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Circuit-based neuromodulation enhances delayed recall in amnestic mild cognitive impairment

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ABSTRACT

Background This study aimed to investigate the efficacy of circuits-based paired associative stimulation (PAS) in adults with amnestic mild cognitive impairment (aMCI).

Methods We conducted a parallel-group, randomised, controlled clinical trial. Initially, a cohort of healthy subjects was recruited to establish the cortical-hippocampal circuits by tracking white matter fibre connections using diffusion tensor imaging. Subsequently, patients diagnosed with aMCI, matched for age and education, were randomly allocated in a 1:1 ratio to undergo a 2-week intervention, either circuit-based PAS or sham PAS. Additionally, we explored the relationship between changes in cognitive performance and the functional connectivity (FC) of cortical-hippocampal circuits.

Results FCs between hippocampus and precuneus and between hippocampus and superior frontal gyrus (orbital part) were most closely associated with the Auditory Verbal Learning Test (AVLT)_N5 score in 42 aMCI patients, thus designated as target circuits. The AVLT_N5 score improved from 2.43 (1.43) to 5.29 (1.98) in the circuit-based PAS group, compared with 2.52 (1.44) to 3.86 (2.39) in the sham PAS group (p=0.003; Cohen's d=0.97). A significant decrease was noted in FC between the left hippocampus and left precuneus in the circuit-based PAS group from baseline to postintervention (p=0.013). Using a generalised linear model, significant group×FC interaction effects for the improvements in AVLT_N5 scores were found within the circuit-based PAS group (B=3.4, p=0.017).

Conclusions Circuit-based PAS effectively enhances long-term delayed recall in adults diagnosed with aMCI, which includes individuals aged 50–80 years. This enhancement is potentially linked to the decreased functional connectivity between the left hippocampus and left precuneus.

Trial registration number ChiCTR2100053315; Chinese Clinical Trial Registry.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Repetitive transcranial magnetic stimulation was recognised for its potential to improve cognitive function in amnestic mild cognitive impairment (aMCI). Existing modalities focused on high-frequency or intermittent theta burst stimulation targeting specific brain regions but suggested the need for more effective protocols and targets due to the complex nature of memory processes.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that circuit-based paired associative stimulation targeting the cortical-hippocampal circuits can significantly enhance long-term delayed recall in adults with aMCI. The improvements were associated with decreased functional connectivity between the left hippocampus and left precuneus, highlighting the potential of this novel stimulation protocol in enhancing cognitive functions related to aMCI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings suggest a new direction for neuromodulation therapies in aMCI, emphasising the importance of targeting specific brain circuits. This approach could refine therapeutic strategies and stimulate further research into personalised neuromodulation interventions for cognitive impairments, potentially influencing clinical practices and policies regarding the treatment of aMCI and similar conditions.

INTRODUCTION

Amnestic mild cognitive impairment (aMCI) has garnered significant attention as a pivotal transitional stage in the continuum form normal cognitive function to dementia, making it a focal point of cognitive research in recent years.[1–3] Within the realm of neuromodulation, repetitive transcranial magnetic stimulation (rTMS) has gained increasing recognition for its potential to ameliorate cognitive function in aMCI.[4–6] Presently, the prevailing stimulation modalities involve high-frequency or intermittent theta burst stimulation applied to brain regions such as the dorsolateral prefrontal cortex, the precuneus cortex and the parietal cortex. Nevertheless, more effective stimulation protocols and targets should be explored.[7] One plausible reason is the inadequacy of single-target stimulation in producing sufficient efficacy, as it may not be fully aligned with the complexities of memory processes.[8 9] The pursuit of a novel stimulation mode and corresponding targets that better align with the memory processes holds the potential to

overcome these therapeutic bottlenecks, bearing substantial clinical and scientific significance.

Episodic memory reflects the ability to recall the temporal and spatial context of previous experiences. The memory processes encompass three stages: information acquisition, encoding, and storage and retrieval. These stages require collaborative engagement of multiple brain regions.[10] The hippocampus stands as the central structure (hub) for episodic memory, yet memory storage engages various brain regions, with diverse types of memory information residing in distinct neural structures. Specifically, the hippocampus plays a pivotal role in integrating memory by fostering information exchange with various brain regions through interconnections among the hippocampus and other neural areas.[11–14] Therefore, the neural circuits associated with the hippocampus play a crucial role in the memory process.

A stimulation pattern that targets these 'circuits' seems to be more congruent with the mechanics of memory. Consequently, there is a pressing need to investigate a form of stimulation that operates on these connections, which appears to be in harmony with the memory processes. In recent years, increasing scholarly attention has been directed towards the pivotal role of neural circuits in both brain function and structure. Fox has contended that disparate sites of brain damage can lead to similar clinical symptoms, and complex symptoms can be mapped to larger distributed brain networks rather than being limited to isolated brain regions.[15]

Damage to specific areas or connections between regions can lead to intricate 'disconnection' syndromes. He has introduced the innovative concept of 'identifying treatment targets based on the connectome'. In 2022, a series of articles have laid the theoretical and methodological foundation for neuromodulation strategies rooted in connections.[16–19] Building on this foundation, we introduce an innovative approach for defining stimulation targets: employing the hippocampus as the seed region and tracing white matter fibre connections with cortical areas in healthy individuals to identify pre-existing structural connections within the hippocampus-cortex circuit. Among these connections, we select those with significant functional associations with long-delayed recall function, a paramount function in aMCI patients,[20 21] were selected as the target circuits.[22]

Subsequently, we delve into the exploration of stimulation patterns and optimal parameters, following the identification of subject-specific target circuits. The theoretical underpinning for the circuit-based stimulation pattern lies in synaptic plasticity mechanisms, predominantly Hebbian plasticity.[23] Paired associative stimulation (PAS) represents a neuromodulation approach potentially rooted in Hebbian theory, as it induces repeated coupling activity between interconnected neuron populations.[24] By adjusting the interstimulus interval between two stimuli, we can invoke spike-timing-dependent plasticity and selectively modulate physiological connections among brain regions.[24] Our proposal involves the application of PAS patterns in aMCI patients, targeting cortical-hippocampal circuits that exhibit the strongest associations with cognitive symptoms. Addressing the technical challenge of stimulating these subject-specific circuits is accomplished through connectivity-based segmentation and a pilot study (online supplemental material 1).

