the asymptomatic phase to dementia onset [1]. Among the several clinical subtypes of MCI [2], amnesic MCI (aMCI) is presumed to have a degenerative etiology and a higher likelihood of conversion to AD dementia [2,3].

Given the limited efficacy of the available pharmaceutical options to restore brain function, AD is recognized as one of the major challenges in the field of non-pharmacological interventions. Cognitive training (CT) is a commonly recommended non-pharmacological intervention in AD and is recognized as an important adjunct, or even alternative, treatment to pharmacological intervention [4,5]. Face-name association is among the most targeted function of CT interventions along the continuum of AD severity (e.g. [6–12]) with promising results. Failure to remember names is one of the earliest and distinctive signs of the episodic memory impairment in AD patients. This difficulty increases as the disease severity progresses along the full spectrum of AD pathology, from very early stages to severe dementia [13]. Several neuroimaging studies have revealed that face-name association memory involves a complex network consisting of highly

* Corresponding author. Cognitive Neuroscience Section, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Via Pilastroni 4; 25125, Brescia, 0039-0303501596, Italy.
E-mail address: chiara.bagattini@cognitiveneuroscience.it (C. Bagattini).

https://doi.org/10.1016/j.brs.2020.09.010

specialized visual areas in the occipitotemporal cortex and other cortical areas associated with higher cognitive functions, as the dorsolateral prefrontal cortex (DLPFC) [14]. Besides being crucially involved in episodic memory, DLPFC is a pivotal hub for networks integration, mediating organizational and executive functions that might operate across multiple types of tasks. Pathological changes and dysfunction of the DLPFC are a hallmark feature of AD from its early stage [15–17]. DLPFC is considered a key region contributing to several large-scale brain networks, such as the Default Mode Network (DMN), the Fronto-Parietal Network (FPN) and the Central Executive Network (CEN) [18,19], whose alterations are associated with the clinical manifestations of AD. Together with cognitive interventions, repetitive transcranial magnetic stimulation (rTMS) is an emerging and promising therapeutic option in the field of non-pharmacological treatments for AD continuum [20–25]. In the last twenty years, rTMS has gained increasing attention as a potential therapeutic tool for the treatment of several neurological and neuropsychiatric disorders [26]. rTMS is a painless technique able to generate a brief magnetic pulse through a stimulating coil placed over the subject's head. The created magnetic field induces a transient electric field in the underneath surface able to depolarize the neurons in the cortex [27,28]. Interestingly, rTMS not only acts locally on interneuronal circuits but the induced activation also spreads to functionally connected brain regions along cortico-cortical connections [29]. In addition, rTMS is able to induce long-lasting changes of cortical excitability, probably reflecting mechanisms similar to long term potentiation and depression [30]. This evidence has prompted great interest for therapeutic application of rTMS in a variety of clinical fields [31,32].

Available rTMS studies in AD suffer from several flaws such as small sample size, variability in stimulation parameters, targeted areas, number of sessions and outcome measures, heterogeneity of patients' disease severity, lacking blindness and the absence of a control group or of an adequate sham procedure.

Recent evidence-based guidelines did not endorse left DLPFC rTMS as an effective therapeutic option for the treatment of AD, whereas suggested the possible efficacy of multisite rTMS combined with CT in improving cognitive functions in AD patients [33].

The rationale underlying the promotion of rTMS as an add-on treatment relies on the results of several studies demonstrating that the most effective way to enhance neuroplasticity (i.e., the ability of our brain to change its functions and structure through the modulation of the synaptic connections) is to combine "exogenous" and "endogenous" stimulation. In this sense, rTMS may be used as a priming tool capable of pre-activating the initial state of the system such that the neural impact of any subsequent intervention depends on the interaction with the ongoing brain activity [31]. These mechanisms have a pivotal role in cognitive intervention, where the addition of rTMS to CT protocols may represent the keystone to potentiate and, possibly, generalize their effects [32].

Available controlled studies combining multisite rTMS with CT in AD patients [34–36] do not allow to shed light on the adjunctive effect of rTMS when combined with CT, as they investigated solely general clinical measures (e.g., ADAS-cog), thus missing to explore the effect on specific cognitive domains and any generalization effect beyond the trained functions. Furthermore, they adopted a complex protocol (NeuroAD; Neuronix, Yokneam, Israel), consisting in the stimulation of six brain regions (i.e., right and left DLPFC, Broca's area, Wernicke's area, right and left parietal somatosensory association cortex) in conjunction with several cognitive tasks (e.g., comprehension of lexical meaning, action and object naming, spatial attention, etc.), which did not allow to disentangle the role of each specific targeted area. Moreover, a recent study [37] comparing the TMS-induced effect of the six-regions stimulation protocol with that of one region stimulation protocol (i.e., left DLPFC), showed that both the treatments improved clinical measures equally, thus assuming that the benefits induced by rTMS are mostly likely due to the stimulation of the left DLPFC. In 2006 Solé-Padulles and colleagues [38] firstly demonstrated the beneficial effect of high frequency rTMS applied over the left prefrontal cortex on face-name association memory among MCI patients. Since then, DLPFC has been the target of most rTMS interventions at different stages of AD pathology [37,39–45]. A recent meta-analysis showed a lateralization of the rTMS effects at the DLPFC in MCI and AD patients, with high frequency rTMS protocols over the left DLPFC (and low-frequency protocols over the right DLPFC) significantly improving memory functions [21].

In the present study we aimed at investigating the add-on effect of left DLPFC high frequency rTMS combined with a face-name associative memory CT in a randomized, double-blind, sham controlled trial in patients with memory deficits across MCI and mild to moderate AD diagnosis.

We were interested in: 1) testing whether patients receiving real rTMS in combination with CT would reach greater improvement in the trained cognitive function (i.e., face-name associative memory) as compared to patients receiving CT alone; 2) evaluating whether the expected adjunctive rTMS effect can also promote an improvement to non-trained cognitive functions (i.e., generalization) belonging, or not, to the same cognitive domain, as measured through a comprehensive neuropsychological battery.

Method

Study design

This was a randomized, double-blind, placebo-controlled study. Enrolled patients were randomly assigned to one of two groups: 1) CT plus real rTMS (CT-real); or 2) CT plus sham rTMS (CT-sham). The treatment consisted of 4 weeks of daily sessions (5 days per week, for a total of 20 sessions) of computerized CT coupled with real (CT-real group; N = 27) or sham rTMS (CT-sham group; N = 23). In each daily session rTMS was delivered immediately before the administration of cognitive training, in order to "prime" the system and increase the efficacy of the face-name associative memory intervention. All patients underwent a comprehensive clinical and neuropsychological assessment at baseline (t0), after 4 weeks of treatment (t4) and 12 weeks after baseline assessment (follow-up; t12). Study design is depicted in Fig. 1. Neuropsychological assessment included standardized tests aimed at evaluating both global cognitive functioning (Mini Mental State Examination; MMSE) and specific cognitive domains as: memory (story recall, immediate and delayed recall of the Rey Auditory Verbal Learning test, delayed recall of the Rey-Osterrieth Complex Figure), language (phonemic and semantic verbal fluency), attention and executive functions (attentive matrices, Trail Making Test), spatial reasoning (Raven Colored Progressive Matrices), praxis and visuo-constructive abilities (copy of the Rey-Osterrieth Complex Figure). Mood was assessed with the Geriatric Depressive Scale (GDS). Cognitive assessments were administered by a trained neuropsychologist who was blind to patients' group allocation. All the tests were administered and scored according to standard procedures [46]. The whole list of administered tests is reported in Table 2.

