Journal of NeuroEngineering and Rehabilitation

RESEARCH

Open Access

Enhanced episodic memory and LTP-like plasticity in subjective cognitive decline following 10-Hz repetitive transcranial magnetic stimulation

Tianjiao Zhang[1,2†], Qian Lu[3†], Jie Song[1†], Manyu Dong[1], Chuan He[3], Zude Zhu[4], Han Yang[1], Yilun Qian[1], Tong Wang[1*], Hanjun Liu[5,6*] and Ying Shen[1*]

Abstract

Background Subjective cognitive decline (SCD) is a self-perceived cognitive complaint in the absence of objective impairment, representing an at-risk state along the continuum of cognitive aging. High-frequency repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (L-DLPFC) has shown cognitive benefits in Alzheimer's disease (AD), yet its effects on cognitive functions in SCD remain largely unexplored.

Objective To evaluate the effects of 10-Hz rTMS over the L-DLPFC in individuals with SCD on cognitive functions and long-term potentiation (LTP)-like plasticity, indexed by changes in motor evoked potential (MEP) following intermittent theta burst stimulation, and examine the relationship between brain plasticity and cognitive outcomes.

Methods In this randomized, sham-controlled trial, 42 individuals with SCD received 20 sessions of either active or sham 10-Hz rTMS ($n=21$ per group) over four weeks. The primary outcome was delayed episodic memory, evaluated using the Auditory Verbal Learning Test-Huashan version (AVLT-H). Secondary outcomes included additional cognitive measures and MEP amplitudes at baseline and at 5 (T_5), 10 (T_{10}), and 30 (T_{30}) minutes post-intervention.

Results The rTMS group exhibited significant improvements in both delayed episodic memory (AVLT-N5) and MEP amplitudes at T_5 and T_{10} following the intervention, whereas such changes were not observed in the sham group. Moreover, increased MEP amplitude at T_{10} was positively correlated with improved AVLT-N5 performance.

†Tianjiao Zhang, Qian Lu and Jie Song contributed equally to this work.

*Correspondence:
Tong Wang
wangtong60621@163.com
Hanjun Liu
lhanjun@mail.sysu.edu.cn
Ying Shen
shenying@njmu.edu.cn

Full list of author information is available at the end of the article

Conclusions These findings provide the first evidence for enhanced delayed episodic memory and LTP-like plasticity in individuals with SCD following 10-Hz rTMS over the L-DLPFC, suggesting a potential role of LTP-like plasticity in elucidating the neurophysiological correlates of cognitive improvements for SCD.

Trial registration The study design and analysis plan were preregistered on September 7th, 2023 at Chinese Clinical Trial Registry (No. ChiCTR2300075517).

Keywords Subjective cognitive decline, Repetitive transcranial magnetic stimulation, Dorsolateral prefrontal cortex, Episodic memory, Long-term potentiation-like plasticity

Background

Alzheimer's disease (AD) is a leading cause of cognitive impairment among older adults, posing a significant global public health challenge [1]. Subjective cognitive decline (SCD) is characterized by persistent, self-reported cognitive complaints in the absence of objective impairment on standardized neuropsychological assessments [2]. SCD has been associated with an elevated risk of progression to mild cognitive impairment (MCI) and AD [3, 4]. Accumulating evidence suggests that SCD may reflect subtle neurobiological changes associated with early AD pathology, including disrupted connectivity and hippocampal dysfunction [5, 6], which positions it a potential window for early intervention. Compared to individuals with MCI or AD, those with SCD typically exhibit preserved cognitive performance and relatively intact brain structure, which may enhance responsiveness to early neuromodulatory or behavioral interventions [2, 7]. Despite promising findings from preliminary trials, there remains no established treatment protocols for SCD [8], highlighting an urgent need to develop novel strategies to address cognitive concerns in this at-risk population.

