General Psychiatry

Effects of a periodic intermittent theta burst stimulation in Alzheimer's disease

Xingqi Wu ,[1,2,3,4] Yibing Yan,[1,3,4] Panpan Hu,[1,2,3,4] Lu Wang ,[1,3,4] Yue Wu,[1,3,4,5] Pan Wu,[1,3,4] Zhi Geng,[1,3,4] Guixian Xiao,[1,3,4,5] Shanshan Zhou,[1,3,4] Gongjun Ji ,[1,2,3,4] Bensheng Qiu,[6] Ling Wei,[1,3,4] Yanghua Tian ,[1,2,3,4,5,7] Hesheng Liu,[8] Kai Wang [1,2,3,4,7]

To cite: Wu X, Yan Y, Hu P, *et al*. Effects of a periodic intermittent theta burst stimulation in Alzheimer's disease. *General Psychiatry* 2024;**37**:e101106. doi:10.1136/gpsych-2023-101106

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gpsych-2023-101106).

XW, YY and PH are joint first authors.

Received 09 May 2023
Accepted 07 November 2023

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Dr Kai Wang;
wangkai1964@126.com

Dr Hesheng Liu;
liuhe@musc.edu

ABSTRACT

Background Previous studies have demonstrated that excitatory repetitive transcranial magnetic stimulation (rTMS) can improve the cognitive function of patients with Alzheimer's disease (AD). Intermittent theta burst stimulation (iTBS) is a novel excitatory rTMS protocol for brain activity stimulation with the ability to induce long-term potentiation-like plasticity and represents a promising treatment for AD. However, the long-term effects of iTBS on cognitive decline and brain structure in patients with AD are unknown.

Aims We aimed to explore whether repeating accelerated iTBS every three months could slow down the cognitive decline in patients with AD.

Methods In this randomised, assessor-blinded, controlled trial, iTBS was administered to the left dorsolateral prefrontal cortex (DLPFC) of 42 patients with AD for 14 days every 13 weeks. Measurements included the Montreal Cognitive Assessment (MoCA), a comprehensive neuropsychological battery, and the grey matter volume (GMV) of the hippocampus. Patients were evaluated at baseline and after follow-up. The longitudinal pipeline of the Computational Anatomy Toolbox for SPM was used to detect significant treatment-related changes over time.

Results The iTBS group maintained MoCA scores relative to the control group (t=3.26, p=0.013) and reduced hippocampal atrophy, which was significantly correlated with global degeneration scale changes. The baseline Mini-Mental State Examination (MMSE) score, apolipoprotein E genotype and Clinical Dementia Rating were indicative of MoCA scores at follow-up. Moreover, the GMV of the left (t=0.08, p=0.996) and right (t=0.19, p=0.977) hippocampus were maintained in the active group but significantly declined in the control group (left: t=4.13, p<0.001; right: t=5.31, p<0.001). GMV change in the left (r=0.35, p=0.023) and right (r=0.36, p=0.021) hippocampus across the intervention positively correlated with MoCA changes; left hippocampal GMV change was negatively correlated with global degeneration scale (r=−0.32, p=0.041) changes.

Conclusions DLPFC-iTBS may be a feasible and easy-to-implement non-pharmacological intervention to slow down the progressive decline of overall cognition and quality of life in patients with AD, providing a new AD treatment option.

Trial registration number NCT04754152.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have demonstrated that excitatory repetitive transcranial magnetic stimulation (rTMS) can improve cognitive function in patients with Alzheimer's disease (AD).

⇒ Recently, Koch *et al* found that precuneus-20-Hz rTMS could reduce the progression of cognitive decline for 24 weeks.

WHAT THIS STUDY ADDS

⇒ Our study makes a significant contribution to the literature because the findings indicate that (1) repeating intermittent theta burst stimulation (iTBS) of the left dorsolateral prefrontal cortex (DLPFC) every three months can slow down the progressive decline of global cognition in patients with AD; (2) significant differences in treatment effects were found between apolipoprotein E ε4 carriers and non-carriers and (3) Clinical Dementia Rating and Mini-Mental State Examination at baseline can aid in assessing patient eligibility for treatment with iTBS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study confirms, for the first time, that DLPFC-iTBS is a feasible and easy-to-implement non-pharmacological intervention to slow down the progressive decline of overall cognition and quality of life in patients with AD, providing a new approach for future AD treatments.

INTRODUCTION

Alzheimer's disease (AD), one of the most disabling, lethal and burdensome diseases of this century, is characterised by progressive cognitive impairment.[1] Regrettably, there are no effective treatments to date. Moreover, up to one-third of patients with AD show a rapid cognitive decline (RCD), with a worse prognosis, a greater impact on families and limited treatment options. Therefore, there is growing interest in developing novel non-pharmaceutical therapies to improve clinical symptoms in patients with AD.

Recent research indicates that impaired neuroplasticity could be associated with

AD pathogenesis and might be related to the progressive cognitive decline in AD.[1] Accordingly, therapeutic modulation of neuroplasticity in some critical areas, such as the dorsolateral prefrontal cortex (DLPFC), might alleviate, delay or halt the progressive clinical deterioration in AD.[2] Repetitive transcranial magnetic stimulation (rTMS) induces local neuronal depolarisation. This modifies the excitability and plasticity of cortical neurons by repetitively delivering a high-intensity magnetic field over a target area of the brain via the scalp. rTMS may impact neuroplasticity in AD and is considered a novel strategy for the treatment of AD.[3 4] Administering a single session of rTMS to the DLPFC can positively influence cognitive function in older participants and patients with AD.[5] More importantly, exposing individuals to multiple rTMS sessions over an extensive period (ie, several weeks) could have long-lasting effects on the modulation of plasticity and behaviour.[6] Recently, Koch *et al* found that rTMS targeting the default mode network may slow down cognitive and functional decline in AD, which could represent a novel therapeutic approach for patients with AD.[7]

Intermittent theta burst stimulation (iTBS) is an accelerated excitatory rTMS parameter consistent with endogenous oscillations. Compared with conventional rTMS, iTBS of the left DLPFC can improve the induction of neuroplasticity and cognitive processing more efficiently.[8] Furthermore, we have previously reported that 2 weeks of left DLPFC-iTBS broadly ameliorated symptoms and improved cognition in patients with AD; the effects were sustained for >2 months after treatment cessation.[9 10] The immediate ameliorating effects of left DLPFC-iTBS on cognition may be achieved by changing the functional connection between the left DLPFC and the brain regions in the executive control network.[11] Previous studies have also demonstrated that high frequency (HF)-rTMS and iTBS on the left DLPFC could alleviate cognitive deficits in patients with AD.[4 9 10 12] Similarly, single-session tractography-guided iTBS can modulate the hippocampal network, enhance associative memory function in individuals with prestage AD and alleviate the pathological changes of AD in mice.[13 14] However, it remains unclear whether multiple iTBS sessions may delay cognitive decline in patients with AD.

We undertook this study to explore whether repeating the iTBS protocol every three months could slow down the cognitive decline in patients with AD. Numerous studies have shown that the hippocampus plays an important role in the pathogenesis and progression of AD.[15 16] Structural magnetic resonance imaging (sMRI) studies have shown that hippocampal volume in patients with AD is significantly reduced, which is closely related to cognitive functions such as memory.[16] Previous studies have found that a single session of iTBS therapy can improve the white matter connectivity between the superficial stimulation site and the hippocampus in patients with cognitive impairment.[13] However, the long-term effects of regular iTBS stimulation on hippocampal volume remain unknown. Hence, we performed sMRI to elucidate the mechanism underlying the effects of iTBS.