In summary, we introduce a novel PAS protocol designed to modulate symptom-related cortical-hippocampal circuits with the aim of enhancing long-delayed recall function in aMCI patients. To substantiate our hypothesis, we conducted a parallel-group, randomised, controlled clinical trial among aMCI patients, placing particular emphasis on evaluating the strength of cortical-hippocampal connectivity and its correlation with cognitive functions.

METHODS

Study design and participants

This study was designed as a parallel-group, randomised, controlled clinical trial. Participants were recruited from the rehabilitation centre at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (online supplemental file 1).

We initially recruited healthy adults to track cortical-hippocampal circuits. These right-handed individuals aged

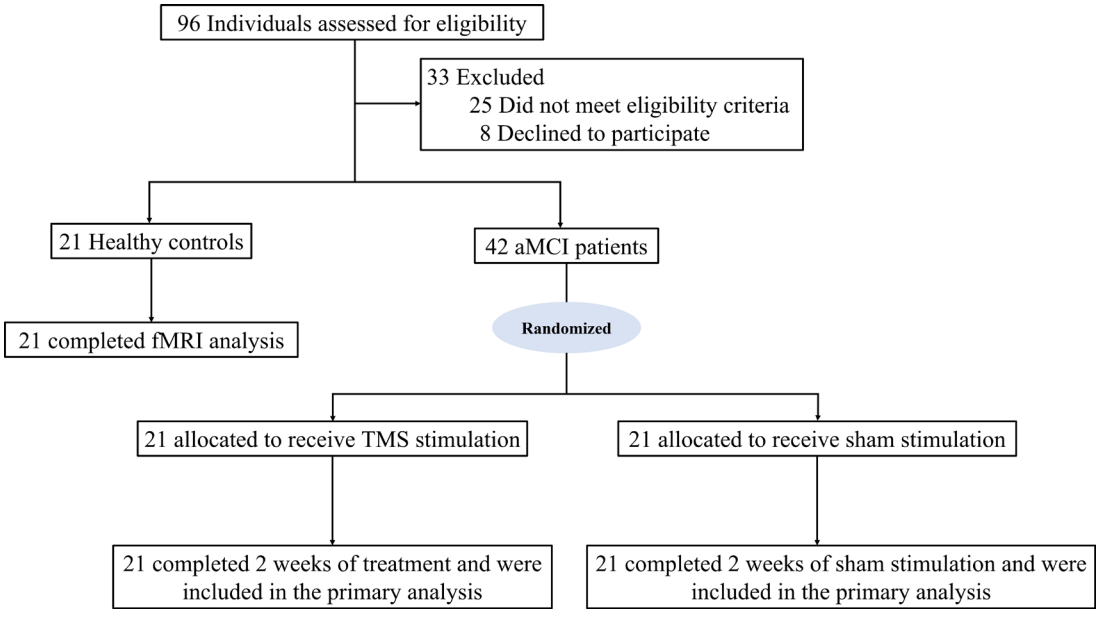

Figure 1 Trial profile. aMCI, amnestic mild cognitive impairment; TMS, transcranial magnetic stimulation.

50–80 years underwent neuropsychological assessments to confirm normal cognitive function. Inclusion criteria required participants to have at least 6 years of education, no reported cognitive decline verified by neuropsychological assessments, and informed consent.

Eligible right-handed participants diagnosed with aMCI were aged 50–80 years. The diagnosis followed Jak/Bondi's diagnostic criteria[25] (online supplemental material 2), did not have taken any cognitive medication, had an education of 6 years or more, complained of memory loss with a decreased long-term delayed recall score in Auditory Verbal Learning Test (AVLT) (an impaired score defined as >1 SD below the age-corrected normative mean). Exclusion criteria for all participants included comorbid tumours, severe heart, liver, kidney, haematologic disorders or infectious diseases as well as a history of neurological disorders (such as cerebrovascular disease, Parkinson's syndrome, epilepsy, dementia from various causes) or psychiatric disorders (such as anxiety, depression, schizophrenia, etc), severe visual or hearing impairment, drug or alcohol abuse and contraindications to MRI and TMS treatment (eg, pacemaker, cardiac stent, artificial heart valve, fixed plate after fracture surgery, etc) (figure 1).

Procedures

The study comprised three main phases: identification of subject-specific cortical-hippocampal circuits related to cognitive function in aMCI, modulation of target circuits, and exploration of their relationship with clinical efficacy. These steps included:

1. Obtaining white matter fibre maps of cortical-hippocampal circuits using probabilistic fibre tracking and diffusion tensor imaging (DTI) in healthy subjects matched in age to aMCI patients.
2. Selecting cortical-hippocampal circuits whose functional connectivity (FC) was significantly related to long-term delayed recall scores in aMCI patients for circuit-based PAS.
3. Randomly assigning aMCI patients to either the circuit-based PAS group or the sham PAS group and locating the target circuits for each patient.
4. Administering 2 weeks of circuits-based PAS or sham PAS.
5. Comparing changes in cognitive functions before and after intervention between the two groups.
6. Comparing changes in functional magnetic resonance imaging (fMRI) data before and after intervention and examining the correlation between these changes and cognitive function (figure 2).

Randomisation and blinding

Patients with aMCI were randomly assigned to receive either circuits-based PAS or sham PAS using a computer-based algorithm. Researchers assigned random identification numbers to participants after they met inclusion and exclusion criteria and signed informed consent forms. Treating therapists were aware of treatment allocation, while outcome assessors were blinded to treatment assignment. Participants were also blinded to treatment allocation.