Episodic memory impairment is among the earliest and most salient cognitive deficits associated with AD [9, 10, 11]. This domain is integral to higher-level processes such as reasoning, judgment, and decision-making [12]. Impairments in episodic memory have been closely linked to disruptions in functional integration among memory-related brain networks in AD [13, 14]. Notably, deficits in episodic memory can be detected as early as the SCD stage [15], and these impairments are not restricted to medial temporal dysfunctions but also involve broader disruptions in cortical and subcortical networks supporting memory consolidation and retrieval processes [16]. Neuropsychological assessments such as the Auditory Verbal Learning Test (AVLT) has shown high sensitivity in detecting early episodic memory deficits, particularly within Chinese populations, where the Huashan version (AVLT-H) is widely used and validated for detecting memory deficits [15].

At the synaptic level, long-term potentiation (LTP)-like plasticity is fundamental to learning and memory processes [17]. Accumulating evidence indicates that disruptions in synaptic plasticity is central to AD pathogenesis and contributes significantly to early memory decline across the cognitive aging spectrum [18, 19]. Therefore, LTP-like plasticity has been emerged as a potential biomarker for cognitive vulnerability, with reduced plasticity associated with greater cognitive impairments in patients with AD [20] and predictive of conversion to dementia in individuals with memory dysfunction [21]. Intermittent theta burst stimulation (iTBS) is a patterned form of repetitive transcranial magnetic stimulation (rTMS) that can induce LTP-like plasticity in the human cortex [21, 22], making it a valuable protocol for investigating early cortical changes in AD [23]. Importantly, iTBS-induced plasticity in the primary motor cortex (M1) shares neruophysiological features with hippocampal plasticity alterations in animal models of AD [24], making it a useful tool for exploring plasticity-related dysfunction in preclinical stages of cognitive decline. However, the extent to which LTP-like plasticity relates to cognitive outcomes in individuals with SCD remains poorly understood.

It is noteworthy that rTMS has emerged as a promising non-invasive neuromodulatory intervention for cognitive impairments in AD [25]. At the neurophysiological level, high-frequency rTMS (HF-rTMS) is thought to facilitate synaptic plasticity by reducing magnesium blockade of N-methyl-D-aspartate (NMDA) receptors during neuronal depolarization, thereby enhancing postsynaptic excitability and promoting LTP-like mechanisms [26]. Although rTMS-induced plasticity changes typically last 30 to 60 min, their longer-term consolidation may be influenced by individual differences in genetic predispositions and brain network integrity, potentially leading to sustained cognitive benefits [27]. Although limited, several studies have investigated the effects of HF-rTMS on domain-specific cognitive functions in SCD. For example, Sole-Padulles et al. [28] found that 5-Hz rTMS over the left prefrontal cortex enhanced face-name associative memory, while Liu et al. [29] reported that 10-Hz rTMS over the left dorsolateral prefrontal cortex (L-DLPFC) enhanced visual working memory, attention, and executive function. In addition, Liang et al. [30] found that rTMS over the precuneus in individuals with SCD modulated their abnormal effective connectivity in the default mode network (DMN) and the executive control network

(CEN), resulting in improved episodic memory performance. Despite these encouraging findings, whether delayed episodic memory, one of the most sensitive cognitive domains in individuals with SCD, can benefit from HF-rTMS remain uncertain.

The L-DLPFC is often chosen as a target in rTMS interventions for cognitive impairments, as it plays an important role in encoding and retrieving episodic memory [31, 32, 33, 34]. In particular, HF-rTMS over the DLPFC is generally associated with excitatory effects, increasing local cortical activity, enhancing functional connectivity, and improving the allocation of cognitive resource within the PFC [35, 36]. There is evidence showing a positive correlation between increased cortical plasticity in the M1 and improved cognitive function in AD patients following HF-rTMS over the DLPFC [37]. Complementing this finding, our previous study also found that 4 weeks of HF-rTMS over the prefrontal cortex in healthy adult rats enhanced spatial episodic learning and memory and modulated receptor-dependent brain plasticity in the PFC, hippocampus, and M1 [38]. Collectively, these findings raise the possibility that HF-rTMS may enhance cognitive function by promoting LTP-like plasticity.

Therefore, the present study investigated whether HF-rTMS (10 Hz) over the L-DLPFC could improve cognitive functions, particularly delayed episodic memory, in individuals with SCD. To explore potential neurophysiological correlates of treatment effects, we also measured changes in LTP-like plasticity, typically indexed by iTBS-induced motor evoked potential (MEP) amplitudes in M1, before and after the intervention. We hypothesized that HF-rTMS would enhance episodic memory performance and promote LTP-like plasticity in individuals with SCD and that these improvements would be associated with changes in LTP-like plasticity. These findings would provide insights into the neurophysiological mechanisms by which rTMS may exert beneficial effects on cognitive declines in SCD.