METHODS

Study protocol clearances, patient consent and registration

On 21 April 2021, the first patient was admitted to this study. On 27 October 2021, the final patient was admitted to the study. By 31 December 2022, all follow-ups were completed. The study was registered with ClinicalTrials.gov (NCT04754152).

Randomisation, allocation and masking

This randomised and assessor-blinded clinical trial assessed the long-term efficacy of regular image-navigational iTBS among patients with AD over one year. Participants were randomised 1:1 in a double-blind manner, using a balanced random assignment, to the active or control group. In the active group, following baseline evaluation (T0, week 0), they received active iTBS treatment over the left DLPFC for 14 consecutive days, and the assessments were conducted within one week after completion of the therapy (online supplemental figure 1). Twelve weeks after completion of the assessment, the second iTBS session was adopted; all patients took cholinesterase inhibitors at stable dosages. The control group was only given medication and regular remote health instruction, and the cognitive assessment was performed at weeks 4 (T1), 19 (T2), 34 (T3) and 49 (T4), which was at the same time as the iTBS group. Patients were randomly assigned by LWang, who was not involved in the examinations or stimulation. The assessor for each subject was a permanent staff member.

Physicians and researchers performed rTMS (YY, YW) and randomisation (LWang) without interacting with patients. Assessors (ZG, GX) were blinded to the treatment process until the completion of the study. To achieve a blind design, patients and their caregivers were instructed not to discuss their treatment assignment with attending physicians or other patients. After the 1-year follow-up, all participants were asked whether they received effective treatment by questionnaire.

Study participants

Patients with AD were recruited from the outpatients of the Memory Clinic of the First Affiliated Hospital of Anhui Medical University in Hefei, China. The definitive diagnosis was made by three senior doctors: SZ, PH and KW.

The inclusion criteria were as follows: (1) satisfaction with the criteria for AD according to the National Institute of Aging and Alzheimer's Association; (2) a Mini-Mental State Examination (MMSE) score of 10–27; (3) a Clinical Dementia Rating (CDR) score of 0.5–2; (4) receipt of a stable dose of donepezil (5 mg) for at least 3 months before randomisation and until completion of the follow-up period; (5) age ≥50 years; (6) rTMS-naïve

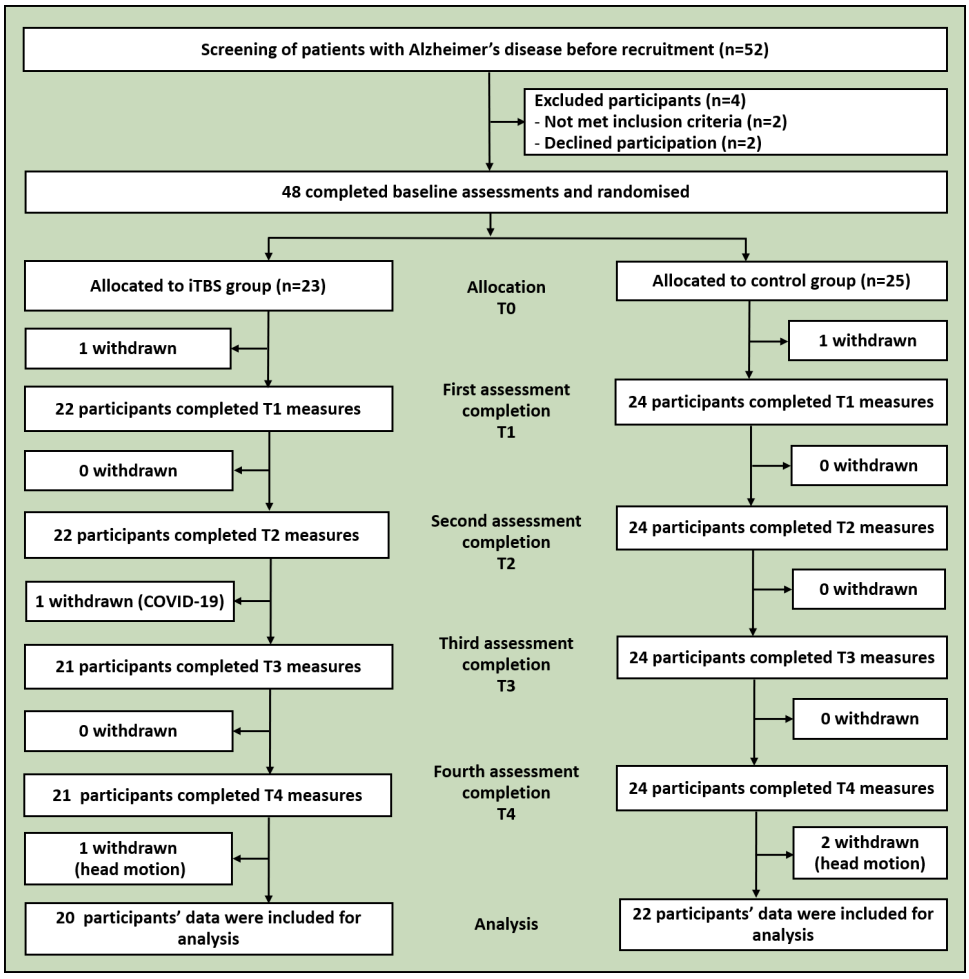

Figure 1 Study flowchart. COVID-19, coronavirus disease 2019; iTBS, intermittent theta burst stimulation.

status and (7) presence of cerebrospinal fluid biomarkers of AD (amyloid and tau) pathology.

The exclusion criteria were: (1) signs or test results suggestive of non-AD pathology; (2) a history of seizures or a close relative with a history of seizures; (3) a history of neurological conditions; (4) focal brain lesions on T1 or T2 images; (5) iatrogenic implants, such as a pacemaker or deep brain stimulator.

Study interventions: iTBS with image navigation

Treatment comprised three cycles of left DLPFC-iTBS on each treatment day, separated by 15 min intervals (total: 1800 pulses/day), for 14 consecutive days at 70% of the resting motor thresholds. The MAGSTIM Rapid^2 variant with a figure-of-eight coil supplied the iTBS (Magstim, Oxford, UK). In the frameless neuro-navigation system, the coil was positioned above the left DLPFC, which was located using the Montreal Neurological Institute and Hospital (MNI) coordinate (MNI coordinates: −38, 44, 26) in the frameless neuro-navigation system (Brainsight; Rogue Research, Montreal, Canada). Treatment was administered every 3 months at intervals determined per a previous study.[10] Details of the treatment are provided in the online supplemental materials.

Patients in the control group received a stable dose of cholinesterase inhibitors and general management, including disease education, training of the patients' family caregivers to manage the patients' daily lives and measurement of the rest motor threshold every 13 weeks, but no iTBS treatment.

MRI data

Data acquisition

For every patient, structural MRI details were collected at baseline and after the 1-year follow-up (GX, BQ). MRI scanning was performed using 3.0 T MRI scanners (Discovery GE 750, General Electric, Waukesha, Wisconsin, USA) at the University of Science and Technology of China. For each participant, a three-dimensional high-resolution magnetisation-prepared rapid gradient echo pulse sequence was used with an isotropic spatial resolution of 1 mm, which was acquired using the following parameters: repetition/echo time=8.16/3.18 ms, flip angle=12°, no intersection gap and 188 sections.