Clinical and neuropsychological assessments

Demographic data were collected at baseline, and clinical and neuropsychological assessments were conducted at baseline (2 weeks before treatment for designation of optimised target) and at the end of the 2-week treatment. Two senior neuropsychologists with >10 years of work experience performed the neuropsychological evaluation without knowledge of the clinical diagnosis; another senior neuropsychologist then reviewed the assessment results. Demographic data include gender, age, handedness, height, weight, average daily sleep time, average daily exercise time, years of education, marital status, times of general anaesthesia and previous history. Clinical data include Hamilton Anxiety Scale,[26] Hamilton Depression Scale[27] and Functional Activities Questionnaire.[28] Neuropsychological evaluations include Mini-Mental State Examination (MMSE),[29] AVLT,[30] shape trails test (STT),[31] symbol digit modalities test (SDMT),[32] Boston naming test (BNT)[33] and complex figure test (CFT).[34] Detailed assessment standards of these scales have been included in online supplemental material 3.

Imaging data

Imaging data were collected at two time points: baseline (2 weeks before intervention) and at the end of the 2-week intervention. MRI scans were scheduled between 16:00 and 18:00 to maintain consistent data quality. Half an hour before the MRI scan, the subject will enter a quiet preparation area without bright light. During the scan, the subject was placed in a lying position with the head fixed in the coil. Before scanning, subjects will wear noise-proof earplugs and will be asked to follow the instructions during the MRI scan: breath calmly, close your eyes, stay awake, stay relaxed, keep your body free of movement, especially your head and raise your hand to indicate any discomfort during the scan.

Image acquisition

MRI data were acquired using a MAGNETOM Verio 3.0-Tesla scanner (Siemens, Erlangen, Germany). Resting-state fMRI data were obtained with a gradient-recalled echo-planar imaging (EPI) sequence with the following parameters: transverse plane; repetition time (TR), 3000 ms; echo time (TE), 30 ms; flip angle, 90°; slice thickness, 3.0 mm; slice number, 43; matrix size, 64×64; field of view (FOV), 230 mm×230 mm; voxel size=3.6 mm×3.6 mm×3.0 mm; and number of acquisitions, 200.

A T1-weighted magnetisation-prepared rapid acquisition gradient echo scan was then performed, with the following parameters: TR, 1900 ms; inversion time, 900 ms; TE, 2.93 ms; flip angle, 9°; FOV, 256 mm×256 mm; slice thickness, 1 mm.

DTI was performed using a single-shot spin EPI in the axial plane: TR, 10 000 ms; TE, 89 ms; flip angle, 90°; slice thickness, 2.0 mm; in-plane resolution, 1.875 mm; 60 non-colinear directions (b, 1000 s/mm^2), and two b0 images.

Imaging data preprocessing and processing

DTI data were processed in the Camino (http://www.cs.ucl.ac.uk/research/medic/camino/) and FMRIB Software Library V.5.0 (University of Oxford Center for Functional MRI of the Brain, http://www.fmrib.ox.ac.uk/)[35] software. Functional image preprocessing and FC calculation were performed using MATLAB 2013b platform (The Mathworks, Natick, USA), Statistical Parametric Mapping V.12 (SPM12) (http://www.fil.ion.ucl.ac.uk/spm/), and Data Processing Assistant for Resting-State fMRI[36] (V.5.0) (http://www.rfmri.org/dpabi). The data processing and construction of individualised target circuits are described in detail in the online supplemental material 4.

Interventions

Stimulus was delivered with a MagPro X100 stimulator equipped with the B70 fluid-cooled coil (MagVenture). The maximum surface magnetic field intensity of the coil was 4.2T. All patients