The study was conducted at Sant'Isidoro FERB Onlus Hospital (Bergamo, Italy), all the procedures were approved by the Ethical Committee of the Province of Bergamo (Italy) and were performed according to the Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from all the patients and from one legal family member before study beginning.

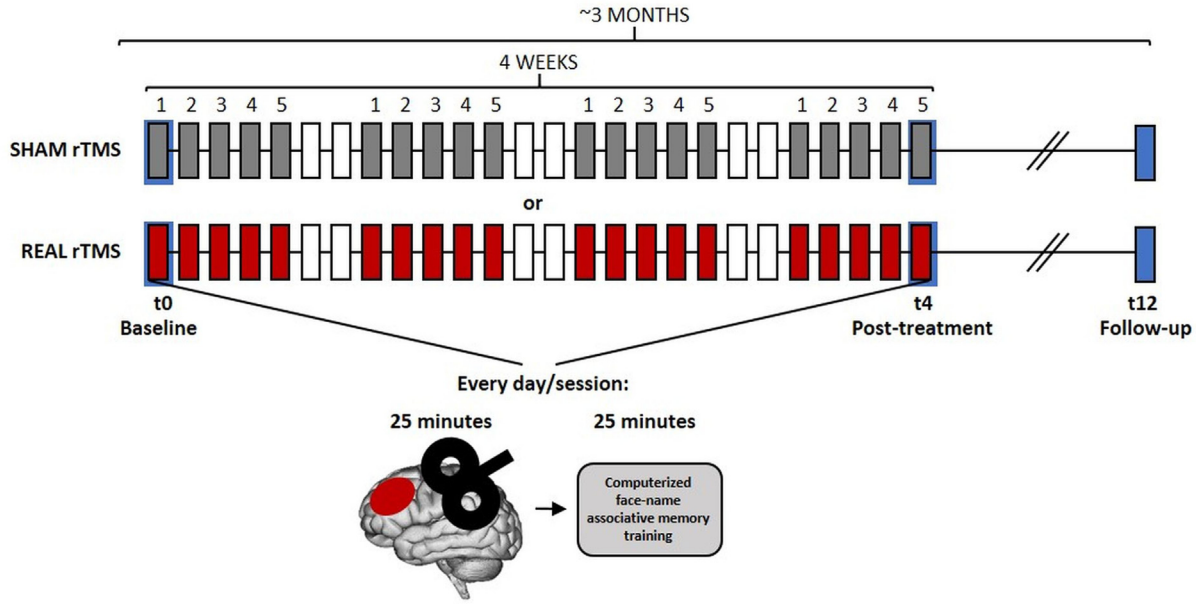

Fig. 1. Study design. Enrolled patients were randomly assigned to one of two groups: 1) CT plus sham rTMS (CT-sham; depicted in grey); or 2) CT plus real rTMS (CT-real; depicted in red) receiving 4 weeks of daily sessions (5 days per week, for a total of 20 sessions) in which rTMS was delivered immediately before the administration of CT. At baseline (t0), after 4 weeks of treatment (t4) and 12 weeks after treatment beginning (follow-up; t12) patients underwent a comprehensive clinical and neuropsychological assessment. rTMS was applied over the lDLPFC (in correspondence to F3 electrode position according to the 10–20 electrode placement system) with the coil placed tangentially to the scalp at 45° with the handle pointing backward toward the midline. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article)

Table 1
The table contains the mean values (±standard deviation) of demographic and clinical data collected at baseline. Results of the independent sample t-tests or chi-square tests (p-values) comparing the two groups (CT-real, CT-sham) in baseline demographic and clinical data are reported.

	CT-real (N = 27)	*CT-sham* (N = 23)	p
Gender (males/females)	17/10	12/11	0.44
Age (years)	73.56 (4.91)	73.35 (1.09)	0.89
Education (years)	8.85 (3.91)	7.91 (0.67)	0.36
Disease duration (months)	23.33 (8.86)	20.09 (15.09)	0.35
BADL (unspared functions)	0.00 (0.00)	0.13 (0.46)	0.14
IADL (unspared functions)	1.00 (1.24)	1.65 (1.82)	0.14
MMSE	23.67 (3.00)	22.77 (0.58)	0.30
CDR	0.98 (0.55)	1.07 (0.55)	0.75
GDS	2.04 (1.70)	3.04 (2.46)	0.10
Acetylcholinesterase inhibitors treatment (Rivastigmine/Donepezil)	4/5	3/4	0.97

Key: BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; MMSE, Mini Mental State Examination; CDR, Clinical Dementia Rating scale; GDS, Geriatric Depression Scale.

Participants

Fifty patients with a diagnosis of amnesic MCI (aMCI) [3] or a diagnosis of mild to moderate probable AD [47] were included in the present study. Inclusion criteria were a MMSE [48] score greater or equal to 16, a Clinical Dementia Rating scale (CDR) score ranging from 0.5 to 2 and age between 60 and 85 years. Diagnosis was done by expert neurologists or geriatricians addressing medical history, clinical examination, neuropsychological testing and laboratory results such as computed tomography, magnetic resonance imaging or positron emission tomography. Patients receiving treatment with cholinesterase inhibitors (donepezil or rivastigmine) had to be on a stable dose for at least 3 months prior to participation in the study. Exclusion criteria were the presence of potentially confounding medical, neurological or psychiatric conditions, and the presence of any contraindication for TMS according to international safety guidelines [27]. Demographic and clinical data collected at baseline are reported in Table 1.

rTMS protocol

rTMS (Deymed DuoMAG XT-100) was delivered with a figure-of-eight 70 mm air-cooled coil (70BF-Cool DuoMAG). rTMS intensity was set at 100% of the individual resting motor threshold (rMT), which was calculated for each subject before starting the treatment. rMT was defined as the lowest intensity able to induce a motor evoked potential of at least 50 μV in at least 5 out of 10 trials [28] in the first dorsal interosseous muscle of the right hand (all participants were right handed). Each rTMS session consisted of 50 trains of high frequency (20 Hz) rTMS delivered in short periods (2 s) separated by pauses of 28 s of no stimulation. The total number of pulses delivered for each session was 2000. rTMS was applied over the left DLPFC (lDLPFC; in correspondence to F3 electrode position according to the 10–20 electrode placement system) and the coil positioning was monitored throughout the entire stimulation session using a stereotaxic neuronavigation system (SofTaxic 3.0, Electro Medical Systems). The coil was placed tangentially to

Table 2
Mean (±standard deviation) scores obtained by patients in the CT-real and CT-sham groups in the tests administered at baseline (t0), after 4 weeks of treatment (t4) and 12 weeks after treatment beginning (follow-up; t12).