Volumetric analysis of the hippocampus

Grey matter volumetric analysis of the hippocampus was performed. We used the Statistical Parametric Mapping

Table 1 Baseline characteristics of patients who completed the treatment

Measures	Active (n=20)	Control (n=22)	t/Z/χ^2	P value
Demographic characteristics				
Age (year)	66.80 (8.84)§	65.32 (7.31)§	0.59*	0.556
Sex (male/female)	6/14	7/15	0.02†	0.899
Education years	10.25 (3.34)§	10.00 (3.32)§	−0.47‡	0.640
Hachinski ischaemic score	1.75 (0.64)§	1.68 (0.72)§	−0.54‡	0.592
ApoE ε4 carrier (%)	14/6 (70.00%)	16/6 (72.72%)	0.04†	0.845
Hypertension (%)	1/19 (5.00%)	1/21 (4.55%)	0.01†	0.945
Diabetes mellitus (%)	1/19 (5.00%)	1/21 (4.55%)	0.01†	0.945
Aβ1–42	565.5 (211.96)§	513.99 (170.14)§	0.87*	0.388
Aβ1–42/Aβ1–40	0.06 (0.02)§	0.06 (0.02)§	0.32*	0.751
Tau181	141.03 (33.20)§	128.44 (37.47)§	1.15*	0.258
Total tau	629.99 (218.77)§	582.55 (185.64)§	0.76*	0.452
Baseline scores on primary outcomes				
Montreal Cognitive Assessment	15.05 (5.85)§	15.64 (4.50)§	−0.37*	0.716
Baseline scores on clinical outcome measures—secondary outcomes				
Mini-Mental State Examination	21.35 (5.40)§	21.18 (3.91)§	0.12*	0.908
Hamilton Depression Rating Scale	4.40 (2.60)§	4.82 (4.58)§	−0.77‡	0.443
Neuropsychiatric Inventory	5.10 (6.90)§	4.73 (3.73)§	−0.48‡	0.628
Activities of Daily Living Scale	26.15 (4.83)§	25.86 (4.75)§	0.19*	0.847
Clinical Dementia Rating	0.83 (0.37)§	0.80 (0.37)§	−0.27‡	0.790
Global Degeneration Scale	3.60 (0.68)§	3.50 (0.60)§	−0.31‡	0.754
AVLT-Immediate	3.38 (1.76)§	3.59 (2.50)§	−0.27‡	0.791
AVLT-Delay	2.10 (3.11)§	1.32 (2.63)§	−0.24‡	0.811
AVLT-Recognition	12.25 (2.17)§	12.00 (4.16)§	−0.97‡	0.334
Digital Span Test-Forward	5.70 (1.22)§	5.68 (1.21)§	−0.43‡	0.671
Digital Span Test-Backward	3.20 (1.01)§	3.64 (1.26)§	−0.56‡	0.579
Clock Drawing Test	2.05 (1.23)§	2.27 (1.20)§	−0.43‡	0.667
Boston Naming Test	18.15 (4.55)§	19.00 (5.18)§	−0.56*	0.577
Verbal Fluency Test-Semantic	10.35 (4.26)§	10.64 (4.12)§	−0.06‡	0.950
Verbal Fluency Test-Letter	3.90 (2.31)§	3.55 (2.61)§	−0.01‡	0.990
GMV of hippocampus				
Hippocampus left	0.33 (0.04)§	0.31 (0.05)§	1.74	0.166
Hippocampus right	0.31 (0.05)§	0.29 (0.05)§	1.58	0.223

*Two-sample t-test.
†χ^2 test.
‡Mann-Whitney U test.
§Values in brackets indicate SD.
ApoE, apolipoprotein E; AVLT, Chinese version of the auditory verbal learning test; GMV, grey matter volume; SD, standard deviation.

analysis package (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) together with the Computational Anatomy Toolbox for SPM (CAT12, http://www.neuro.uni-jena.de/cat/) for structural data analyses. Data were processed according to the longitudinal processing pipeline, as implemented in CAT12. In brief, each participant's original T1 image was spatially normalised and segmented into grey and white matter and cerebrospinal fluid. All models were adjusted for age, sex and total intracranial volume. After data preprocessing, the modulated normalised grey matter volume (GMV) was smoothed using an 8 mm full-width half-maximum Gaussian kernel. Following the processing guideline, we adopted the anatomical automatic labelling-based structural region of interest (ROI) method for the *ex vivo* measurement of each individual ROI signal, and the volume of the bilateral hippocampus was extracted

and compared across groups using a linear mixed-effect model.

Primary and secondary outcomes

The Montreal Cognitive Assessment (MoCA, Beijing version) score was the primary outcome, and it was measured at baseline (T0) and within one week of the completion of each treatment cycle (T1, T2, T3 and T4).

The neuropsychology assessment score, estimated simultaneously, was the main secondary outcome, and the ratio of RCD during the 1-year follow-up period in each group was another secondary outcome. The RCD was defined as a greater-than-expected loss in MMSE cognitive performance (≥3 points per year).[17]

Throughout the trial, participants self-reported adverse events, such as sleep disturbances, unpleasant scalp sensations, twitching eyelids, tinnitus or epileptic seizures.

Neuropsychological assessments included the MMSE, Hamilton Depression Rating Scale (HDRS), Neuropsychiatric Inventory (NPI), CDR, Activities of Daily Living (ADL) Scale, Global Deterioration Scale (GDS), the Chinese version of the Auditory Verbal Learning Test (AVLT), Digital Span Test (forward/backward (DST-F/B)), Clock-Drawing Test (CDT), Boston Naming Test (BNT) and Verbal Fluency Test-semantic/letter (VFT-S/L).[18]

Statistical analyses

Baseline and treatment effectiveness

The χ^2 test was used to compare categorical variables, and the t-test or Mann-Whitney U test was used for continuous variables. Linear mixed-effect models nested among participants were used to analyse treatment outcomes. Sidak's multiple comparison test was employed for post hoc analysis.

Correlation and regression analysis

The relationships between the clinical variables and changes in the MoCA score were analysed using Pearson's or Spearman's correlation coefficient analysis according to the data distribution. We used a multivariable linear regression model with normalised MoCA changes after 1 year of follow-up as the dependent variable and baseline assessments as the independent factors. We defined a normalised change as the percentage difference between post-treatment and baseline results.

Using logistic regression, protective predictors of RCD were identified, with clinical features as independent variables. The outcomes of rTMS therapy (RCD or non-RCD) were used as dependent variables.

Correlation analyses between the GMV change in the hippocampus and the normalised neuropsychological score change at the 1-year follow-up were performed to explore a potential neural mechanism for the cognitive functional maintenance induced by iTBS.

Effects of apolipoprotein E ε4

Linear mixed-effect models with time (T0, T1, T2, T3 and T4) as within-subject factors and apolipoprotein E (ApoE) ε4 carrier/non-carrier status as between-subject factors were used to explore the effects of ApoE ε4 on rTMS treatment. Sidak's multiple comparison test was employed for post hoc analysis.