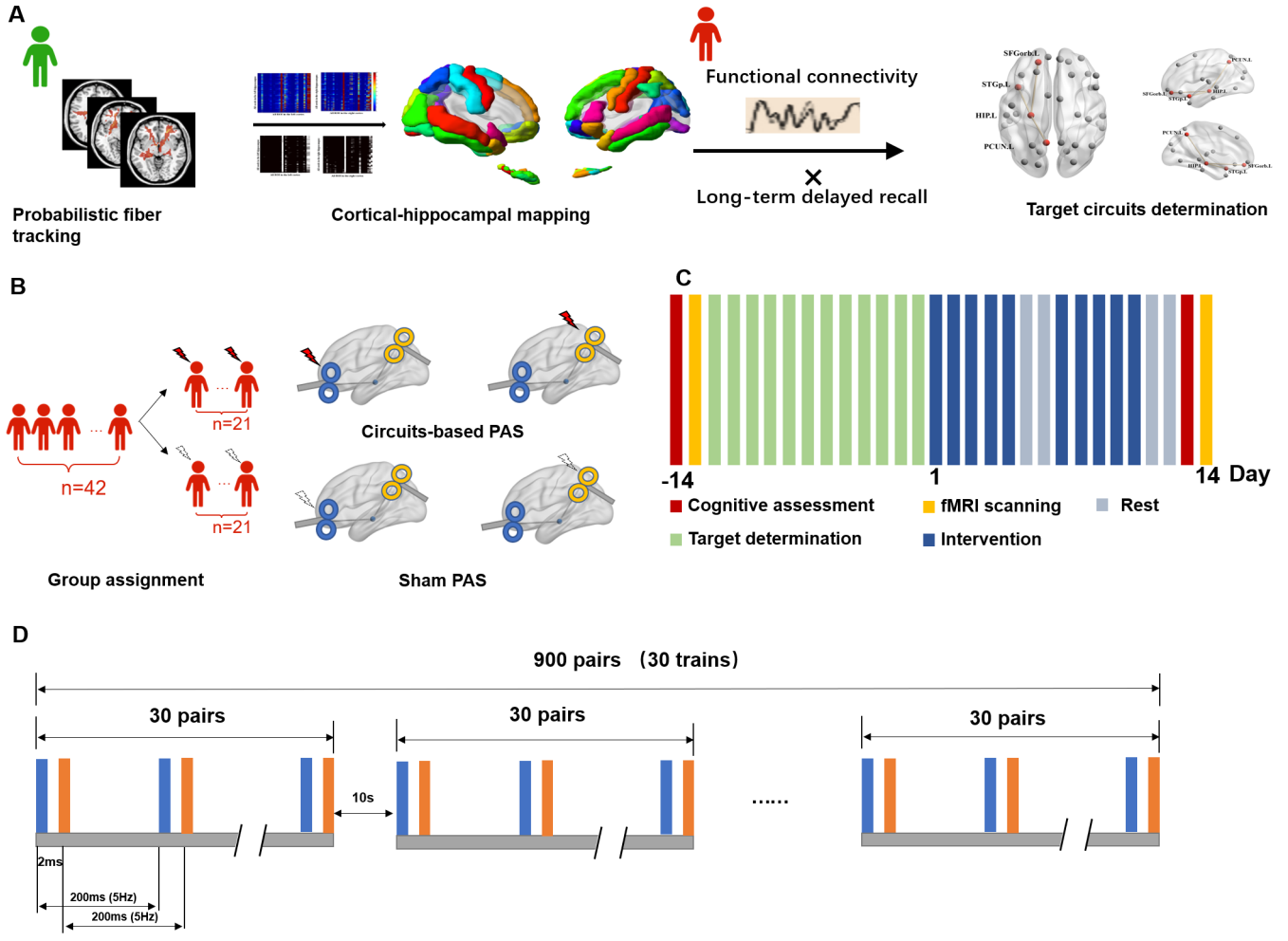

Figure 2 The research procedure. (A) Identification of subject-specific cortical-hippocampal circuits related to cognitive function in aMCI: obtaining white matter fibre maps of cortical-hippocampal circuits using probabilistic fibre tracking and DTI in healthy subjects matched in age to aMCI patients, And selecting cortical-hippocampal circuits whose functional connectivity was significantly related to long-term delayed recall scores in aMCI patients for circuit-based PAS; (B) modulation of target circuits: randomly assigning aMCI patients to either the circuit-based PAS group or the sham PAS group and locating the target circuits for each patient; (C) processing the data and constructing individualised target circuits and 3D precise localisation, and administering 2 weeks of circuit-based PAS or sham PAS; (D) stimulus pattern: all patients received 10 trials with an inter-stimulus interval of 2 ms, 900 pairs pulses in total (five trials a week for 2 weeks). aMCI, amnestic mild cognitive impairment; DTI, diffusion tensor imaging; PAS, paired associative stimulation.

received 10 trials (five trials a week for 2 weeks). Each patient's resting motor threshold (RMT) was tested in accordance with the standard practice[37] (online supplemental material 5).

Circuit-based PAS

Two B70 fluid-cooled eight-figure coils were applied to left prefrontal lobe and left precuneus (online supplemental material 4). Paired stimulation included a 80% RMT stimulus on the left prefrontal lobe, followed by a 120% RMT stimulus on the left precuneus. A trial of circuits-based PAS consisted of trains of 5 Hz paired stimulations with an interstimulus interval of 2 ms, 900 pairs pulses in total.

Sham PAS

Two sham coils were placed vertically on the scalp of the patients. The coils generated stimulating sounds but with no virtual effect on the brain. Other parts of protocol were the same as the circuits-based PAS group (figure 2B).

Outcome measures

The primary outcome measure was the change in long-term delayed recall performance following the 2-week intervention, measured by the age- and education-normalised AVLT_N5 score (Delta AVLT_N5). Secondary outcome measures included MMSE, AVLT items (excluding AVLT_N5), STT, SDMT, BNT, CFT and fMRI data. Correlations between changes in cognitive performance and functional connections (FC) were explored.

Safety measures

Adverse effects and accidents were monitored and recorded during the course of the intervention. Serious adverse events (SAEs) and treatment discontinuation were documented and evaluated for their relevance to clinical interventions.

Sample size calculation

Sample size calculation was calculated based on long delay recall score as the main observation index. As this study adopts a new treatment method, sample size was acquired from our preliminary study. As a result, the mean (5.1) and SD (2.23)

Table 1 Characteristics of the healthy subjects and patients with aMCI

Characteristics	Healthy subjects (n=21)	Patients with aMCI		P value*
		Circuits-based PAS (n=21)	Sham PAS (n=21)	
Basic characteristics				
Gender (% female)	14 (66.67)	16 (76.19)	9 (42.86)	0.78
Age, years	63.19 (7.35)	66.33 (7.41)	65.14 (5.95)	0.17
Education, years	9.43 (2.98)	8.76 (2.10)	9.86 (1.39)	0.87
Height, cm	164.81 (7.41)	161.86 (6.98)	165.05 (7.20)	0.49
Weight, kg	62.67 (9.72)	61.76 (11.92)	64.22 (7.68)	0.90
Average exercise duration, min/day	87.14 (76.43)	77.14 (78.56)	82.86 (90.45)	0.74
Average sleep duration, min/day	382.86 (69.65)	391.43 (74.99)	415.24 (99.78)	0.36
Daily life performance				
FAQ	0.48 (2.18)	0.43 (1.57)	1.67 (4.68)	0.50
Emotional performance				
HAMD	1.00 (1.26)	1.19 (1.75)	1.33 (1.59)	0.53
HAMA	2.71 (1.55)	2.95 (2.04)	2.91 (2.17)	0.68
Cognitive performance				
MMSE	28.29 (1.31)	26.81 (1.81)	25.95 (1.53)	<0.001
AVLT	35 (7.94)	17.81 (6.07)	18.62 (6.02)	<0.001
AVLT_IR	20.43 (4.62)	12.43 (3.30)	13.19 (3.80)	<0.001
AVLT_N1	4.71 (1.35)	2.71 (1.15)	2.91 (1.09)	<0.001
AVLT_N2	7.19 (2.06)	4.43 (1.21)	4.71 (1.59)	<0.001
AVLT_N3	8.52 (1.94)	5.29 (1.68)	5.57 (1.99)	<0.001
AVLT_N4	7.38 (1.99)	2.95 (1.96)	2.91 (1.48)	<0.001
AVLT_N5	7.19 (2.04)	2.43 (1.43)	2.52 (1.44)	<0.001
AVLT_N6	6.86 (2.57)	2.29 (1.85)	2.86 (1.56)	<0.001
AVLT_N7	21.76 (2.64)	18.52 (2.66)	19.81 (2.04)	<0.001
BNT	25.24 (1.51)	19.81 (3.78)	21.33 (3.43)	<0.001
STT_B, s	112.01 (31.75)	212.75 (99.34)	185.57 (86.92)	<0.001
SDMT_correct	45.48 (9.09)	24.33 (12.09)	29.71 (11.95)	<0.001
CFT_copy	32.29 (3.02)	27.21 (6.41)	29.21 (5.85)	<0.001