Methods

Participants

This study was designed as a randomized, sham-controlled clinical trial. Participants were recruited from local communities and memory clinics at the Department of Rehabilitation Medicine of The Affiliated Jiangsu Shengze Hospital of Nanjing Medical University in China between September 2023 and March 2024. Ethical approval was granted by the Human Research Ethics Committee of The Affiliated Jiangsu Shengze Hospital (No. 2023-002-01), and all participants provided written informed consent prior to enrollment. The study protocol was preregistered with the Chinese Clinical Trial Registry (No. ChiCTR2300075517) and published [39] in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized clinical trials. A detailed flow diagram of participant enrollment, allocation, and analysis is presented in Fig. 1.

Inclusion/exclusion criteria

Participants were included in this study if they met the following inclusion criteria [40, 41]: (1) not meeting the diagnostic criteria for MCI as determined by standardized neuropsychological assessments of memory, executive function, and language; (2) self-reported memory decline persisting for at least six months; (3) personal concerns about memory performance being worse than that of age-matched peers; (4) age between 55 and 80 years old; and (5) ability and willingness to provide written informed consent.

Patients were excluded if they if they met any of the following criteria: (1) a Modified Hachinski Ischemic Score > 4, or a diagnosis of vascular dementia or other forms of dementia based on the NINDS-AIREN criteria as assessed by two psychiatrists; (2) medical or neurological conditions that could interfere with cognitive function or study participation; (3) symptoms of depression, defined by a score of ≥ 6 on the Geriatric Depression Scale; (4) any contraindications to TMS (e.g., history of seizures, metallic implants in the head); (5) a history of substance or alcohol abuse within the past six months; (6) recent treatment with central nervous system medications within the past three months; or (7) a history of severe cardiovascular or cerebrovascular diseases.

Sample size calculation

The sample size was determined based on an anticipated effect size of Cohen's $d = 0.80$ [42]. With an alpha level of 0.05 and a power $(1 - \beta)$ of 80%, the minimum sample size per group was calculated using G*Power software (version 3.1).To account for an estimated 5% attrition rate, a total of 24 participants were recruited in the present study.

TMS intervention

TMS was administered using a D-MT500 magnetic biphasic stimulator (Neurosoft Ltd., Russia) equipped with a figure-of-eight coil (AFEC-02-100-C; Neurosoft Ltd., Russia). The stimulation target was the L-DLPFC, localized using the F3 scalp position according to the international 10–20 EEG system [43]. Participants in the active rTMS group received 10 Hz stimulation over the L-DLPFC at 90% of their resting motor threshold (RMT). Each session consisted of 50 pulses that were delivered in 5-second trains with a 10-second intertrain interval, resulting in a total of 40 trains (2,000 pulses). Sessions lasted approximately 10 min and were administered 5 times per week over a 4-week period (total of 20 sessions). Participants in the sham group underwent