IBM SPSS Statistics V.26 (IBM; Armonk, New York, USA) and GraphPad Prism V.8.0 were used for all analyses and visualisation. Cohen's d and η^2 were reported as statistical effects. A significance threshold of 0.05 (two-tailed tests) was used in all hypothesis tests.

RESULTS

Characteristics of participants

Forty-eight of the 52 patients who completed the screening process were randomly assigned to undergo active iTBS (n=23) or control therapy (n=25). Forty-five patients completed the follow-up. Three patients were exempted from the analysis due to head motion in MRI scanning (figure 1).

Baseline measures

Demographics, neuropsychological evaluations and comorbidities, that is, ApoE ε4 carrier, hypertension and diabetes, did not differ between the active and control groups at baseline (table 1).

Primary outcome

Based on the MoCA scores, there was a time (T0, T1, T2, T3 and T4) and group (active and control) interaction effect ($F_{(4,160)}$=25.22; p<0.001). MoCA scores were maintained, or demonstrated a numerical improvement, in the active group (from 15.05 (5.85) to 18.05 (7.60); t=4.29; p=0.004; effect size=1.36; 95% confidence interval (CI): −0.62 to 1.92), but they showed a significant decline in the control group (from 15.64 (4.50) to 11.50 (5.01); t=9.55; p<0.001; effect size=2.88; 95% CI: 1.82 to 3.92) at T4 (table 2, figure 2A). At T4, after one year of follow-up, the active group showed significantly higher MoCA scores than the control group (mean difference=6.55; t=3.26; p=0.013; effect size=1.01; 95% CI: 0.35 to 1.65) (table 2, figure 2A). The RCD ratio in the active group was significantly lower than that in the control groups (15.00% vs 50.00%; χ^2=5.78; p=0.016) (figure 2B) (more details in online supplemental tables e1–e5).

Furthermore, we found that unlike the control group (t=8.40; p<0.001), the active group (t=0.07; p=1.000) showed no difference in MoCA scores between T1 and T4 (more details in online supplemental table e6).

Symptom measures

For symptom measures, group (active and control) and time (T0, T1, T2, T3 and T4) interaction effects were observed in the MMSE ($F_{(4,160)}$=15.90, p<0.001), ADL ($F_{(4,160)}$=8.04, p<0.001), HDRS ($F_{(4,160)}$=7.02, p<0.001), NPI ($F_{(4,160)}$=5.39, p=0.001) and GDS ($F_{(4,160)}$=6.42, p<0.001) scores (table 2, online supplemental table e1). All symptoms were better in the active group than the control group following treatment at T4, except for CDR ($t_{(2,40)}$=1.14, p=0.779) and NPI ($t_{(2,40)}$=2.68, p=0.057) (online supplemental table e5).

Table 2 Estimated mean score and effect sizes in primary and secondary outcome variables

	Time×Group*			Scores after follow-up	
	$F_{(4,160)}$	FDR-P	η^2	Active (n=20)	Control (n=22)
Montreal Cognitive Assessment	25.22	<0.001	0.39	18.05 (7.60)	11.50 (5.01)
Mini-Mental State Examination	15.90	<0.001	0.28	22.65 (6.01)	17.32 (5.92)
Hamilton Depression Rating Scale	7.02	<0.001	0.15	2.10 (1.52)	5.50 (4.79)
Neuropsychiatric Inventory	5.39	0.001	0.12	2.10 (3.99)	7.59 (8.64)
Activities of Daily Living Scale	8.04	<0.001	0.17	25.20 (4.80)	32.27 (9.06)
Clinical Dementia Rating	2.30	0.064	0.05	0.90 (0.60)	1.11 (0.62)
Global Degeneration Scale	6.42	<0.001	0.14	3.50 (0.89)	4.09 (0.68)
AVLT-Immediate	4.33	0.003	0.10	4.55 (2.85)	2.20 (2.34)
AVLT-Delay	2.55	0.046	0.06	2.30 (3.16)	0.73 (2.66)
AVLT-Recognition	5.74	<0.001	0.13	13.42 (1.30)	9.55 (4.33)
Digital Span Test-Forward	7.26	<0.001	0.15	5.80 (1.01)	4.36 (1.22)
Digital Span Test-Backward	15.72	<0.001	0.28	3.80 (1.36)	1.91 (1.48)
Clock Drawing Test	5.68	0.001	0.12	2.40 (1.27)	1.50 (1.01)
Boston Naming Test	4.00	0.005	0.09	16.75 (3.67)	14.05 (6.73)
Verbal Fluency Test-Semantic	3.48	0.011	0.08	11.10 (2.40)	9.32 (4.54)
Verbal Fluency Test-Letter	1.76	0.140	0.04	3.95 (2.48)	2.82 (2.40)
Hippocampus left	8.48	0.011	0.17	0.33 (0.05)	0.30 (0.05)
Hippocampus right	12.43	0.007	0.17	0.31 (0.05)	0.27 (0.05)

Values in brackets indicate SD. P values are FDR corrected.
*Interaction effect in linear mixed-effect models indicating outcome changes (from baseline to T1, T2, T3 and T4) between groups (active and control).
AVLT, Chinese version of the auditory verbal learning test; FDR, false discovery rate; SD, standard deviation.

Multidomain cognition tests

For multidomain cognition tests, significant group×time interaction effects were observed in the AVLT-Immediate ($F_{(4,160)}$=4.33, p=0.003)/Delay ($F_{(4,160)}$=2.55, p=0.046)/Recognition ($F_{(4,160)}$=5.74, p<0.001), DST-F ($F_{(4,160)}$=7.26, p<0.001)/B ($F_{(4,160)}$=15.72, p<0.001), CDT ($F_{(4,160)}$=5.68, p=0.001), BNT ($F_{(4,160)}$=4.00, p=0.005) and VFT-S scores ($F_{(4,160)}$=3.48, p=0.011) (table 2). Most tests (AVLT-Immediate/Recognition and DST-F/B) revealed better performance in the active group than the control group at T4 (online supplemental table e5).

Prediction of MoCA improvements with baseline clinical variables

In the active group (β=0.76, t=13.41, p<0.001), the baseline MMSE scores (β=0.19, t=2.85, p=0.007), baseline CDR scores (β=−0.22, t=−3.64, p<0.001) and ApoE ε4 carrier statuses (β=−0.33, t=−5.50, p=0.001) significantly predicted MoCA changes at T4, according to multivariate linear regression (R^2=0.52; F=9.60; p<0.001). However, age, sex, education, family history, Hachinski ischaemic score and baseline MoCA, NPI, ADL, HDRS, GDS, AVLT, DST, CDT, BNT and VFT scores did not (t=−1.88–1.33, p=0.068–0.909, online supplemental table e7).

Efficiency of prevention of RCD

Logistic regression showed that no iTBS treatment (odds ratio (OR): 13.32; 95% CI: 1.62 to 109.33; p=0.016) and ApoE ε4 carrier status (OR: 11.58; 95% CI: 1.00 to 133.66; p=0.050) at baseline were risk factors for RCD (online supplemental table e8). In other words, long-term regular rTMS was an effective protective factor for preventing RCD.

Correlations between clinical variables

There was no significant (r=−0.12, p=0.616) correlation between MoCA changes and HDRS changes at T4. However, MoCA changes at T4 and ApoE ε4 carrier status (r=−0.72, p<0.001) and changes in GDS (r=−0.45, p=0.048) at T4 were significantly correlated (online supplemental table e9).