	CT-real			CT-sham		
	t0	t4	t12	t0	t4	t12
Face-name associative memory	7.67 (0.78)	15.48 (3.26)	–	7.83 (0.72)	13.52 (2.97)	–
Global cognitive functioning						
MMSE	23.67 (3.00)	24.33 (2.38)	24.16 (2.36)	22.77 (3.09)	22.88 (3.65)	22.80 (3.91)
Memory						
Story recall	7.41 (3.25)	10.61 (4.49)	9.41 (4.00)	6.44 (4.17)	8.41 (5.20)	8.09 (4.92)
RAVL, immediate recall	31.67 (6.48)	38.71 (9.81)	37.15 (10.49)	29.66 (7.79)	34.88 (10.26)	34.10 (10.84)
RAVLT, delayed recall	4.56 (2.55)	6.67 (3.00)	5.70 (3.35)	4.34 (2.59)	5.51 (2.94)	5.38 (2.68)
ROCF, delayed recall	7.88 (4.69)	12.62 (7.44)	11.82 (6.52)	7.13 (2.92)	9.76 (4.76)	10.57 (3.49)
Attention						
Attentive matrices	40.96 (12.43)	42.89 (12.52)	42.43 (12.57)	37.16 (10.66)	37.42 (12.49)	38.99 (11.20)
TMT-A	62.41 (59.46)	52.85 (54.45)	57.74 (57.85)	68.55 (44.36)	49.05 (26.99)	53.48 (34.10)
Language						
Phonemic verbal fluency	31.41 (8.81)	33.67 (9.36)	32.52 (8.23)	26.44 (7.99)	28.70 (9.32)	29.00 (8.32)
Semantic verbal fluency	30.52 (9.10)	32.11 (9.53)	31.78 (8.55)	28.48 (7.32)	29.17 (7.11)	28.17 (8.05)
Visuospatial reasoning						
RCPM	27.56 (5.82)	29.87 (4.10)	29.00 (5.03)	25.24 (5.17)	25.37 (6.23)	25.30 (5.13)
Praxis						
ROCF, copy	28.54 (6.99)	30.84 (6.51)	30.04 (7.69)	28.58 (6.45)	29.64 (5.64)	28.05 (6.06)
Mood						
GDS	2.04 (1.70)	2.19 (1.44)	1.89 (1.47)	3.04 (2.40)	3.17 (2.62)	2.91 (2.55)

Key: MMSE, Mini Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure; TMT, Trail Making Test; RCPM, Raven Colored Progressive Matrices; GDS, Geriatric Depression Scale.

the scalp at 45° with the handle pointing backward toward the midline (Fig. 1). For sham stimulation, we used the same parameters as for the real condition but, in order to reduce the intensity of the magnetic field reaching the scalp [49], a custom made 3-cm thick block of wood was placed between the coil and the scalp [50]. rTMS was well tolerated by all the patients and none reported any major adverse effect.

Face-name associative memory training

CT was administered by means of a computer-based CT software (RehaCom, Hasomed, GmbH) which is among the most extensively adopted software in the field of computer-assisted cognitive rehabilitation. CT was delivered immediately after the application of rTMS (both real and sham) and lasted 25 min to match rTMS duration. Training was focused on episodic memory and specifically on face-name associative memory. Each training session consisted in a "learning phase", during which the patient had to memorize the association between faces and names, followed by a "recognition phase" in which the patient had to identify the correct face for each displayed name. The recognition response format has been previously adopted in several non-invasive brain stimulation studies [12,38,51,52] and functional imaging studies [53–55]. Because it is easier as compared to the recall format, it avoids floor effect and prevents from frustration in more impaired patients. All participants began the training with the same starting level of the RehaCom software, which consisted in the presentation of two face-name associations to be learned. Thanks to the individualized adaptive methodology, training's difficulty automatically adapted to the patient's performance. Depending on whether the patient succeeded or failed the task, the difficulty levels were adjusted to meet patient's capacity. To do so, the system calculated the percentage number of the correct responses. If the accuracy level achieved was above 80%, then the patient was administered with a more difficult level. Conversely, if the accuracy level achieved by the patient was below 60% the patient was administered with an easier level of difficulty. This process was continuously repeated until the cognitive training session ended (i.e., after 25 min). The difficulty of the task was modulated by the number of face-name associations to be learned. As the difficulty further increased, higher levels consisted in an increasing number of face-name-profession associations to be learned. Highest difficulty levels consisted in an increasing number of face-name-profession-phone number associations to be learned.

Face-name training was administered adopting errorless learning and vanishing cue techniques, which are considered as the most effective evidence-based cognitive strategies for the improvement of face-name memory in persons with AD (for reviews see [13,56]). Face-name associative memory performance was measured as the number of difficulty level achieved by the patients. Baseline performance (t0) was referred to the level achieved by the patients at the end of the first day of the treatment, whereas t4 performance was considered as the level achieved at the end of the last treatment session.

Statistical analysis

To investigate clinical and demographical differences at baseline among the two groups (CT-real, CT-sham), appropriate statistical tests (i.e., independent sample t-tests or Chi-squared tests) have been performed and are reported in Table 1.

To investigate whether real rTMS combined with CT induced an add-on effect on the trained function, a repeated measures ANOVA was conducted on the performance obtained at the face-name associative memory task with "Time" (t0, t4) as within-subjects factor and "Treatment" (CT-real, CT-sham) as between-subjects factor. Post-hoc comparisons were performed with Sidak correction. In order to verify the impact of clinical and demographical variables on the possible add-on rTMS effect, repeated measures ANCOVAs with age, education, disease severity and disease duration as covariates were separately conducted in case of a significant "Time x Treatment" interaction.

To identify add-on generalization effects induced by real rTMS combined with CT to non-trained cognitive functions, repeated measures ANOVAs with "Time" (t0, t4, t12) as within-subjects factor and "Treatment" (CT-real, CT-sham) as between-subjects factor were applied to age- and education-adjusted scores obtained at the neuropsychological tests (MMSE, story recall, RAVLT

immediate recall, RAVLT delayed recall, ROCF copy, ROCF delayed recall, TMT-A, RCPM, phonemic verbal fluency, semantic verbal fluency; whole list is reported in Table 2). In order to account for the influence of disease severity and disease duration in modulating the add-on effect of rTMS (as eventually revealed by a significant "Time x Treatment" interaction"), we computed two repeated measures ANCOVAs testing "Time" and "Treatment" as factors and considering "disease severity" (that is the MMSE score obtained at baseline) and "disease duration" as covariates, respectively (except for MMSE score for which "diseases duration" only was considered). "Age" and "Education" were not included as covariates given that neuropsychological scores were already age-and education-adjusted and no significant difference in these variables emerged between CT-real and CT-sham groups (Table 1).

Results

No significant differences in clinical and demographic variables at baseline emerged between groups (Table 1). Table 2 reports the mean and the standard deviation performance scores obtained by CT-real and CT-sham groups at baseline (t0) after 4 weeks of treatment (t4) and at 12 weeks follow-up (t12).

Face-name associative memory

ANOVA results on the performance at the face-name associative memory training showed a significant main effect of "Time" ($F(1,48) = 270.06$, $p < 0.001$, $\eta_p^2 = 0.85$), a trend toward significance for "Treatment" ($F(1,48) = 3.26$, $p = 0.077$, $\eta_p^2 = 0.064$) and a significant "Time x Treatment" interaction ($F(1,48) = 6.64$, $p = 0.013$, $\eta_p^2 = 0.122$). Post-hoc comparisons revealed that patients in the CT-real group (mean = 15.48, sd = 3.26) showed a better face-name associative memory performance at t4 as compared to patients in the CT-sham group (mean = 13.52, sd = 2.97; $p = 0.032$) (Fig. 2A). When adjusted by differences in demographical and clinical covariates, the "Time x Treatment" interaction effect remained significant (when controlling for "Age": $F(1,47) = 6.483$, $p = 0.014$, $\eta_p^2 = 0.121$; "Education": $F(1,47) = 5.59$, $p = 0.022$, $\eta_p^2 = 0.106$; "Disease severity": $F(1,47) = 5.33$, $p = 0.025$, $\eta_p^2 = 0.102$; "Disease duration": $F(1,47) = 7.63$, $p = 0.008$, $\eta_p^2 = 0.140$). Interestingly, when accounting for the effect of "Disease severity", ANCOVA results showed a significant "Time x Treatment x Disease severity" interaction ($F(2,46) = 4.88$, $p = 0.012$, $\eta_p^2 = 0.175$), revealing that the add-on effect of rTMS on face-name memory was affected by the baseline cognitive status, with less impaired patients showing a greater advantage from the add-on rTMS treatment (Fig. 2B). Also "Education" was found to impact the add-on effect of rTMS, as revealed by a significant "Time x Treatment x Education" interaction ($F(1,46) = 3.45$, $p = 0.040$, $\eta_p^2 = 0.131$). More educated patients exhibited a greater face-name memory amelioration induced by rTMS (Fig. 2C). "Age" and "Disease duration" did not affect the "Time x Treatment" interaction (all p's > 0.331).