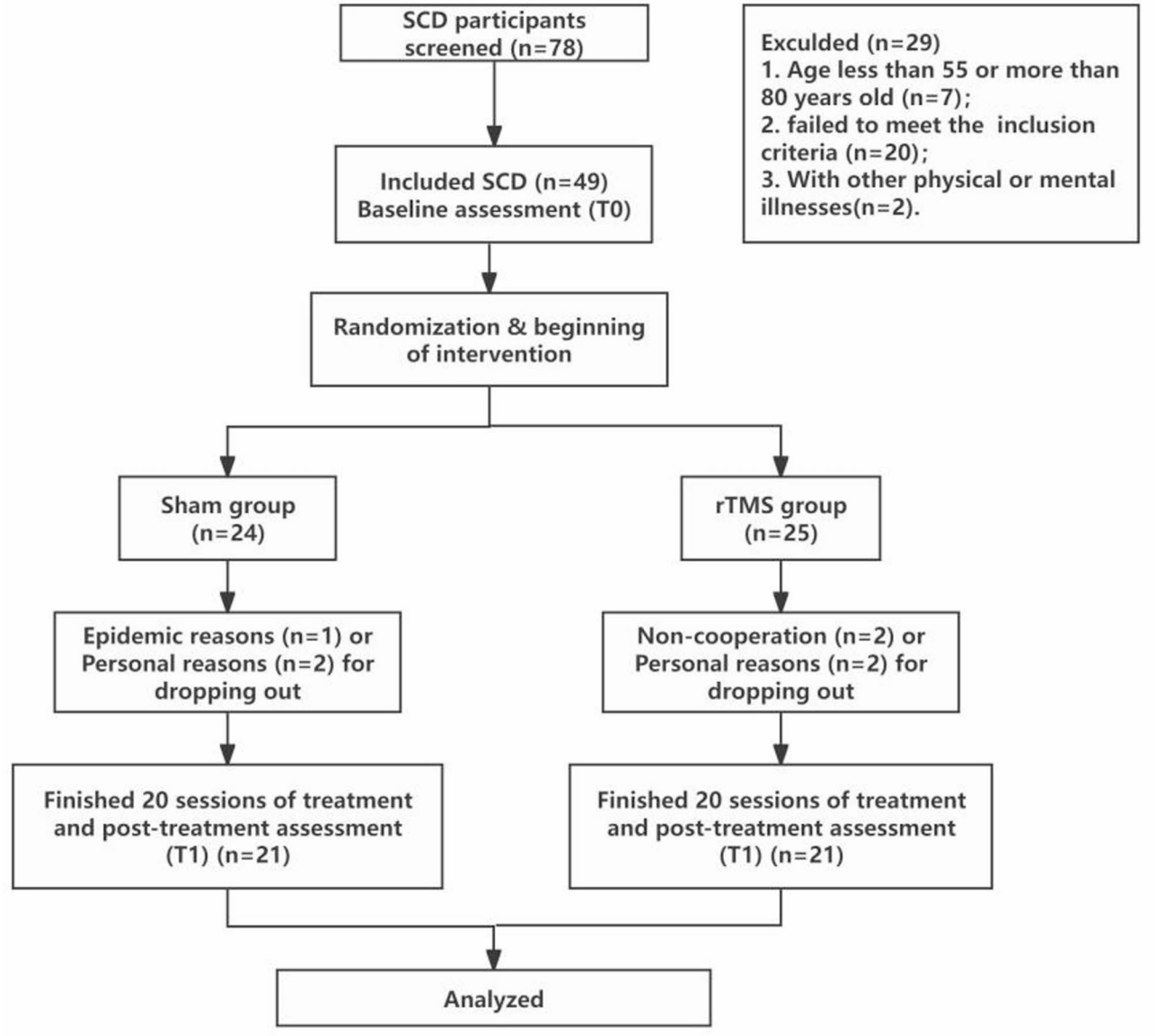

Fig. 1 The CONSORT diagram of the clinical trial

an identical procedure using a self-contained sham stimulation protocol to maintain blinding and ensure comparability.

Primary outcomes

The primary outcome was episodic memory performance, assessed using the AVLT-H. This assessment has been validated as an effective and robust measure of verbal memory and semantic categorization in mainland Chinese populations [44]. The AVLT-H is widely used in clinical and research settings to detect cognitive impairment in individuals with SCD and MCI [45]. Previous studies have shown that measures such as delayed recall and memory retention are effective in identifying memory impairments associated with AD [44].

Secondary outcomes

Secondary outcomes included assessments of additional cognitive domains and LTP-like cortical plasticity. To minimize individual variability, all assessments were conducted on the same day for each participant, with cognitive tests performed in the morning and neurophysiological evaluations scheduled in the afternoon. Global cognitive function was assessed using the Mini-Mental State Examination (MMSE). Language function was evaluated using the Animal Fluency Test (AFT) and the Boston Naming Test China version (BNT-C). Executive function was assessed by measuring the completion time on the Trail Making Test (TMT) parts A and B [40]. In addition, working memory and inhibitory control were assessed using a 1-back task and a Go/No-Go task,

respectively. These tasks were administered via E-Prime 2.0 software (Psychology Software Tools Inc., Pittsburgh, PA), which recorded both task accuracy and reaction times for further analysis.