Multivariate linear regression (R^2=0.81; F=57.73; p<0.001) showed that the active group (β=0.63, t=7.87, p<0.001), ApoE ε4 carrier status (β=−0.34, t=−4.53, p<0.001) and changes in ADL (β=−0.26, t=−3.03, p=0.004) could predict MoCA changes at T4, although changes in MMSE, NPI, HDRS, CDR, GDS, AVLT, DST, CDT, BNT and VFT scores did not (online supplemental table e10).

Volumetric analysis of the hippocampus

At the end of the follow-up period, there was a significant group×time interaction for hippocampal GMV (table 2,

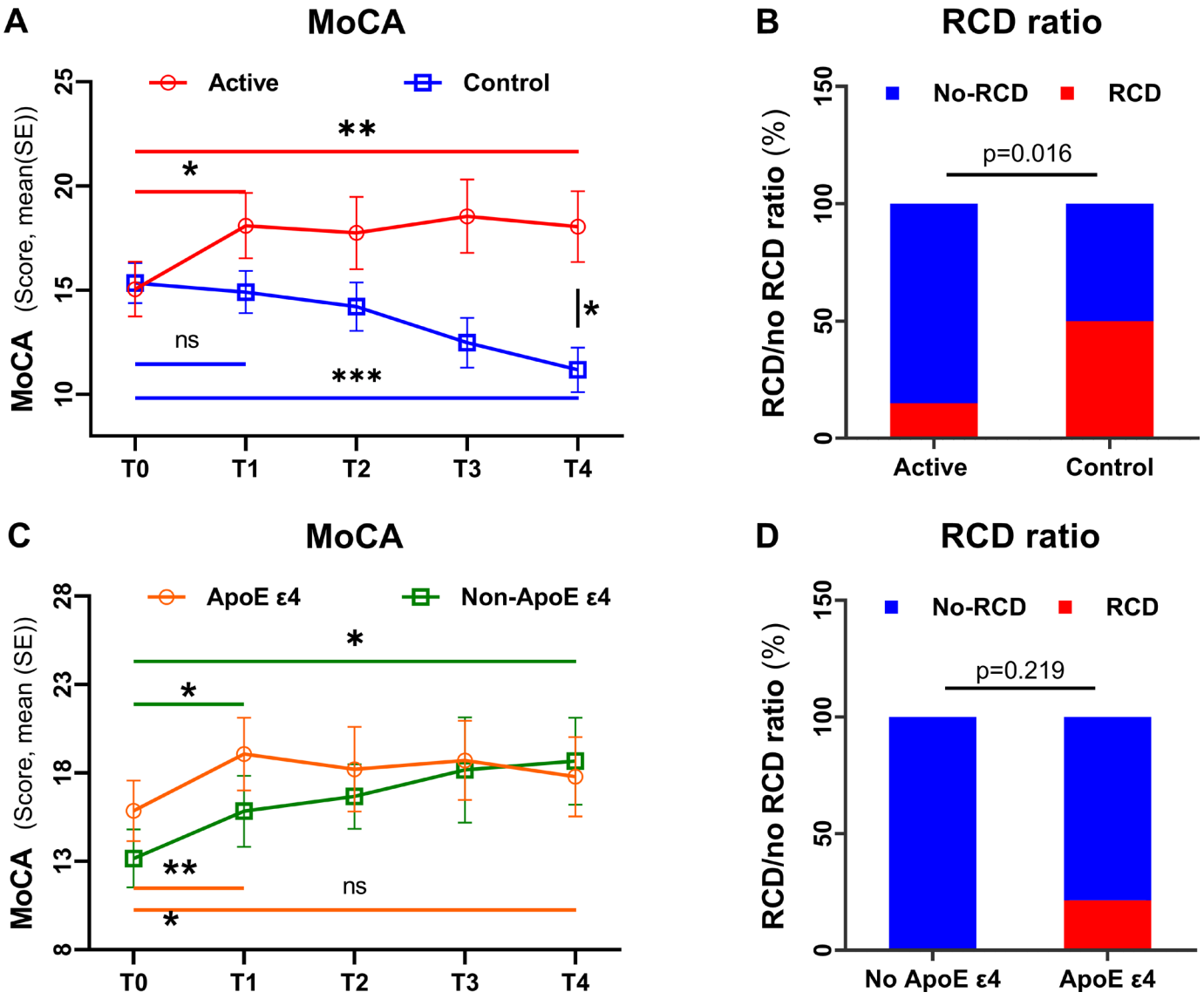

Figure 2 Long-term effects of iTBS treatment in patients with AD and the heterogeneity between ApoE ε4 carriers and non-ApoE ε4 carriers. The active group showed well-maintained MoCA scores (A; mean (SE)) and a lower RCD ratio (B; %) than the control group at the 1-year follow-up. The MoCA of the active group but not the control group was significantly improved at T1; the MoCA score of the active group was better than that of the control group at T4, but there was no difference at T0. The non-ApoE ε4-carrier group showed significantly improved MoCA scores at T1 and at the end of 1 year; the ApoE ε4-carrier group showed well-maintained MoCA scores at the end of 1 year (C; mean (SE)). The MoCA score of both ApoE ε4 carriers and non-ApoE ε4 carriers was significantly improved at T1. The non-ApoE ε4-carrier group showed a lower RCD ratio than the ApoE ε4-carrier group after the 1-year follow-up, but it was not significant (D). AD, Alzheimer's disease; ApoE, apolipoprotein E; MoCA, Montreal Cognitive Assessment; ns, not significant; RCD, rapid cognitive decline; iTBS, intermittent theta burst stimulation. *p<0.05; **p<0.01;***p<0.001.

figure 3A). Furthermore, left (t=0.08, p=0.996, figure 3B) and right (t=0.19, p=0.977, figure 3C) hippocampal GMV were maintained in the active group but significantly declined in the control group (left: t=4.13, p<0.001, figure 3B; right: t=5.31, p<0.001, figure 3C). Hippocampal GMV in the control group was smaller than that in the active group at T4 (left: t=2.53, p=0.026, figure 3B; right: t=2.46, p=0.032, figure 3C; online supplemental tables e11, e12). Changes in GMV in the left (r=0.35, p=0.023; r=0.38, p=0.016, figure 3D) and right (r=0.36, p=0.021; r=0.39, p=0.013, figure 3E) hippocampus across the intervention were positively correlated with MoCA and MMSE changes (online supplemental table e13). Left hippocampal GMV changes were negatively correlated with GDS (r=−0.32, p=0.041, figure 3F), and right hippocampal GMV changes were positively correlated with VFT-S (r=0.44, p=0.004, figure 3G) (online supplemental table e13).