Effect on non-trained cognitive functions

Global cognitive functioning

Global cognitive functioning was assessed by means of MMSE. ANOVA conducted on the MMSE score showed no significant main effect of "Time" or "Treatment" factor, and no significant "Time" x "Treatment" interaction effect (all $p > 0.13$).

Memory

The memory domain aimed at investigating both verbal and visuospatial long-term memory.

ANOVA conducted on the *story recall* scores showed a significant main effect of "Time" ($F(2,96) = 29.13$, $p < 0.001$, $\eta_p^2 = 0.378$), but no significant main effect of "Treatment" ($F(1,48) = 1.65$, $p = 0.206$, $\eta_p^2 = 0.033$) and no "Time x Treatment" interaction effect ($F(2,96) = 1.639$, $p = 0.200$, $\eta_p^2 = 0.033$) emerged. Post-hoc comparisons revealed that 4 weeks (i.e., t4) of CT (both with real and sham rTMS) improved episodic memory scores (mean = 9.60, sd = 4.90) as compared to baseline (mean = 6.96, sd = 3.70; $p < 0.001$). The amelioration persisted also at 12 weeks (i.e., t12) follow-up evaluation (mean = 8.80, sd = 4.45; $p < 0.001$).

Immediate recall of RAVLT results showed a significant effect of "Time" ($F(2,96) = 30.73$, $p < 0.001$, $\eta_p^2 = 0.390$) with post-hoc comparisons revealing an improvement of RAVLT scores at t4 (mean = 36.95, sd = 10.10; $p < 0.001$) that persisted at t12 (mean = 35.74, sd = 10.65; $p < 0.001$), as compared to baseline (mean = 30.75, sd = 7.11). No significant "Treatment" ($F(1,48) = 1.42$, $p = 0.239$, $\eta_p^2 = 0.029$) nor "Time x Treatment" interaction effect ($F(2,96) = 0.61$, $p = 0.548$, $\eta_p^2 = 0.012$) emerged.

A significant main effect of "Time" emerged also when considering the *delayed recall* of both *RAVLT* ($F(2,96) = 20.29$, $p < 0.001$, $\eta_p^2 = 0.297$) and *ROCF* ($F(2,86) = 19.66$, $p < 0.001$, $\eta_p^2 = 0.314$). No significant "Treatment" nor "Time x Treatment" interaction effect emerged (all $p > 0.149$). Again, the induced amelioration was visible at t4 (*delayed RAVLT recall*: mean = 6.14, sd = 2.30; *delayed ROCF recall*: mean = 11.32, sd = 6.45; both $p < 0.001$) and persisted at follow-up (*delayed RAVLT recall*: mean = 5.55, sd = 3.03; *delayed ROCF recall*: mean = 11.25, sd = 5.33; both $p \leq 0.001$) as compared to baseline (*delayed RAVLT recall*: mean = 4.46, sd = 2.54; *delayed ROCF recall*: mean = 7.53, sd = 3.94).

Attention

Attention was primarily measured with tasks assessing sustained attention and processing speed. ANOVA conducted on the scores obtained in the *attentive matrices* showed a trend toward significance for the main effect of "Time" ($F(2,96) = 2.84$, $p = 0.064$, $\eta_p^2 = 0.056$), whereas no significant "Treatment" ($F(1,48) = 1.63$, $p = 0.208$, $\eta_p^2 = 0.033$) or "Time x Treatment" ($F(2,96) = 1.18$, $p = 0.31$, $\eta_p^2 = 0.024$) effects emerged. Post-hoc comparisons indicated greater scores at t12 (mean = 40.85, sd = 11.96; $p = 0.060$) as compared to baseline (mean = 39.22, sd = 11.69). No difference emerged when comparing t4 (mean = 40.38, sd = 12.68; $p = 0.350$) with baseline.

TMT-A results showed a significant effect of "Time" ($F(2,92) = 6.41$, $p = 0.002$, $\eta_p^2 = 0.122$) but no "Treatment" ($F(1,46) = 0.007$, $p = 0.936$, $\eta_p^2 = 0.000$) nor "Time x Treatment" ($F(2,92) = 0.84$, $p = 0.436$, $\eta_p^2 = 0.018$). Post-hoc comparisons revealed that CT improved *TMT-A* performance at t4 (mean = 51.19, sd = 44.20; $p = 0.011$) as compared to baseline (mean = 65.16, sd = 52.77). The improvement persisted also at t12 (mean = 55.88, sd = 48.48; $p = 0.027$).

Visuospatial reasoning

Raven Colored Progressive Matrices (Raven et al., 1965) has been administered to assess abstract and logic reasoning.

Results of the ANOVA analysis showed significant main effects of "Time" ($F(2,92) = 3.27$, $p = 0.042$, $\eta_p^2 = 0.066$) and of "Treatment" ($F(1,46) = 5.66$, $p = 0.022$, $\eta_p^2 = 0.110$) and a trend toward significance of the "Time x Treatment" interaction ($F(2,92) = 2.72$, $p = 0.071$, $\eta_p^2 = 0.056$). Post-hoc comparisons indicated that a greater improvement in RCPM task was observed at t4 after real rTMS as compared to sham rTMS (CT-real: mean = 29.87, sd = 4.10; CT-sham: mean = 25.37, sd = 6.23; $p = 0.006$). This greater improvement persisted over t12 assessment (CT-real: mean = 29.00, sd = 5.03; CT-sham: mean = 25.30, sd = 5.13; $p = 0.015$), indicating a robust and lasting generalization of the add-