Data are mean (SD), unless otherwise indicated.
*Comparisons between healthy subjects (n=21) and patients with aMCI (n=42).
aMCI, amnestic mild cognitive impairment; AVLT, Auditory Verbal Learning Test; AVLT_IR, Auditory Verbal Learning Test, total score of immediate recall; AVLT_N1, Auditory Verbal Learning Test, first immediate recall; AVLT_N2, Auditory Verbal Learning Test, second immediate recall; AVLT_N3, Auditory Verbal Learning Test, the third immediate recall; AVLT_N4, Auditory Verbal Learning Test, short-term delay recall; AVLT_N5, Auditory Verbal Learning Test, long-term delay recall; AVLT_N6, Auditory Verbal Learning Test, long delay cued recall; AVLT_N7, Auditory Verbal Learning Test, recognition; BNT, Boston naming test; CFT_copy, Complex figure test, copy part; FAQ, Functional Activity Questionnaire; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Examination; PAS, paired associative stimulation; SDMT_correct, Symbol Digit Modalities Test, correct number; STT_B, Shape Trails Test, part B.

after treatment, as well as the mean (2.6) after false stimulation, a minimum total sample size of 33 treatment completers was required to achieve 90% power at α=0·05. To account for attrition and ensure adequate power at 2 weeks after treatment, 42 participants need to be included, with 21 subjects in each group.

Statistical analysis

SPSS V.21.0 (SPSS, Chicago, USA) software was used for statistical analysis for clinical data. Continuous variables were expressed as mean±SD. Independent sample t-test was used in the comparison between two groups when the data conform to the normal distribution and homogeneity test of variance.

A generalised linear model was constructed with AVLT_N5 score as dependent variable and every FC value of cortical-hippocampal circuits as independent variable.

The repeated measurement analysis of variance (ANOVA) was performed in comparison between two groups before and after treatment, the test of within-subject effect was corrected by Greenhouse-Geisser, and the post test was performed by least significant difference (LSD) method. Effect sizes (Cohen's d)[38] were interpreted as small=0.2, medium=0.5, large=0.8. Non-parametric test was adopted when the data did not conform to normal distribution or homogeneity of variance. The discrete data were expressed by frequency/rate, and the comparison between the two groups was conducted by χ^2 test or Fisher exact probability method. The $p<0.05$ (two-sided) indicated significant statistical difference.

The statistical analysis of magnetic resonance data was carried out using SPM12, GRETNA and the Resting State fMRI Data Analysis Toolkit[39 67] (RESTV.1.8) based on Matlab 2013b (The MathWorks, USA). The flexible factorial of the second order analysis was used to design the statistical matrix, and the three factors included subjects, group and time, in which group and time were set as fixed factors, while the number of subjects was random factors, and then the main effect and Group×Time interaction matrix were set for statistical analysis, respectively. Brain regions with $p<0.05$ and voxel >50 were extracted for post hoc analysis. The results were reported using bspmview software (https://www.bobspunt.com/software/bspmview/), and the brain regions were referred to anatomical automatic labeling (AAL) template. For correlation analysis, a generalised linear model was fitted with the delta AVLT_N5 as the dependent variable, group and the delta FC value between left hippocampus and left precuneus as independent/ interactive variables, using age and years of education as covariates.