To evaluate LTP-like plasticity, MEPs were recorded from the abductor pollicis brevis (APB) muscle of the right hand using SKINTACT RT-34 electrodes (Fannin Ltd., Dublin, Ireland; 10.5 mm × 25 mm) connected to an electromyography (EMG) system (Neuro-MEP-Micro, Russia). Participants were seated in a relaxed, semi-reclined position during assessment. The TMS coil was positioned over the left M1, with the handle angled 45° backward from the midline of the sagittal plane of the brain. The individual RMT, defined as the minimum stimulation intensity required to elicit MEPs ≥ 50 μV in at least 5 out of 10 consecutive trials, was used to determine subsequent stimulation intensities.

LTP-like plasticity was indexed by changes in MEP amplitude in response to iTBS. Single-pulse TMS was applied at the left motor hotspot at 120% of the RMT, and 20 consecutive MEPs were recorded per time point. MEP measurements were obtained at five time points: two baseline recordings (separated by 5 min) and three recordings at 5 (T_5), 10 (T_{10}), and 30 (T_{30}) minutes post-iTBS (see Fig. 2). To ensure baseline reliability, iTBS was administered only if the difference between the two baseline MEP averages was less than 20% [46]. The iTBS protocol consisted of 2-second trains of three stimuli delivered at 50 Hz, repeated every 10 s over a total duration of 192 s, resulting in 600 pulses at 80% of the RMT [46, 47]. All MEPs were peak-to-peak amplitude averaged and normalized relative to baseline to quantify the degree of induced plasticity.

Statistical analysis

Statistical analyses were performed using SPSS (v. 23.0; IBM Corp., Armonk, NY). Statistical significance was defined as $p < 0.05$ (two-tailed), with a 95% confidence interval. Demographic and baseline characteristics were compared between groups using independent samples t-tests for continuous variables and Fisher's exact tests for categorical variables. Cognitive function performance was analyzed using two-way repeated-measures analysis of variance (RM-ANOVA), with session (pre- and post-intervention) as a within-subject factor, group (rTMS and sham) as a between-subjects factor. To evaluate LTP-like plasticity, independent-samples t-tests were first performed on raw MEP amplitudes before and after the intervention to determine whether both groups were comparable at baseline. Next, two-way RM-ANOVAs with factors group (rTMS vs. sham) and timepoint (T_5, T_{10}, T_{30}) were performed on normalized post-iTBS MEP amplitudes before and after the intervention to examine between-group differences in post-iTBS changes. Finally, separate one-way RM-ANOVAs were conducted within each group to compare normalized MEP amplitudes across four timepoints (T_0, T_5, T_{10}, T_{30}) before and after the intervention to determine rTMS-induced changes in LTP-like plasticity. Bonferroni correction was applied for adjustment of multiple comparisons. In addition, to assess the association between changes in cognitive performance and LTP-like plasticity, we calculated post–pre differences for both memory performance scores and MEP amplitudes, standardized these values into z-scores, and examined their relationship using Spearman's rank-order correlation. Effect sizes were quantified using partial eta-squared (η^2_p) values, with η^2_p values of 0.01–0.05,