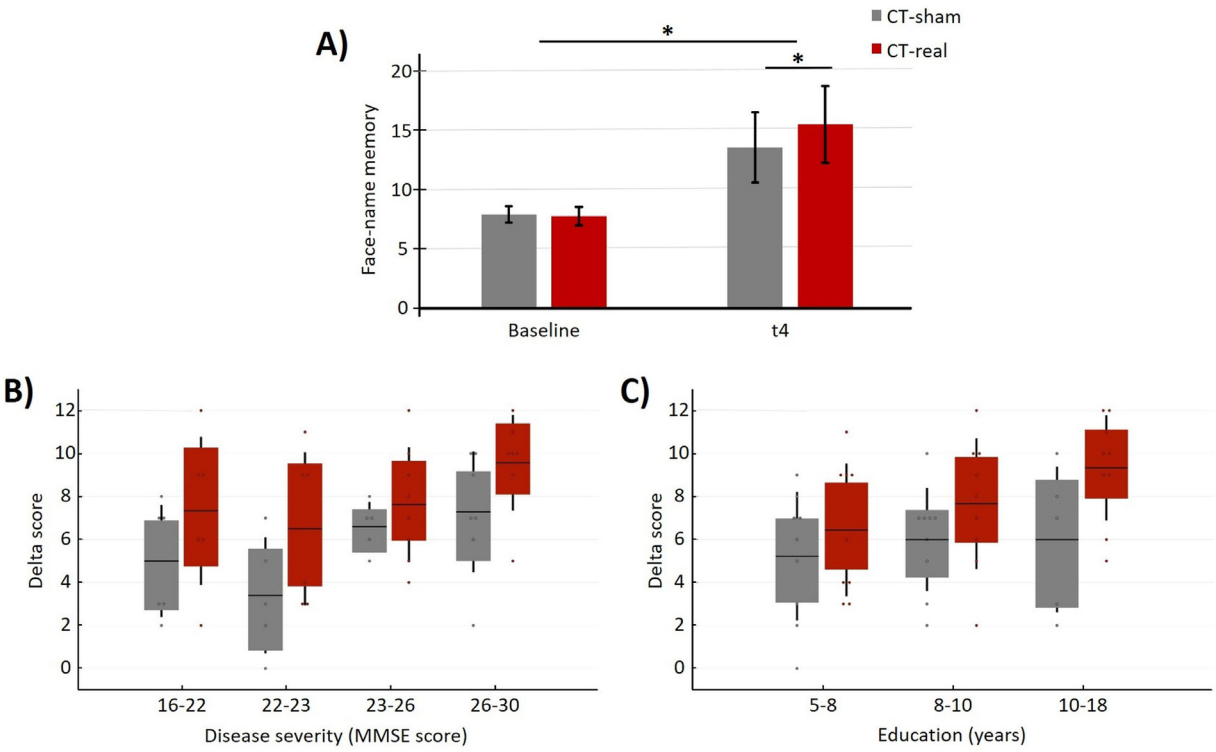

Fig. 2. Face-name associative memory CT results. A) Mean face-name associative memory performance at baseline and at t4 in the CT-sham (grey) and CT-real (red) groups. Error bars represents standard deviation; B) Delta face-name associative memory scores (t4-t0 difference) plotted as a function of disease severity (MMSE score obtained at baseline) in the CT-sham (grey) and CT-real (red) groups; C) Delta face-name associative memory scores (t4-t0 difference) plotted as a function of education levels (in years) in the CT-sham (grey) and CT-real (red) groups. Mean values (horizontal black lines) are layed over the 95% confidence interval (red and grey bars) and standard deviation (vertical black lines). Circles represent single subject scores. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article)

on effect of lDLPFC rTMS to this cognitive function (Fig. 3). No significant difference emerged when comparing real rTMS and sham rTMS at baseline (CT-real: mean = 27.56, sd = 5.82; CT-sham: mean = 25.24, sd = 5.17; p = 0.185).

When controlling for the impact of "Disease severity" and "Disease duration" the interaction of interest was still found to be significant ($F(2,90) = 16.36$, $p = 0.055$, $\eta_p^2 = 0.062$; $F(2,90) = 3.59$, $p = 0.031$, $\eta_p^2 = 0.074$, respectively). No significant "Time x Treatment x disease severity" nor "Time x Treatment x disease duration" interaction effects emerged (all $p > 0.08$), thus assuming that these covariates did not impact on the add-on rTMS effect on visuospatial reasoning.

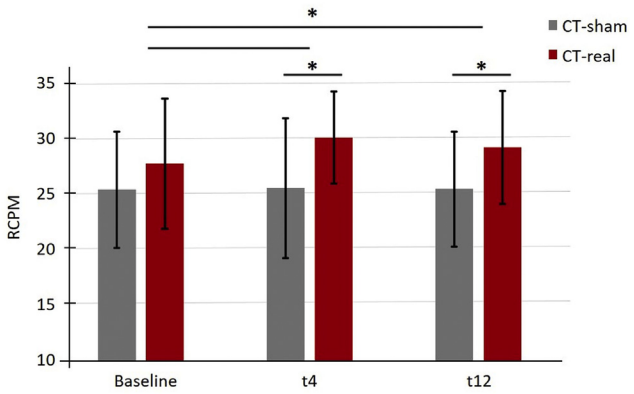

Fig. 3. Add-on generalization effect to visuospatial reasoning induced by real rTMS. Mean RCPM performance at baseline, at t4 and at t12 in CT-sham (grey) and CT-real (red) groups. Error bars represents standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article)

Language

ANOVA conducted on the *phonemic verbal fluency* scores showed a significant main effect of "Time" ($F(2,96) = 4.04$, $p = 0.021$, $\eta_p^2 = 0.078$) with an improvement in the performance at t4 (mean = 31.38, sd = 9.58; $p = 0.014$) as compared to baseline (29.12, sd = 8.72) and a significant effect of "Treatment" ($F(1,48) = 3.92$, $p = 0.054$, $\eta_p^2 = 0.075$), but no significant "Time x Treatment" interaction ($F(2,96) = 0.49$, $p = 0.613$, $\eta_p^2 = 0.010$) effect emerged.

Semantic verbal fluency results revealed no significant effects (all $p > 0.17$).

Praxis

ANOVA analysis on *Rey Osterrieth Complex Figure* scores showed no significant "Time", "Treatment", nor "time x Treatment" effects (all $p > 0.22$).

Generalization effects to non-trained cognitive functions induced by CT combined with both real and sham rTMS are depicted in the Supplementary Fig. 1 of the Appendix.

Mood

ANOVA analysis on *GDS* scores showed a trend toward significance for "Treatment" ($F(1,48) = 3.90$, $p = 0.054$, $\eta_p^2 = 0.075$) but no significant "Time" ($F(2,96 = 0.56$, $p = 0.572$, $\eta_p^2 = 0.012$) nor "Time x Treatment" interaction ($F(2,96) = 0.002$, $p = 0.998$, $\eta_p^2 = 0.000$) effect emerged.

Discussion

The purpose of the present study was to investigate the adjunctive beneficial effect of four weeks of lDLPFC high frequency rTMS combined with CT targeting face-name association memory in a sample of patients along the continuum of AD severity. We aimed at verifying whether the hypothesized add-on rTMS effect would be induced in the trained function (i.e., face-name associative memory) and whether it would generalize to other cognitive abilities.

First of all, our results proved the efficacy of the employed CT: four weeks of daily computerized CT sessions demonstrated to be effective in improving face-name associative memory. Importantly, when CT was primed by 20 Hz rTMS at lDLPFC, we observed an enhancement of the CT improvement, thus suggesting an add-on effect of rTMS in the trained face-name associative memory. Interestingly, the extent of the additional improvement induced by rTMS was influenced by disease severity and education. Less impaired and more educated patients showed a greater additional improvement in face-name associative memory, after real rTMS treatment in comparison to sham rTMS. A recent meta-analysis on the effects of rTMS as a cognitive enhancer in AD [21] revealed a significant effect of rTMS both in MCI and in AD patients. When considering face-name associative memory, our data partly confirm this finding, showing that rTMS effects (at least when rTMS was employed as an add-on treatment) were modulated by cognitive status. These results indicate a lower effectiveness of rTMS in enhancing cognition in more impaired patients. In this sense, the present findings adhere to the recommendation that rTMS treatments should be proposed as early as possible, before neuronal loss has disrupted cortical connections [57]. High frequency rTMS is thought to involve long term potentiation-like changes in synaptic strength, whose dysfunction is considered the key pathophysiological correlate of cognitive decline in AD [58] and an important predictor of disease severity [59]. In this sense, we may speculate that a worse cognitive impairment reflecting greater synaptic dysfunction somehow prevents rTMS from inducing any change in synaptic strength. More severe cognitive deterioration and poorer face-name association memory performance have been recently associated to an increase in long-distance effective connectivity between the lDLPFC and posterior regions [52]. A recent resting-state fMRI study [60] demonstrated that less activated baseline functional connectivity promotes a better therapeutic effect of rTMS protocol. In this framework, the beneficial effect found only in less impaired patients might be explained by the reduced activation of the targeted network that facilitates the process of reallocating resources towards task-positive networks under active use (i.e., those subserving face-name associative memory) [60].

Education is considered the major proxy of cognitive reserve. Higher cognitive reserve is thought to result not only in better cognitive performances, but also in aiding the recruitment of compensatory networks to act against the AD processes [61,62]. Accordingly, we may hypothesize that patients with higher education achievements benefited more from our adjunctive rTMS treatment thanks to their capacity to activate alternative brain's pathways in response to the stimulation. How cognitive reserve mediates rTMS effects is an intriguing but still unexplored topic which deserves further investigations.