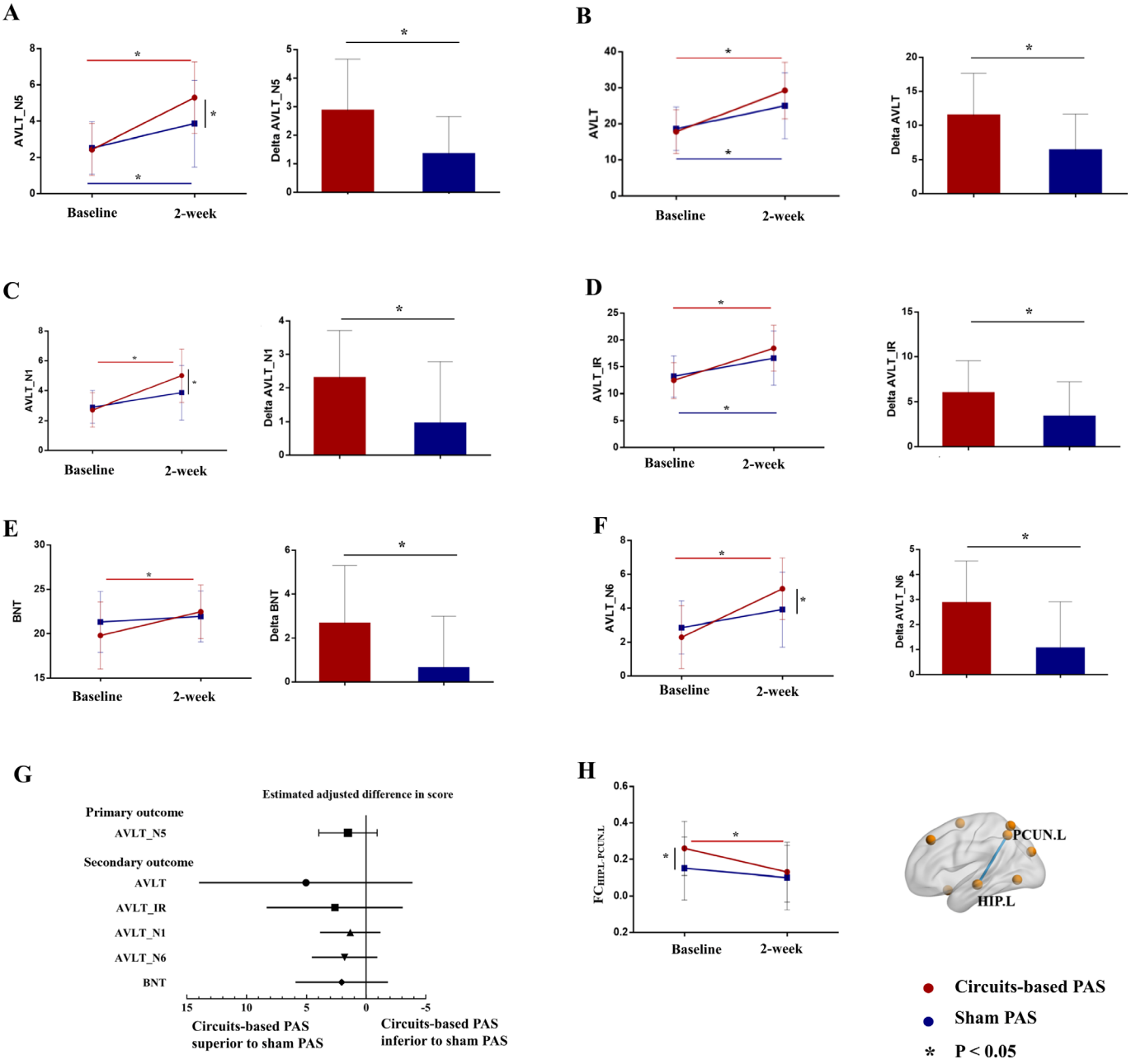

Figure 3 Primary and key secondary endpoints. (A) showed the results for the primary endpoint (Delta AVLT_N5), the score on the AVLT_N5. Scores range from 0 to 12, with lower scores indicating greater impairment. (B–F) showed the results for the key secondary endpoints; values were calculated in the same manner as those for the primary endpoint. (G) showed estimated adjusted difference shown with 2-sided lower and upper 90% CIs. (H) showed the mean change from baseline in functional connectivity between left hippocampus and left precuneus. Green represents circuit-based PAS group, red represents Sham PAS group, and asterisk represents p<0.05. AVLT_IR, Auditory Verbal Learning Test, total score of immediate recall; AVLT_N1, Auditory Verbal Learning Test, first immediate recall; AVLT_N5, Auditory Verbal Learning Test, long-term delay recall; AVLT_N6, Auditory Verbal Learning Test, long delay cued recall; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; HIP.L, left hippocampus; PAS, paired associative stimulation; PCUN.L, left precuneus.

RESULTS

Characteristics of participants

Participants were recruited between 1 November 2021 and 30 February 2022. A total of 26 healthy subjects underwent initial screening, with 21 (80.77%) subsequently enrolled for tracking cortical-hippocampal circuits. Eligibility assessments were conducted on 70 aMCI patients, resulting in the enrolment of 42 (60%) who were randomly assigned to either the circuit-based PAS or sham PAS groups. Notably, significant disparities in cognitive performance scores existed between the healthy subjects and aMCI patients (p<0.05), while no significant difference was found between the circuit-based PAS and sham PAS groups at baseline (all p>0.05) (table 1).

Target circuits related to long-term delayed recall function

The FC value between the left hippocampus and the left superior frontal gyrus (orbital part) exhibited a positive correlation with the AVLT_N5 scores in aMCI patients (B=3.44; p=0.045). Conversely, the FC values between the left hippocampus and the left precuneus, as well as between the hippocampus and the left temporal pole (superior temporal gyrus), demonstrated negative

Table 2 Primary and secondary outcomes

Outcome measures	Mean (SD) at week 2		Mean (SD) change (week 2 vs baseline)		Estimated adjusted difference (95% CI)*	P value†	Effect size (Cohen's d)
	Circuit-based PAS (n=21)	Sham PAS (n=21)	Circuit-based PAS (n=21)	Sham PAS (n=21)			
Primary outcome							
AVLT_N5	5.29 (1.98)	3.86 (2.39)	2.86 (1.80)	1.33 (1.32)	1.52 (0.54 to 2.51)	0.003	0.97
Secondary outcomes							
AVLT	29.24 (7.84)	25.00 (9.15)	11.43 (6.22)	6.38 (5.27)	5.06 (1.46 to 8.65)	0.007	0.88
AVLT_IR	18.43 (4.28)	16.57 (5.06)	6.00 (3.54)	3.38 (3.81)	2.46 (0.20 to 4.73)	0.034	0.71
AVLT_N1	5.00 (1.79)	3.86 (1.82)	2.29 (1.42)	0.95 (1.83)	1.27 (0.27 to 2.28)	0.014	0.82
AVLT_N2	6.33 (1.53)	5.86 (1.77)	1.91 (1.34)	1.14 (1.11)	0.70 (−0.05 to 1.45)	0.066	
AVLT_N3	7.10 (1.70)	6.86 (1.85)	1.81 (1.91)	1.29 (2.15)	0.34 (−0.69 to 1.37)	0.512	
AVLT_N4	5.52 (2.23)	4.57 (2.29)	2.57 (1.94)	1.67 (1.53)	0.91 (−0.16 to 1.99)	0.094	
AVLT_N6	5.14 (1.82)	3.91 (2.21)	2.86 (1.68)	1.05 (1.86)	1.57 (0.52 to 2.62)	0.004	1.02
AVLT_N7	20.33 (2.69)	20.81 (2.50)	1.81 (3.19)	1.00 (2.28)	0.55 (−1.44 to 1.55)	0.941	
MMSE	27.29 (1.95)	27.10 (1.73)	0.48 (2.38)	1.14 (1.77)	−0.08 (−1.18 to 1.02)	0.883	
STT-B, s	200.24 (58.81)	192.79 (104.31)	−12.51 (82.47)	7.22 (50.10)	−9.61 (−47.25 to 28.04)	0.609	
SDMT_correct	32.57 (14.57)	31.05 (13.72)	8.24 (12.33)	1.33 (9.98)	5.32 (−1.45 to 12.09)	0.12	
BNT	22.48 (3.03)	21.95 (2.87)	2.67 (2.63)	0.62 (2.36)	1.37 (0.99 to 2.63)	0.035	0.82
CFT_copy	29.61 (4.17)	31.37 (4.51)	2.39 (5.61)	2.16 (4.16)	−0.89 (−3.17 to 1.40)	0.436	