ApoE ε4 subgroup analysis

All participants in the active group were divided into ApoE ε4 carriers (n=14) and non-ApoE ε4 carriers (n=6) to account for the predictive power of ApoE ε4; the baseline characteristics were balanced between the groups

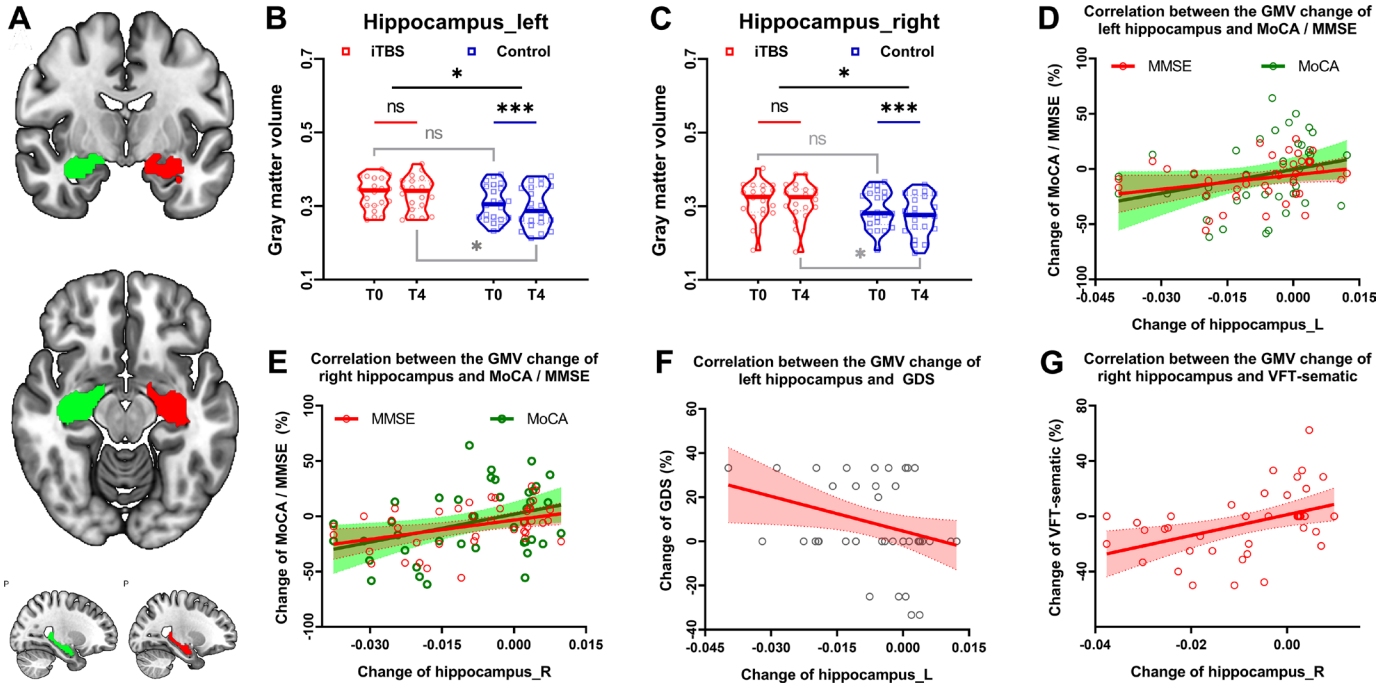

Figure 3 iTBS effects on the hippocampal volume. The hippocampus was defined by Anatomical Automatic Labelling: sagittal, coronal and axial views displaying the ROI (A). A significant effect on hippocampal volume was found in either hemisphere; the GMV of the left and right hippocampus of the active and control groups were not different at T0 but were different at T4 (active>control) (B, C). Red represents the active group and blue represents the control group. The changed GMV of both the left (D) and right (E) hippocampus, across the intervention, was positively correlated with MoCA and MMSE changes. The changed GMV of the left hippocampus was negatively correlated with the GDS (F); the changed GMV of the right hippocampus was positively correlated with the VFT-semantic (G) scores. GDS, global deterioration scale; GMV, grey matter volume; iTBS, intermittent theta burst stimulation; L, left; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; ns, not significant; R, Rright; ROI, region of interest; VFT, verbal fluency test. *p<0.05; **p<0.01;***p<0.001.

(online supplemental table e14). Linear mixed-effect models nested within participants were used for the analyses. The distribution of ApoE ε4 carriers was similar in the active and control groups (χ^2=0.034, p=0.845).

There was a significant interaction effect between time and group (ApoE ε4 carriers vs non-ApoE ε4 carriers) for MoCA scores ($F_{(4,72)}$=2.68; p=0.039) in the active group (online supplemental table e15). MoCA scores after 1 year of DLPFC-iTBS treatment significantly improved in the non-ApoE ε4 carriers (from 13.17 to 18.67; mean difference: 5.50; 95% CI: −1.62 to 9.39; $t_{(1,5)}$=5.37; p=0.012) but not in the carriers (from 15.86 to 17.79; mean difference: 1.93; 95% CI: −0.22 to 4.08; $t_{(1,13)}$=2.59; p=0.087) (online supplemental table e15; figure 2C). The RCD ratio in ApoE ε4 carriers was higher than that in non-ApoE ε4 carriers but the difference was not significant (21.43% vs 0%; χ^2=1.51; p=0.219) (figure 2D).

Similarly, the improvement in the CDT was more significant in non-ApoE ε4 carriers than in ApoE ε4 carriers ($F_{(4,72)}$=0.23; p=0.037) but not in other neuropsychological assessments (online supplemental table e5) (more details are in online supplemental tables e16–e20).

Adverse effects

No serious adverse events (such as epilepsy or epileptic seizures) were reported in either group. Two patients in the active group complained of uncomfortable scalp sensations; one in the control group complained of sleep issues. All the events were tolerable.

DISCUSSION

Main findings

Accumulating evidence suggests that HF-rTMS can alter neuroplasticity, with therapeutic potential in patients with AD.[6 9 10] However, studies have rarely examined the feasibility and long-term efficacy of HF-rTMS for AD. This randomised, controlled, assessor-blind study assessed the protective effect of left DLPFC iTBS on cognitive decline in patients with AD and its long-term maintenance. This study demonstrated that 1 year of regular iTBS interventions could delay hippocampal GMV loss. Moreover, there were significant differences in treatment effects between ApoE ε4 carriers and non-carriers; the protective effect of iTBS on cognitive decline was reduced in ApoE ε4 carriers. The present findings indicate that iTBS may slow AD progression. To the best of our knowledge, this randomised controlled trial is the first to evaluate the long-term protective effect of rTMS of the left DLPFC on cognitive decline in patients with AD.

rTMS may enhance plasticity to promote the maintenance of cognition and counteract, or at least slow down, cognitive decay. Recent evidence suggests that cortical

plasticity impairment might cause cognitive deficits and play a key role in AD pathogenesis.[1 6 19] Thus, targeting cortical plasticity in patients with AD could slow the progression of AD and cognitive decline.[2] Moreover, studies have shown the immediate and lasting effects of HF-rTMS on cortical plasticity and that repeated sessions of HF-rTMS could generally restore cortical plasticity.[2] The DLPFC is a promising rTMS target to promote cognitive and cortical plasticity.[4 12] Promoting the cortical plasticity of the DLPFC increases the efficiency of the frontal cortex, with subsequent effects on improving cognitive function. A recent study showed that the changes in DLPFC cortical plasticity associated with rTMS treatment improved cognitive function in patients with AD.[6] The promotion and reserve of cortical plasticity induced by regular iTBS on the left DLPFC may be a mechanism for slowing the progression of cognitive decline in patients with AD.[19] However, we observed no significant difference in cognitive performance between regular stimulation for four sessions and a single session, possibly due to the long interval between interventions, which failed to meet the cumulative effect between the two interventions. We have previously reported that the iTBS therapeutic effect of a single course persisted for approximately 8 weeks.[10] Besides, the failure of the cumulative effect of iTBS may be attributed to the ceiling effects of iTBS on AD. Further explorations are warranted to determine the long-term effects of rTMS, its therapeutic potential, and a more accurate duration of sequelae for patients with AD.