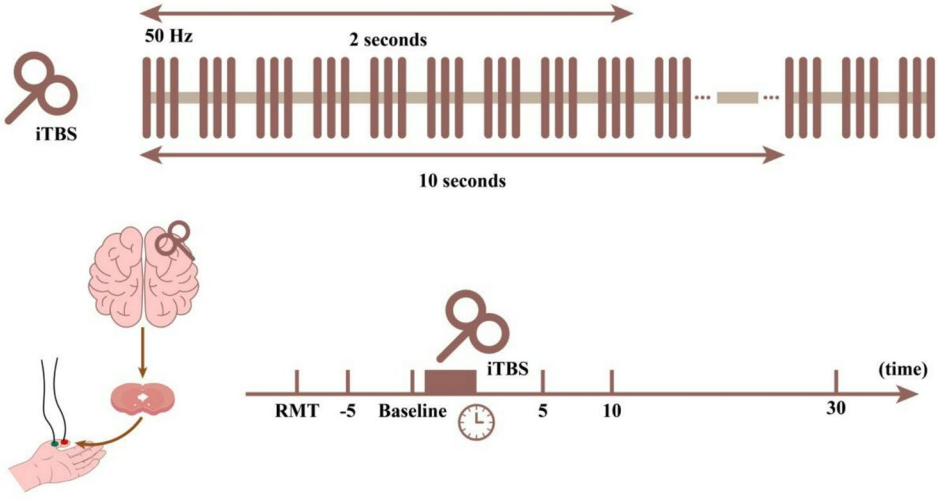

Fig. 2 Flow of LTP-like plasticity assessment. MEPs were elicited by delivering 20 consecutive single-pulse TMS stimuli on the motor hotspot in the left M1. The peak-to-peak amplitudes of the 20 MEPs were measured and averaged for further analysis. MEPs were assessed at five time points: two baseline assessments with 5 min apart (the second used as the reference baseline) and three measurements obtained at 5, 10, and 30 min post-iTBS

Table 1 Demographic and clinical characteristics of participants in the rTMS and Sham groups

	rTMS group	Sham group	t/χ^2	*P* value
Age (years)	69.48 ± 6.86	65.38 ± 6.52	1.982	0.054
Sex (F, %)	13 (60%)	16 (75%)	1.000	0.317
Education (years)	10.10 ± 2.61	8.76 ± 2.95	-1.553	0.128
MMSE (scores)	28.76 ± 1.30	29.33 ± 1.15	1.506	0.140
PSQI (scores)	6.84 ± 4.37	8.38 ± 4.99	-1.032	0.309

Note: Between-group comparisons of categorical variables (sex distribution) were analyzed using chi-square tests, while continuous variables were assessed using independent samples t-tests. The results were reported as mean ± standard deviation (SD). MMSE: Mini Mental State Examination; PSQI: Pittsburgh sleep quality index

0.06–0.13, and > 0.14 indicating small, medium, and large effects, respectively [48].

Results

Participants

Table 1 presents the demographic and baseline characteristics of both the rTMS and sham groups. No significant differences were observed between the two groups in terms of age, sex, education background, MMSE scores, and PSQI scores, indicating that the two groups were well-matched across these variables.

Episodic memory

Table 2 shows the results of statistical analyses examining performance on all AVLT-H subsets as a function of group and time. Two-way RM-ANOVAs revealed significant main effects of time for all AVLT-H subtests ($p < 0.003$) except AVLT-N7 ($p = 0.443$), reflecting overall improvements from pre- to post-intervention across the two groups. In contrast, no significant main effects of group were observed for any subtest (all $p > 0.05$). However, a significant time × group interaction was found specifically for AVLT-N5 ($F(1, 40) = 9.774$, $p = 0.003$, $\eta^2_p = 0.196$). Follow-up analyses revealed a significant improvement in AVLT-N5 in the rTMS group (t=-1.952, $p < 0.001$), whereas no significant difference was observed in the sham group (t=-0.048, $p = 0.913$).

Secondary cognitive functions

Table 3 shows the statistical results regarding changes in performance on secondary cognitive functions as a function of group and time. There were significant main effects of time on AFT ($F(1, 40) = 6.949$, $p = 0.012$, $\eta^2_p = 0.148$), BNT-C ($F(1, 40) = 4.915$, $p = 0.032$, $\eta^2_p = 0.109$), and TMT-A-C assessments ($F(1, 40) = 4.401$, $p = 0.042$, $\eta^2_p = 0.099$), while the main effects of time failed to reach significance for the other subscales ($p > 0.2$). However, no significant main effects of group (all $p > 0.5$) or time × group interactions were found across any secondary cognitive functions ($p > 0.05$).