*For estimated adjusted difference values, positive values indicate greater change in the treatment group, while negative values indicate greater change in the sham stimulation group.
†p values represent the statistical significance of differences in the change of outcome measures from baseline to the intervention's end across groups.
AVLT_IR, Auditory Verbal Learning Test, total score of immediate recall; AVLT_N1, Auditory Verbal Learning Test, first immediate recall; AVLT_N2, Auditory Verbal Learning Test, second immediate recall; AVLT_N3, Auditory Verbal Learning Test, the third immediate recall; AVLT_N4, Auditory Verbal Learning Test, short-term delay recall; AVLT_N5, Auditory Verbal Learning Test, long-term delay recall; AVLT_N6, Auditory Verbal Learning Test, long delay cued recall; AVLT_N7, Auditory Verbal Learning Test, recognition; BNT, Boston Naming Test; CFT_copy, Complex Figure Test, copy part; MMSE, Mini-Mental State Examination; SDMT_correct, Symbol Digit Modalities Test, correct number; STT_B, Shape Trails Test, part B.

correlations with the AVLT_N5 scores in aMCI patients, respectively (B=−4.71, p=0.032; B=−3.09; p=0.025) (figure 2A). Notably, the interaction effect of age and years of education on AVLT_N5 scores had not been found (p=0.759). FC between hippocampus and precuneus, and between hippocampus and superior frontal gyrus (orbital part), were most closely associated with the AVLT_N5 score in 42 aMCI patients, thus designated as target circuits.

Efficacy outcomes

Primary outcome

At baseline, the mean AVLT_N5 score was 2.43 (1.43) in the circuit-based PAS group and 2.52 (1.44) in the sham PAS group, consistent with the diagnostic criteria for aMCI. The mean change from baseline to the end of the 2-week intervention was 2.86 (1.80) in the circuit-based PAS group and 1.33 (1.32) in the sham PAS group. An estimated adjusted difference of 1.52 (95% CI 0.54 to 2.51; p=0.003) was observed between the two groups, favouring circuit-based PAS (figure 3A, table 2).

Secondary outcomes

At baseline, the mean AVLT score was 17.81 (6.07) in the circuit-based PAS group and 18.62 (6.02) in the sham PAS group. The mean change from baseline to the end of the 2-week intervention was 11.43 (6.22) in the circuit-based PAS group and 6.38 (5.27) in the sham PAS group (estimated adjusted difference, 5.06; 95% CI 1.46 to 8.65; p=0.007). The mean AVLT_IR score at baseline was 12.43 (3.30) in the circuit-based PAS group and 13.19 (3.80) in the sham PAS group. The mean change of AVLT_IR was 6.00 (3.54) in the circuit-based PAS group and 3.38 (3.81) in the sham PAS group (estimated adjusted difference, 2.46; 95% CI 0.20 to 4.73; p=0.034). The mean AVLT_N1 score at baseline was 2.71 (1.15) in the circuit-based PAS group and 2.91 (1.09) in the sham PAS group. The mean change of AVLT_N1 was 2.29 (1.42) in the circuit-based PAS group and 0.95 (1.83) in the sham PAS group (estimated adjusted difference, 1.27; 95% CI 0.27 to 2.28; p=0.014). The mean AVLT_N6 score at baseline was 2.29 (1.85) in the circuit-based PAS group and 2.86 (1.56) in the sham PAS group. The mean change of AVLT_N6 was 2.86 (1.68) in the circuit-based PAS group and 1.05 (1.86) in the sham PAS group (estimated adjusted difference, 1.57; 95% CI 0.52 to 2.62; p=0.004). The mean BNT score at baseline was 19.81 (3.78) in the circuit-based PAS group and 21.33 (3.43) in the sham PAS group. The mean change in BNT was 2.67 (2.63) in the circuit-based PAS group and 0.62 (2.36) in the sham PAS group (estimated adjusted difference, 1.37; 95% CI 0.99 to 2.63; p=0.035) (figure 3E and tables 1 and 2). No between-group differences were found in AVLT_N2, AVLT_N3, AVLT_N4, AVLT_N7, MMSE, STT-B, SDMT_correct or CFT_copy scores (online supplemental material 6).

Correlation between changes of FC and cognitive performance

On reanalysis, we observed a significant decrease in the FC between the left hippocampus and left precuneus across both groups from baseline to the conclusion of the 2-week intervention period (estimated adjusted difference, −0.02; 95% CI −0.12 to 0.07, p=0.67). Specifically, the circuit-based PAS group exhibited a change of −0.13±0.23 (p=0.013), while the sham PAS group showed a change of −0.05±0.10 (p=0.318) (figure 3H). A generalised linear model was fitted, with the delta AVLT_N5 as the dependent variable and the group×delta FC between the left hippocampus and the left precuneus as group×FCs as interactive variable, using age and years of education as covariates. A significant group×FC interaction effects for the improvements in AVLT_N5 scores were found within the circuit-based PAS

group (B=3.4, p=0.017), which was absent in the sham PAS group (p=0.533). Another generalised linear model was fitted with the delta AVLT, delta AVLT_IR, delta AVLT_N1, delta AVLT_N6, delta BNT as the dependent variable and the delta FC between the left hippocampus and the left precuneus as independent variables, using age and years of education as covariates. No significant differences were found in the five secondary endpoints (p>0.05).