The decreased RCD ratio may be due to the protective effects of repeated DLPFC-rTMS every 3 months on cognitive reserve (CR), which is the ability to maintain cognition relatively well in the presence of brain pathology, and it may delay the cognitive damage caused by AD pathological changes; however, RCD would occur once the burden of AD-related pathological outcomes is high enough to overcome the reserve's protective mechanisms.[20 21] Recent research indicates that increased global connectivity of the left frontal cortex may serve as a neurological underpinning for CR in AD.[22] iTBS of the DLPFC may increase cortical excitability and synaptic plasticity, resulting in enhanced global connectivity of the DLPFC, which has subsequent implications for CR. Restoring the connections between the left DLPFC, a central hub of the frontoparietal control network, and other brain areas may reduce the impact of AD-related pathology on cognition.[23] Our results showed the protective effects of repeated DLPFC-iTBS every 3 months on RCD, suggesting that iTBS might slow down pathological progression. Further studies are needed to explore the mechanisms underlying the beneficial effect of rTMS on CR.

The ApoE genotype is a possible means to select candidates for rTMS due to its effects on the treatment efficiency of rTMS. Previous studies have found that the ApoE ε4 allele may affect the treatment efficiency of rTMS.[24 25] The ApoE ε4 allele can reduce the number and impair the function of GABAergic interneurons, and increase cortical excitability in the brain.[26] Functional impairment of GABAergic interneurons can reduce gamma oscillations, which are strongly associated with AD symptoms.[24 25] According to traditional conjecture, rTMS can boost gamma oscillation power, amplitude and cognitive function, while HF-rTMS can increase cortical excitability by inducing long-duration enhancement potentials. However, HF-rTMS therapy, specifically iTBS, increases gamma oscillatory activity and enhances therapeutic benefits. Consequently, for ApoE ε4 carriers with a more significant loss of GABAergic neurons, HF-rTMS therapy, such as iTBS, may be less beneficial, as suggested by the findings of the current study.[25] These results show that rTMS treatment protocols should vary according to ApoE genotypes.

The GMV study demonstrated that DLPFC-iTBS might delay atrophy of the hippocampus, supporting the protective benefits observed in cognitive functions. Interactions between the hippocampus and DLPFC play a significant role in cognitive functioning, such as global cognition and memory.[27] Therefore, a decrease or disruption in these interactions, induced by ageing and pathology, may contribute to the pathophysiology of various psychiatric diseases, including AD.[28] It has been shown that the application of rTMS to the DLPFC can alter hippocampal activity, connectivity patterns and GMV, which, in turn, influence cognition.[29] The potential neuro-mechanism may be the theta-phase and gamma-amplitude coupling (TGC), as evidenced by a resting-state electroencephalography study.[29] The HF left DLPFC-rTMS could induce a significant increase in TGC, which was significantly associated with cognitive improvement.[29]

The iTBS consists of a gamma frequency (50 Hz) of three pulses bursting at theta frequency (5 Hz), more in line with the endogenous theta rhythm. A previous study showed that DLPFC-iTBS could significantly increase the GMV of the left hippocampus in patients with depression.[30] Regular DLPFC-iTBS in AD may reduce the progression of cognitive decline and atrophy of the hippocampus by TGC. Considering the involvement of the left hippocampus in overall cognitive function, we hypothesised that left DLPFC-iTBS primarily improved the volume of the left hippocampus and delayed the atrophy of hippocampal volume and decline of overall function. Although previous observations suggest that iTBS may induce neuroplasticity and change brain structure, the exact mechanisms subserving these neuroplastic effects, their relationship with neurotransmitter systems and their functional significance remain to be determined.

Limitations

This study has some limitations. First, the sample size was relatively small, thereby limiting the ability to conduct subgroup analyses. Thus, a large-scale, multi-centre clinical trial should be undertaken to confirm our findings. Second, we did not assess cortical plasticity or explain the mechanisms underlying cortical plasticity enhancement. Third, our control group was not set up as a sham coil

stimulus, mainly considering that previous studies have shown that true stimuli are useful and that future studies should still apply reasonable sham stimuli as a control. Fourth, there were significant individual differences in treatment effects among different patients. Although our findings suggest that ApoE genotypes should be considered when selecting a treatment strategy, such specific disparities also highlight the need for more precise rTMS schemes in the future.

Implications

This study showed that repeated iTBS of the left DLPFC every three months could slow down the progressive decline of global cognition in patients with AD, which may be correlated with maintaining the GMV of the hippocampus. The ameliorating effects were more powerful and robust in individuals with moderate AD and no ApoE ε4 than in patients with severe AD and ApoE ε4. These findings provide an objective basis for assessing the effectiveness of iTBS in slowing the progressive decline of global cognition in patients with AD. Our results also indicate that different ApoE genotypes can guide the precise treatment of AD with rTMS. Future studies should assess the effects of iTBS on functional connections and cortical plasticity to better understand the mechanisms of brain stimulation in AD. Moreover, multi-centre trials and studies involving more biomarkers should also be considered.

Author affiliations
[1]Department of Neurology, First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China
[2]School of Mental Health and Psychological Sciences, Anhui Medical University, Hefei, Anhui, China
[3]Anhui Province Key Laboratory of Cognition and Neuropsychiatric Disorders, Hefei, Anhui, China
[4]Collaborative Innovation Center of Neuropsychiatric Disorders and Mental Health, Hefei, Anhui, China
[5]Department of Psychology and Sleep Medicine, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China
[6]Center for Biomedical Imaging, University of Science and Technology of China, Hefei, Anhui, China
[7]Institute of Artificial Intelligence, Hefei Comprehensive National Science Center, Hefei, Anhui, China
[8]Department of Neuroscience, Medical University of South Carolina, Charleston, South Carolina, USA

Acknowledgements We are grateful to the participants for their participation and cooperation during the study. The authors would like to thank the Information Science Laboratory Center of the University of Science and Technology of China for the measurement services.

Contributors XW: conceptualisation, methodology, formal analysis, data curation, writing—original draft and visualisation. YY: investigation, assessment. PH: investigation, supervision, funding acquisition. LWang: investigation, randomisation, visualisation. YW: investigation. PW: data curation. GX: investigation. ZG: investigation. SZ: investigation, supervision, data curation. GJ: software, formal analysis. BQ: data curation. YT: conceptualisation, supervision, project administration. LWei: writing—review and editing. HL: writing—review and editing. KW: conceptualisation, supervision, project administration, funding acquisition, writing—review and editing , and responsible for the study. XW, YY and PH contributed equally to this work as co-first authors.