The second effect obtained in this study involves what is usually defined as "generalization" (i.e., the beneficial effects on non-trained cognitive functions). We found a beneficial effect of CT combined with both sham and real rTMS on verbal and visuospatial memory (i.e., story recall, immediate and delayed recall of RAVLT, delayed recall of ROCF), attention (i.e., TMT-A), visuospatial reasoning (i.e., RCPM) and phonemic verbal fluency. Since an actual "not treated" group was missing as all the participants received 4 weeks of CT, we might also suppose that the improvement observed as a consequence of CT alone may be caused by a learning effect due to the repetition of the administered tests.

Crucially for the present work, an add-on generalization effect of real rTMS (combined with CT) was observed in spatial reasoning (RCPM). No other add-on rTMS effects were visible. Differently from a previous study, which reported a selective improvement in the delayed recall of RAVLT after an rTMS treatment targeting the precuneus in prodromal AD patients [63], our rTMS protocol did not induce a further amelioration in episodic memory. This discordant finding might be explained by the different target site and, conceivably, by the different stimulated functional network.

DLPFC is a functionally and structurally heterogeneous region of the brain and represents a key hub for episodic memory, executive functions and reasoning. DLPFC exhibit a "rich club" organization with highly interconnected nodes which show a strong tendency to connect with other highly connected nodes thus resulting in numerous between network connections [64]. In fact, DLPFC is a major cortical node of both DMN and FPN. Accordingly, Opitz and colleagues [19] identified three distinct DLPFC stimulation areas that differed according to the network that was affected by stimulation (DMN, FPN or both). Thus, targeting rTMS at DLPFC may promote interconnected networks activity and integration, which may be directly related to the observed multi-domain cognitive improvements [37]. Indeed, logical and relational reasoning, both assessed by the RCPM task, are supported by the dynamic interaction between prefrontal and parietal regions [65–67].

Face-name associative memory is a multifaceted function that requires several cognitive processes involving not only episodic and semantic memory, but also visuo-perceptual processes, and relies on a complex interplay between different brain networks [13]. Our results seem to provide evidence that the effect of rTMS are cognitive or site specific and independent from a generalized attentional enhancement. Although DLPFC represents a crucial area for executive functions, the neuropsychological battery administered in the present study overlooked frontal tasks (e.g., Stroop test, Frontal Assessment Battery, etc.) thus possibly failing to grasp additional generalization effects within this cognitive domain.

High frequency rTMS applied over the lDLPFC is also the recommended approach for the treatment of depression [33]. Our results showed no significant effect of rTMS on depressive symptoms, thus ruling out the possibility that the observed improvement was caused by mood improvement rather than by a genuine effect on cognitive functions.

To our knowledge this is the first study investigating the add-on effect of rTMS when combined with cognitive training on both trained and non-trained cognitive functions. In previous studies combining rTMS with CT [34–36], patients in the sham group did receive neither stimulation nor cognitive training, thus preventing to disentangle whether the reported beneficial effect was due to rTMS, CT or to their combination. Furthermore, they focused on general clinical measures as ADAS-cog or MMSE only, not allowing to explore the effect on trained cognitive functions nor to examine any generalization effect.

Despite the results of the present study appear promising, there are few weaknesses that need to be taken into account in their interpretation. One limitation is represented by the approach used to identify the target area of stimulation. Coil location was determined employing the 10–20 EEG system, which represents a coarse approach when stimulating high order multimodal association areas. However, at an anatomical level, we may reasonably presume that we were stimulating the DLPFC. Herwig and colleagues [68] demonstrated that F3 electrode position corresponds to the left DLPFC in about 90% of the subjects. Even if anatomical

landmarks have been consistently targeted across participants, the anatomo-functional relationships in the DLPFC are highly variable among individuals [19]. Furthermore, brain's functional architecture undergoes massive changes and networks' reorganization over the course of AD progression, thus hampering to identify the targeted network and ultimately increasing the inter-individual variability in response to rTMS. In future studies, the combination of stimulation techniques with single-subjects resting-state fMRI to map whole-brain networks connectivity might improve clinical efficacy of rTMS treatments by targeting the networks primarily affected by AD pathology [69].

Finally, we recognized that the lack of pathophysiological markers of AD (i.e., cerebrospinal fluid Amyloid beta 42 or amyloid positron emission tomography) prevented us from drawing any firm conclusion regarding the etiology underlying the cognitive deficits in our sample.

Conclusions

To our knowledge this was the first study employing rTMS to prime and enhance the efficacy of CT and to demonstrate the generalization of treatment effects beyond the trained cognitive function and the trained cognitive domain. The present results provide evidence suggesting the usefulness of rTMS as an add-on instrument to enhance face-name associative memory training effects and to induce a generalization to spatial reasoning in AD. Future studies combining rTMS with CT protocols focusing on different cognitive domains (e.g., executive functions) are needed to examine the beneficial effect of adjunctive rTMS more in depth. Furthermore, the present finding revealed that the extent of the rTMS add-on effect depends on the stage of the disease severity and on the education level of the patients. This finding is particularly significant in order to maximize treatments' effects, as patients with different degrees of cognitive impairment and cognitive reserve may benefit differently from rTMS, envisaging the potential of a personalized medicine approach. Longitudinal studies, with patients in a prodromal stage of AD and followed up for longer period of time, might address the key issue of whether rTMS treatments can delay the progression of the disease or even halt the conversion to overt AD.

CRediT authorship contribution statement

Chiara Bagattini: Project administration, Methodology, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Mara Zanni:** Resources, Investigation, Data curation, Writing - review & editing. **Federica Barocco:** Resources, Investigation, Writing - review & editing. **Paolo Caffarra:** Supervision, Writing - original draft, Writing - review & editing. **Debora Brignani:** Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Carlo Miniussi:** Conceptualization, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Carlo Alberto Defanti:** Project administration, Funding acquisition, Supervision, Writing - original draft, Writing - review & editing.

Declaration of competing interest

This work has not been published and has not been submitted for publication elsewhere while under consideration. The authors declare no potential conflict of interest.

Acknowledgements

This work was supported by Fondazione Europea Ricerca Biomedica (FERB Onlus). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. CB and CM have been supported by the projects of the Italian Ministry of Health Ricerca Finalizzata (RF-2013-02356444) and Ricerca Corrente 2019. We thank Marco Esposito for his assistance in manuscript editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.09.010.