Safety

Adverse events related to the intervention included headache (n=3), fatigue (n=2), nausea (n=1) and dizziness (n=1) in the circuit-based PAS group, compared with two cases of headache and one case of fatigue in the sham PAS group, as detailed in online supplemental material 7. None of these participants reported any SAE.

DISCUSSION

The concept of PAS was initially reported two decades ago, introducing a non-invasive brain stimulation protocol involving paired stimuli with a fixed repetition interval.[40] Initially, PAS employed a pair of stimuli, one in the periphery and the other in the cortex, capable of inducing Hebbian plasticity changes.[40] Subsequently, this protocol has been extensively replicated and led to the development of cortico-cortical PAS (ccPAS), which has found application in various functional systems. It is clear that ccPAS exhibits feasibility and potential for research and application in neural plasticity. In this study, we chose the left frontal lobe and left precuneus for paired stimulation, based on prior research, a preliminary research foundation and clinical experience. Throughout the study, participants did not report any discomfort, and the results demonstrated a significant improvement in long-term delayed recall scores in the circuit-based PAS group compared with the baseline and the sham PAS group. This provides initial confirmation of the effectiveness of the paired stimulation protocol using the 'Hebbian pattern' for enhancing cognitive function in aMCI patients. Changes in FC between the left hippocampus and left precuneus appear to be a potential central mechanism for improving long-term delayed recall function.

Presently, in most studies, the construction of functional networks is grounded in brain regions with statistically significant differences in functional indicators, such as amplitude of low frequency fluctuation (ALFF), regional homogeneity (ReHo) and FC, or through the utilisation of existing functional network templates.[41] In our review of literature on aMCI-related functional networks, we observed widespread abnormalities in brain regions and network function, predominantly involving the default network, salience network and visual network.[42–46] The construction of symptom-related functional networks based on existing research results displays significant heterogeneity. In our study, we amalgamated brain structure and function to construct the 'hippocampus-cortex' network, revealing circuits closely linked to the AVLT long-term delayed recall score. The prefrontal lobe and precuneus were chosen as stimulation targets. The results exhibited significant improvement in the AVLT long-term delayed recall scores in the circuit-based PAS group compared with baseline and the sham PAS group. This demonstrates the feasibility of utilising structural and FC to determine brain network targets and identify clinically relevant circuits for neuroregulatory treatment. Notably, executive function, attention and visuospatial ability exhibited no significant changes post-intervention, indirectly signifying the precision of this method. Zhao *et al* also found that structural damage and functional changes in aMCI are interconnected.[47] Grey matter volume reductions were observed in several regions in aMCI patients, and ALFF values in these regions also exhibited variable changes. In the network model fitted by Zhu *et al* for predicting AVLT delayed recall, the prefrontal lobe and parietal lobe were key nodes.[48] Cui *et al* found that spontaneous neural activity in the left prefrontal lobe was positively correlated with AVLT long-term delayed recall scores.[49] The severity of cognitive impairment in aMCI is related to spontaneous activity in the cuneus gyrus/precuneus cortex.[42] These studies support our research results. In our study, we noted a significant increase in BNT scores in the circuits-based PAS group after paired stimulation using the "Hebbian pattern". Early symptoms of AD encompass progressive episodic memory impairment, followed by other cognitive deficits, including language.[50] Aphasia may be related to AD progression, and early intervention is effective.[51] Therefore, evaluating naming function is crucial in clinical practice.[52] BNT is among the most commonly used naming function assessment scales. MCI patients with reduced BNT scores are at a higher risk of converting to AD, closely linked to episodic memory.[53] The BNT scores in AD patients are significantly lower than those in aMCI patients and the normal population. While BNT scores in aMCI patients are not significantly lower than in the normal population, semantic errors significantly increase.[54] In AD patients, the decrease in BNT scores positively correlates with hippocampus volume reduction and is closely related to the temporal lobe, thalamus and prefrontal cortex.[55 56] These may underlie the improvement in BNT scores with stimulation of the 'hippocampus-cortex' circuit. We also extended our analysis to include a comprehensive evaluation of global network metrics that there were no statistically significant changes across these metrics (online supplemental material 8).

In our study, we observed that stimulating the 'cortical-hippocampal' circuits led to decreased abnormal FC between the left hippocampus and the left precuneus cortex in aMCI patients compared with baseline. We also found that FC changes between the left hippocampus and the left precuneus cortex likely play a central role in improving long-term delayed recall function. Qin 46 *et al* demonstrated through linear regression analysis that atrophy of the left precuneus is a risk factor for memory impairment in aMCI patients.[57] Chen *et al* applied rTMS to the anterior precuneus in patients with subjective cognitive decline and observed functional changes in the anterior precuneus-hippocampal subregion and improved episodic memory.[58] Although their subjects and treatment methods differed from ours, the results were consistent.

Limitations

While this study has yielded promising results, there are limitations, including a small sample size, single-centre design and a single control group. In future studies, we plan to expand the sample size and extend the observation period to verify the reproducibility and sustainability of therapeutic efficacy. Additionally, we will consider increasing the number of pulses per session and treatment duration to evaluate the potential for enhanced efficacy. Furthermore, a comparison of efficacy between the two stimulation modes, using the currently clinically used single target point stimulation pattern as a control group, should be explored.

Summary

This study proposes the use of paired TMS to modulate the 'cortical-hippocampus' circuits for the treatment of aMCI. The

method combines individualised FC based on white matter fibre tracking related to symptoms to determine stimulation targets. The originality of employing the 'Hebbian pattern' paired stimulation in precise neuromodulation treatment has been demonstrated and its efficacy has been confirmed.

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