Funding We thank the support of the Hefei Comprehensive National Science Center Hefei Brain Project. This work was supported by the National Natural Science Foundation of China (No. 82101498 to XW); STI2030-Major Projects of China (No. 2021ZD0201801 to PH); National Natural Science Foundation of China (No. 82171917 to PH, No. 82090034 and 31970979 to KW and 32071054 to YT) and the 2021 Youth Foundation Training Program of the First Affiliated Hospital of Anhui Medical University (No. 2021kj19 to XW).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by China's Anhui Medical University's institutional ethics committee (No. 5101007). Participants provided informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data supporting the findings of this trial are accessible on request from the corresponding authors.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Xingqi Wu http://orcid.org/0000-0003-0646-1353
Lu Wang http://orcid.org/0000-0002-0184-9570
Gongjun Ji http://orcid.org/0000-0002-7073-5534
Yanghua Tian http://orcid.org/0000-0001-5038-0599
Kai Wang http://orcid.org/0000-0002-6197-914X

REFERENCES

1 Koch G, Spampinato D. Alzheimer disease and neuroplasticity. *Handb Clin Neurol* 2022;184:473–9.
2 Yuan T-F, Li W-G, Zhang C, *et al*. Targeting neuroplasticity in patients with neurodegenerative diseases using brain stimulation techniques. *Transl Neurodegener* 2020;9:44.
3 Teselink J, Bawa KK, Koo GK, *et al*. Efficacy of non-invasive brain stimulation on global cognition and neuropsychiatric symptoms in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review. *Ageing Res Rev* 2021;72:101499.
4 Chu C-S, Li C-T, Brunoni AR, *et al*. Cognitive effects and acceptability of non-invasive brain stimulation on Alzheimer's disease and mild cognitive impairment: a component network meta-analysis. *J Neurol Neurosurg Psychiatry* 2021;92:195–203.
5 Nilakantan AS, Mesulam M-M, Weintraub S, *et al*. Network-targeted stimulation engages neurobehavioral hallmarks of age-related memory decline. *Neurology* 2019;92:e2349–54.
6 Li X, Qi G, Yu C, *et al*. Cortical plasticity is correlated with cognitive improvement in Alzheimer's disease patients after rTMS treatment. *Brain Stimul* 2021;14:503–10.
7 Koch G, Casula EP, Bonnì S, *et al*. Precuneus magnetic stimulation for Alzheimer's disease: a randomized, sham-controlled trial. *Brain* 2022;145:3776–86.
8 Wu X, Wang L, Geng Z, *et al*. Improved cognitive promotion through accelerated magnetic stimulation. *eNeuro* 2021;8:ENEURO.0392-20.2020.
9 Wu X, Ji G-J, Geng Z, *et al*. Strengthened theta-burst transcranial magnetic stimulation as an adjunctive treatment for Alzheimer's disease: an open-label pilot study. *Brain Stimul* 2020;13:484–6.
10 Wu X, Ji G-J, Geng Z, *et al*. Accelerated intermittent theta-burst stimulation broadly ameliorates symptoms and cognition in Alzheimer's disease: a randomized controlled trial. *Brain Stimulation* 2022;15:35–45.
11 Xiao G, Wu Y, Yan Y, *et al*. Optimized magnetic stimulation induced hypoconnectivity within the executive control network yields cognition improvements in Alzheimer's patients. *Front Aging Neurosci* 2022;14:847223.

12 Menardi A, Rossi S, Koch G, *et al*. Toward noninvasive brain stimulation 2.0 in Alzheimer's disease. *Ageing Res Rev* 2022;75:101555.
13 Chen Y-C, Ton That V, Ugonna C, *et al*. Diffusion MRI-guided theta burst stimulation enhances memory and functional connectivity along the inferior longitudinal fasciculus in mild cognitive impairment. *Proc Natl Acad Sci U S A* 2022;119:e2113778119.
14 Stanojevic JB, Zeljkovic M, Dragic M, *et al*. Intermittent theta burst stimulation attenuates oxidative stress and reactive astrogliosis in the streptozotocin-induced model of Alzheimer's disease-like pathology. *Front Aging Neurosci* 2023;15:1161678.
15 Cao Z, Hou Y, Xu C. Leucocyte telomere length, brain volume and risk of dementia: a prospective cohort study. *Gen Psychiatr* 2023;36:e101120.
16 Murtza M, Bangash A, Rehman A-U. A case of neurosyphilis with psychosis and hippocampal atrophy. *Gen Psychiatr* 2022;35::e100674.
17 Jia J, Gauthier S, Pallotta S, *et al*. Consensus-based recommendations for the management of rapid cognitive decline due to Alzheimer's disease. *Alzheimers Dement* 2017;13:592–7.
18 Lee T, Yuen K, Chan C. Normative data for neuropsychological measures of fluency, attention, and memory measures for Hong Kong Chinese. *J Clin Exp Neuropsychol* 2002;24:615–32.
19 Di Lorenzo F, Motta C, Bonnì S, *et al*. LTP-like cortical plasticity is associated with verbal memory impairment in Alzheimer's disease patients. *Brain Stimul* 2019;12:148–51.
20 Cabeza R, Albert M, Belleville S, *et al*. Publisher correction: maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat Rev Neurosci* 2018;19:772.
21 Menardi A, Pascual-Leone A, Fried PJ, *et al*. The role of cognitive reserve in Alzheimer's disease and aging: a multi-modal imaging review. *J Alzheimers Dis* 2018;66:1341–62.
22 Franzmeier N, Düzel E, Jessen F, *et al*. Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease. *Brain* 2018;141:1186–200.
23 Pu Y, Cheyne D, Sun Y, *et al*. Theta oscillations support the interface between language and memory. *Neuroimage* 2020;215:116782.
24 Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. *Lancet Neurol* 2021;20:68–80.
25 Najm R, Jones EA, Huang Y. Apolipoprotein E4, inhibitory network dysfunction, and Alzheimer's disease. *Mol Neurodegener* 2019;14:24.
26 Mimura Y, Nishida H, Nakajima S, *et al*. Neurophysiological biomarkers using transcranial magnetic stimulation in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2021;121:47–59.
27 Han SD, Fleischman DA, Yu L, *et al*. Cognitive decline and hippocampal functional connectivity within older Black adults. *Hum Brain Mapp* 2022;43:5044–52.
28 Ankudowich E, Pasvanis S, Rajah MN. Age-related differences in prefrontal-hippocampal connectivity are associated with reduced spatial context memory. *Psychol Aging* 2019;34:251–61.
29 Noda Y, Zomorrodi R, Daskalakis ZJ, *et al*. Enhanced theta-gamma coupling associated with hippocampal volume increase following high-frequency left prefrontal repetitive transcranial magnetic stimulation in patients with major depression. *Int J Psychophysiol* 2018;133:169–74.
30 Baeken C, Wu G, Sackeim HA. Accelerated iTBS treatment applied to the left DLPFC in depressed patients results in a rapid volume increase in the left hippocampal dentate gyrus, not driven by brain perfusion. *Brain Stimul* 2020;13:1211–7.

Xingqi Wu is an attending neurology physician at the First Affiliated Hospital of Anhui Medical University in Hefei, China, and a member of the Anhui Province Key Laboratory of Cognition and Neuropsychiatric Disorders in China. He obtained his MD degree from Anhui Medical University, China in 2020. He has published over ten articles in journals such as Brain Stimulation, eNeuro and Journal of Neuroscience Research. He has presided over the National Natural Science Foundation of China, the Youth Foundation Training Program of the First Affiliated Hospital of Anhui Medical University in China, and other programs. He has participated in four national key research and development programs. He supervised a single-centre, randomised, double-blind controlled experiment employing rTMS to treat Alzheimer's disease that was featured in international media; the published study was recognized as one of Elsevier's High Download Papers of the Quarter in 2022. His main research interests include neuropsychology, the neural mechanisms of dementia and non-pharmacological interventions.