Long-term potentiation-like plasticity

Table 4 shows changes in LTP-like plasticity, indexed by normalized MEP amplitudes in M1, across the rTMS and sham groups before and after the intervention. At baseline, independent sample t-tests on raw MEPs confirmed that the rTMS and sham groups did not

Table 2 Changes of AVLT-H subscales before and after the intervention in the rTMS and Sham groups

	rTMS group		Sham group		*P* value			ηp2		
	Baseline	Post-treatment	Baseline	Post-treatment	Group	Time	Group x Time	Group	Time	Group x Time
AVLT-N1 + N2 + N3	15.05 ± 3.88	18.33 ± 3.81	15.33 ± 3.45	17.14 ± 3.44	0.617	0.001*	0.286	0.006	0.258	0.028
AVLT-N4	4.71 ± 2.33	6.29 ± 1.52	5.52 ± 1.81	6.86 ± 1.82	0.175	< 0.001*	0.694	0.045	0.369	0.004
AVLT-N5	3.90 ± 1.79	5.86 ± 1.98	4.86 ± 1.42	4.90 ± 1.79	0.842	0.002*	0.003*	0.000	0.212	0.196
AVLT-N1 + N2 + N3 + N4 + N5	23.67 ± 6.18	30.48 ± 6.64	25.72 ± 4.98	28.90 ± 5.01	0.873	< 0.001*	0.063	0.001	0.412	0.084
AVLT-N7	21.42 ± 1.78	21.19 ± 3.03	20.43 ± 2.25	21.48 ± 2.42	0.504	0.443	0.226	0.011	0.015	0.036

AVLT-H: auditory verbal learning Test-Huashan; *$P < 0.05$

Table 3 Changes of secondary cognitive functions before and after the intervention in the rTMS and Sham groups

	rTMS group		Sham group		*P* value			ηp2		
	Baseline	Post-treatment	Baseline	Post-treatment	Group	Time	Group x Time	Group	Time	Group x Time
AFT	16.00 ± 3.48	17.52 ± 3.98	17.19 ± 3.37	18.42 ± 3.19	0.277	0.012*	0.786	0.029	0.148	0.002
BNT-C	23.57 ± 2.62	24.81 ± 3.78	21.90 ± 3.43	23.05 ± 3.73	0.067	0.032*	0.930	0.082	0.109	0.000
TMT-A-C (s)	69.24 ± 25.42	62.57 ± 28.20	69.14 ± 24.53	61.28 ± 17.14	0.917	0.042*	0.864	0.000	0.099	0.001
TMT-B-C (s)	153.81 ± 38.47	145.57 ± 37.77	158.62 ± 65.68	158.38 ± 34.85	0.714	0.294	0.632	0.003	0.028	0.006
Go RT (ms)	336.17 ± 17.78	329.07 ± 14.85	336.44 ± 17.18	328.45 ± 19.08	0.164	0.930	0.818	0.053	0.000	0.001
No-Go ERR (%)	0.06 ± 0.11	0.06 ± 0.11	0.07 ± 0.13	0.07 ± 0.13	0.838	0.249	0.616	0.001	0.034	0.007
1-back ACC (%)	0.83 ± 0.22	0.87 ± 0.11	0.88 ± 0.14	0.89 ± 0.07	0.452	0.308	0.521	0.015	0.027	0.011

AFT: animal fluency test; BNT-C: Boston naming test China version; TMT-A/B-C: trail making test parts A and B China version; go RT: the average response time of the go task; No-Go ERR: No-Go task error rate; 1-back ACC: 1-back task accuracy; *$P < 0.05$

Table 4 LTP-like responses indexed by normalized MEP amplitudes at T_5, T_{10}, and T_{30} time points before and after the intervention in the rTMS and Sham groups

	Baseline (mV)	T_5 (%)	T_{10} (%)	T_{30} (%)	Group (*P*)	Time (*P*)	Group x Time (*P*)	Group (η2p)	Time (η2p)	Group x Time (η2p)
Pre-intervention					0.454	0.071	0.206	0.014	0.064	0.039
rTMS group	0.81 ± 0.50	101 ± 21.20	114 ± 28.74	106 ± 19.60						
Sham group	0.86 ± 0.48	115 ± 30.18	118 ± 31.02	103 ± 28.25						
Post-intervention					0.104	0.004*	0.231	0.065	0.142	0.036
rTMS group	0.66 ± 0.29	130 ± 36.45	143 ± 38.01	109 ± 24.92						
Sham group	0.76 ± 0.09	118 ± 32.07	119 ± 32.39	108 ± 36.01						