References

[1] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–9. https://doi.org/10.1016/j.jalz.2011.03.008.
[2] Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133–42. https://doi.org/10.1212/wnl.56.9.1133.
[3] Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–94. https://doi.org/10.1111/j.1365-2796.2004.01388.x.
[4] Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for persons with mild to moderate dementia of the Alzheimer's or vascular type: a review. Alzheimer's Res Ther 2013;5:35. https://doi.org/10.1186/alzrt189.
[5] Buschert V, Bokde ALW, Hampel H. Cognitive intervention in Alzheimer disease. Nat Rev Neurol 2010;6:508–17. https://doi.org/10.1038/nrneurol.2010.113.
[6] Belleville S, Clément F, Mellah S, Gilbert B, Fontaine F, Gauthier S. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. Brain 2011;134:1623–34. https://doi.org/10.1093/brain/awr037.
[7] Clare L, Wilson BA, Carter G, Roth I, Hodges JR. Relearning face-name associations in early Alzheimer's disease. Neuropsychology 2002;16:538–47. https://doi.org/10.1037//0894-4105.16.4.538.
[8] Clare L, Woods RT, Moniz Cook ED, Orrell M, Spector A. Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev 2003:CD003260. https://doi.org/10.1002/14651858.CD003260.
[9] Davis RN, Massman PJ, Doody RS. Cognitive intervention in Alzheimer disease: a randomized placebo-controlled study. Alzheimer Dis Assoc Disord 2001;15:1–9. https://doi.org/10.1097/00002093-200101000-00001.
[10] Hampstead BM, Stringer AY, Stilla RF, Deshpande G, Hu X, Bacon Moore A, et al. Activation and effective connectivity changes following explicit memory training for face-name pairs in patients with mild cognitive impairment: a pilot study. Neurorehabilitation Neural Repair 2011;25:210–22. https://doi.org/10.1177/1545968310382424.
[11] Hampstead BM, Stringer AY, Stilla RF, Giddens M, Sathian K. Mnemonic strategy training partially restores hippocampal activity in patients with mild cognitive impairment. Hippocampus 2012;22:1652–8. https://doi.org/10.1002/hipo.22006.
[12] Cotelli M, Manenti R, Brambilla M, Petesi M, Rosini S, Ferrari C, et al. Anodal tDCS during face-name associations memory training in Alzheimer's patients. Front Aging Neurosci 2014;6:38. https://doi.org/10.3389/fnagi.2014.00038.
[13] Tak SH, Hong SH. Face-name memory in Alzheimer's disease. Geriatr Nurs 2014;35:290–4. https://doi.org/10.1016/j.gerinurse.2014.03.004.
[14] Elizabeth A Hoffman, Haxby James V, Gobbini M Ida. The distributed human neural system for face perception. Trends Cognit Sci 2000;4(6):223–33. https://doi.org/10.1016/s1364-6613(00)01482-0.
[15] Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239–59. https://doi.org/10.1007/BF00308809.
[16] Kumar S, Zomorrodi R, Ghazala Z, Goodman MS, Blumberger DM, Cheam A, et al. Extent of dorsolateral prefrontal cortex plasticity and its association with working memory in patients with Alzheimer disease. JAMA Psychiatry 2017;74:1266–74. https://doi.org/10.1001/jamapsychiatry.2017.3292.
[17] Kaufman LD, Pratt J, Levine B, Black SE. Executive deficits detected in mild Alzheimer's disease using the antisaccade task. Brain Behav 2012;2:15–21. https://doi.org/10.1002/brb3.28.

[18] Agosta F, Pievani M, Geroldi C, Copetti M, Frisoni GB, Filippi M. Resting state fMRI in Alzheimer's disease: beyond the default mode network. Neurobiol Aging 2012;33:1564–78. https://doi.org/10.1016/j.neurobiolaging.2011.06.007.
[19] Opitz A, Fox MD, Craddock CR, Colcombe S, Milham MP. An integrated framework for targeting functional networks via transcranial magnetic stimulation. Neuroimage 2016;127:86–96. https://doi.org/10.1016/j.neuroimage.2015.11.040.
[20] Birba A, Ibáñez A, Sedeño L, Ferrari J, García AM, Zimerman M. Non-invasive brain stimulation: a new strategy in mild cognitive impairment? Front Aging Neurosci 2017;9:1–13. https://doi.org/10.3389/fnagi.2017.00016.
[21] Chou Y, That VT, Sundman M. A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2019;86:1–10. https://doi.org/10.1016/j.neurobiolaging.2019.08.020.
[22] Gonsalvez I, Baror R, Fried P, Santarnecchi E, Pascual-Leone A. Therapeutic noninvasive brain stimulation in Alzheimer's disease. Curr Alzheimer Res 2016;13. https://doi.org/10.2174/1567205013666160930113907.
[23] Pini L, Manenti R, Cotelli M, Pizzini FB, Frisoni GB, Pievani M. Non-invasive brain stimulation in dementia: a complex network story. Neurodegener Dis 2018;18:281–301. https://doi.org/10.1159/000495945.
[24] Wang X, Mao Z, Ling Z, Yu X. Repetitive transcranial magnetic stimulation for cognitive impairment in Alzheimer's disease: a meta-analysis of randomized controlled trials. J Neurol 2019;267(3):791–801. https://doi.org/10.1007/s00415-019-09644-y.
[25] Lin Y, Jiang WJ, Shan PY, Lu M, Wang T, Li RH, et al. The role of repetitive transcranial magnetic stimulation (rTMS) in the treatment of cognitive impairment in patients with Alzheimer's disease: a systematic review and meta-analysis. J Neurol Sci 2019;398:184–91. https://doi.org/10.1016/j.jns.2019.01.038.
[26] Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125:1–57. https://doi.org/10.1016/j.clinph.2014.05.021.
[27] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120. https://doi.org/10.1016/j.clinph.2009.08.016. 2008–39.
[28] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015;126:1071–107. https://doi.org/10.1016/j.clinph.2015.02.001.
[29] Bortoletto M, Veniero D, Thut G, Miniussi C. The contribution of TMS–EEG coregistration in the exploration of the human cortical connectome. Neurosci Biobehav Rev 2015;49:114–24. https://doi.org/10.1016/j.neubiorev.2014.12.014.
[30] Hoogendam JM, Ramakers GMJ, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stimul 2010;3:95–118. https://doi.org/10.1016/j.brs.2009.10.005.
[31] Miniussi C, Rossini PM. Transcranial magnetic stimulation in cognitive rehabilitation. Neuropsychol Rehabil 2011;21:579–601. https://doi.org/10.1080/09602011.2011.562689.
[32] Miniussi C, Vallar G. Brain stimulation and behavioural cognitive rehabilitation: a new tool for neurorehabilitation? Neuropsychol Rehabil 2011;21:553–9. https://doi.org/10.1080/09602011.2011.622435.
[33] Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clin Neurophysiol 2020;131:474–528. https://doi.org/10.1016/j.clinph.2019.11.002.
[34] Rabey JM, Dobronevsky E, Aichenbaum S, Gonen O, Marton RG, Khaigrekht M. Repetitive transcranial magnetic stimulation combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: a randomized, double-blind study. J Neural Transm 2013;120:813–9. https://doi.org/10.1007/s00702-012-0902-z.
[35] Lee J, Choi BH, Oh E, Sohn EH, Lee YA. Treatment of Alzheimer's disease with repetitive transcranial magnetic stimulation combined with cognitive training: a prospective, randomized, double-blind, placebo-controlled study. J Clin Neurol 2016;12:57–64. https://doi.org/10.3988/jcn.2016.12.1.57.
[36] Sabbagh M, Sadowsky C, Tousi B, Agronin ME, Alva G, Armon C, et al. Effects of a combined transcranial magnetic stimulation (TMS) and cognitive training intervention in patients with Alzheimer's disease. Alzheimer's Dementia 2020;16:641–50. https://doi.org/10.1016/j.jalz.2019.08.197.
[37] Alcalá-Lozano R, Morelos-Santana E, Cortés-Sotres JF, Garza-Villarreal EA, Sosa-Ortiz AL, González-Olvera JJ. Similar clinical improvement and maintenance after rTMS at 5 Hz using a simple vs. complex protocol in Alzheimer's disease. Brain Stimul 2018;11:625–7. https://doi.org/10.1016/j.brs.2017.12.011.
[38] Solé-Padullés C, Bartrés-Faz D, Junqué C, Clemente IC, Molinuevo JL, Bargalló N, et al. Repetitive transcranial magnetic stimulation effects on brain function and cognition among elders with memory dysfunction. A randomized sham-controlled study. Cerebr Cortex 2006;16:1487–93. https://doi.org/10.1093/cercor/bhj083.
[39] Cotelli M, Calabria M, Manenti R, Rosini S, Zanetti O, Cappa SF, et al. Improved language performance in Alzheimer disease following brain stimulation. J Neurol Neurosurg Psychiatry 2011;82:794–7. https://doi.org/10.1136/jnnp.2009.197848.
[40] Devi G, Voss HU, Levine D, Abrassart D, Heier L, Halper J, et al. Open-label, short-term, repetitive transcranial magnetic stimulation in patients with Alzheimer's disease with functional imaging correlates and literature review. Am J Alzheimers Dis Other Demen 2014;29:248–55. https://doi.org/10.1177/1533317513517047.
[41] Drumond Marra HL, Myczkowski ML, Maia Memória C, Arnaut D, Leite Ribeiro P, Sardinha Mansur CG, et al. Transcranial magnetic stimulation to address mild cognitive impairment in the elderly: a randomized controlled study. Behav Neurol 2015;2015:1–13. https://doi.org/10.1155/2015/287843.
[42] Rutherford G, Lithgow B, Moussavi Z. Short and long-term effects of rTMS treatment on alzheimer's disease at different stages: a pilot study. J Exp Neurosci 2015;9:43–51. https://doi.org/10.4137/JEN.S24004.
[43] Ahmed M a, Darwish ES, Khedr EM, El Serogy YM, Ali AM. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. J Neurol 2012;259:83–92. https://doi.org/10.1007/s00415-011-6128-4.
[44] Balconi M. Dorsolateral prefrontal cortex, working memory and episodic memory processes: insight through transcranial magnetic stimulation techniques. Neurosci Bull 2013;29:381–9. https://doi.org/10.1007/s12264-013-1309-z.
[45] Haffen E, Chopard G, Pretalli JB, Magnin E, Nicolier M, Monnin J, et al. A case report of daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) as an adjunctive treatment for Alzheimer disease. Brain Stimul 2012;5:264–6. https://doi.org/10.1016/j.brs.2011.03.003.
[46] Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. fifth ed. New York: Oxford University Press, Inc.; 2012.
[47] McKhann GM, Drachman D, Folstein MF, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of Health and human services task force on Alzheimer's disease. Neurology 1984;34:939–44. https://doi.org/10.1212/wnl.34.7.939.
[48] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98. https://doi.org/10.1016/0022-3956(75)90026-6.
[49] Stokes MG, Chambers CD, Gould IC, Henderson TR, Janko NE, Allen NB, et al. Simple metric for scaling motor threshold based on scalp-cortex distance: application to studies using transcranial magnetic stimulation. J Neurophysiol 2005;94:4520–7. https://doi.org/10.1152/jn.00067.2005.
[50] Rossi S, Ferro M, Cincotta M, Ulivelli M, Bartalini S, Miniussi C, et al. A real electro-magnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). Clin Neurophysiol 2007;118:709–16. https://doi.org/10.1016/j.clinph.2006.11.005.
[51] Cotelli M, Calabria M, Manenti R, Rosini S, Maioli C, Zanetti O, et al. Brain stimulation improves associative memory in an individual with amnestic mild cognitive impairment. Neurocase 2012;18:217–23. https://doi.org/10.1080/13554794.2011.588176.
[52] Bagattini C, Mutanen TP, Fracassi C, Manenti R, Cotelli M, Ilmoniemi RJ, et al. Predicting Alzheimer's disease severity by means of TMS–EEG coregistration. Neurobiol Aging 2019;80:38–45. https://doi.org/10.1016/j.neurobiolaging.2019.04.008.
[53] Kirwan CB, Stark CEL. Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. Hippocampus 2004;14:919–30. https://doi.org/10.1002/hipo.20014.
[54] Sperling R, Chua E, Cocchiarella A, Rand-Giovannetti E, Poldrack R, Schachter DL, et al. Putting names to faces: successful encoding of associative memories activates the anterior hippocampal formation. Neuroimage 2003;20:1400–10. https://doi.org/10.1038/jid.2014.371.
[55] Westerberg CE, Voss JL, Reber PJ, Paller KA. Medial temporal contribution to successful face-name learning. Hum Brain Mapp 2012;33:1717–26. https://doi.org/10.1038/jid.2014.371.
[56] Cotelli M, Manenti R, Zanetti O, Miniussi C. Non-pharmacological intervention for memory decline. Front Hum Neurosci 2012;6:1–17. https://doi.org/10.3389/fnhum.2012.00046.
[57] Weiler M, Stieger KC, Long JM, Rapp PR. Transcranial magnetic stimulation in Alzheimer's disease: are we ready? eNeuro 2020;7. https://doi.org/10.1523/ENEURO.0235-19.2019.
[58] Terry RD, Masliah E, Salmon DP, Butters N, Deteresa R, Hill R, et al. Phisical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991;30(4):572–80. https://doi.org/10.1002/ana.410300410.
[59] Motta C, Di Lorenzo F, Ponzo V, Pellicciari MC, Bonnì S, Picazio S, et al. Transcranial magnetic stimulation predicts cognitive decline in patients with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2018;89:1237–42. https://doi.org/10.1136/jnnp-2017-317879.
[60] Cui H, Ren R, Lin G, Zou Y, Jiang L, Wei Z, et al. Repetitive transcranial magnetic stimulation induced hypoconnectivity within the default mode network yields cognitive improvements in amnestic mild cognitive impairment: a randomized controlled study. J Alzheim Dis 2019;69:1137–51. https://doi.org/10.3233/JAD-181296.
[61] Amieva H, Mokri H, Le Goff M, Meillon C, Jacqmin-Gadda H, Foubert-Samier A, et al. Compensatory mechanisms in higher-educated subjects with

Alzheimer's disease: a study of 20 years of cognitive decline. Brain 2014;137:1167–75. https://doi.org/10.1093/brain/awu035.
[62] Menardi A, Pascual-Leone A, Fried PJ, Santarnecchi E. The role of cognitive reserve in Alzheimer's disease and aging: a multi-modal imaging review. J Alzheim Dis 2018;66:1341–62. https://doi.org/10.3233/JAD-180549.
[63] Koch G, Bonnì S, Pellicciari MC, Casula EP, Mancini M, Esposito R, et al. Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease. Neuroimage 2018;169:302–11. https://doi.org/10.1016/j.neuroimage.2017.12.048.
[64] van den Heuvel MP, Sporns O. Rich-club organization of the human connectome. J Neurosci 2011;31:15775–86. https://doi.org/10.1523/JNEUROSCI.3539-11.2011.
[65] Prado J, Der Henst JB Van, Noveck IA. Recomposing a fragmented literature: how conditional and relational arguments engage different neural systems for deductive reasoning. Neuroimage 2010;51:1213–21. https://doi.org/10.1016/j.neuroimage.2010.03.026.
[66] Houde O, Zago L, Mellet E, Moutier S, Pineau A, Mazoyer B, et al. Shifting from the perceptual brain to the logical brain: the neural impact of cognitive inhibition training. J Cognit Neurosci 2000;12:721–8. https://doi.org/10.1162/089892900562525.
[67] Momi D, Neri F, Coiro G, Smeralda C, Veniero D, Sprugnoli G, et al. Cognitive enhancement via network-targeted cortico-cortical associative brain stimulation. Cerebr Cortex 2020;30:1516–27. https://doi.org/10.1093/cercor/bhz182.
[68] Herwig U, Satrapi P, Schönfeldt-Lecuona C. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 2003;16:95–9. https://doi.org/10.1023/B:BRAT.0000006333.93597.9d.
[69] Cocchi L, Zalesky A. Personalized transcranial magnetic stimulation in psychiatry. Biol Psychiatry Cogn Neurosci Neuroimaging 2018;3:731–41. https://doi.org/10.1016/j.bpsc.2018.01.008.