*$P < 0.05$

differ significantly before (t=-0.359, $p = 0.722$) or after the intervention (t=-0.873, $p = 0.388$). To assess group differences in iTBS-induced plasticity before and after the intervention, two-way RM-ANOVAs were conducted on normalized post-iTBS MEPs at T_5, T_{10}, and T_{30}. Before the intervention, no significant main effects of timepoint ($F(2, 80) = 2.729$, $p = 0.071$) or group ($F(1, 40) = 0.571$, $p = 0.454$) as well as their interaction ($F(2, 80) = 1.609$, $p = 0.206$) were observed. After the intervention, there was a significant main effect of timepoint ($F(2, 40) = 6.596$, $p = 0.004$, η^2_p=0.142), with MEP amplitudes at T_{30} significantly smaller that at T_5 ($p = 0.032$) and T_{10} ($p = 0.015$). However, neither the main effect of group ($F(1, 40) = 2.775$, $p = 0.104$) nor group × timepoint interaction ($F(2, 80) = 1.491$, $p = 0.231$) reached significance.

To further determine changes in LTP-like plasticity within each group, separate one-way RM-ANOVAs were performed on normalized MEPs across T_0, T_5, T_{10}, and T_{30}. In the rTMS group, no significant main effect of timepoint was found before the intervention ($F(3, 60) = 2.655$, $p = 0.057$), but there was a significant main effect of time after the intervention ($F(3, 60) = 11.067$, $p < 0.001$, η^2_p=0.356). Post hoc comparisons revealed significantly higher MEP amplitudes at T_5 ($p = 0.007$) and T_{10} ($p < 0.001$) relative to baseline (see Fig. 3). In contrast, the sham group exhibited no significant main effects of timepoint either before ($F(3, 60) = 2.548$, $p = 0.088$) or after the intervention ($F(3, 60) = 2.988$, $p = 0.099$).

Association between cognitive function with LTP-like plasticity

To explore whether changes in LTP-like plasticity were associated with improvements in memory performance, we examined the relationship between z-score–transformed post–pre changes in AVLT-N5 and normalized MEP amplitudes at T_{10} within the rTMS group. The results revealed a significant positive correlation ($\rho = 0.453$, $p = 0.045$; Fig. 4), indicating that individuals with greater increases in MEP amplitudes tended to show larger gains in delayed recall following rTMS over the left DLPFC. However, when accounting for individual variability in baseline memory performance using a linear regression model with post-intervention AVLT-N5 as the dependent variable, baseline AVLT-N5 as a covariate, and T_{10} MEP change as the predictor, the results did not to show a significant correlation ($F(2, 20) = 2.294$, $p = 0.131$).

Discussion

This study investigated the cognitive and neurophysiological effects of HF-rTMS in individuals with SCD. Following a four-week session of 10-Hz rTMS over the L-DLPFC, participants in the rTMS group exhibited improved delayed episodic memory and LTP-like plasticity, as reflected by enhanced AVLT-N5 scores and MEP amplitudes at T_5 and T_{10}. Importantly, improvement of AVLT-N5 scores was significantly correlated with enhancement of MEP amplitudes at T_{10}. In contrast, the sham group exhibited no significant changes in cognitive outcome or MEP amplitudes. These findings provide the first evidence that 10-Hz rTMS over the L-DLPFC can lead to domain-specific cognitive benefits in individuals with SCD and highlight the potential role of LTP-like plasticity in elucidating the neurophysiological correlates of treatment-induced cognitive improvement in this at-risk population.

Previous research has demonstrated the beneficial effects of rTMS on episodic memory in healthy individuals [49, 50]. Our study extends these findings to a cognitively at-risk population, showing that individuals with SCD following HF-rTMS over the L-DLPFC exhibited significant improvements in episodic memory, particularly tasks requiring delayed recall. This finding is consistent with prior studies in AD, where rTMS was found to improve both immediate and delayed recall [51, 52]. Our findings suggest that delayed episodic memory may be particularly sensitive to HF-rTMS, potentially because it is one of the earliest cognitive functions to deteriorate along the AD continuum. The observed improvements in episodic memory may reflect enhanced functional integration or compensatory recruitment within fronto-hippocampal networks, a hypothesis supported by as previous studies linking episodic memory performance (e.g., Rey AVLT) and hippocampal activity in patients with AD [53]. Notably, no significant improvements were

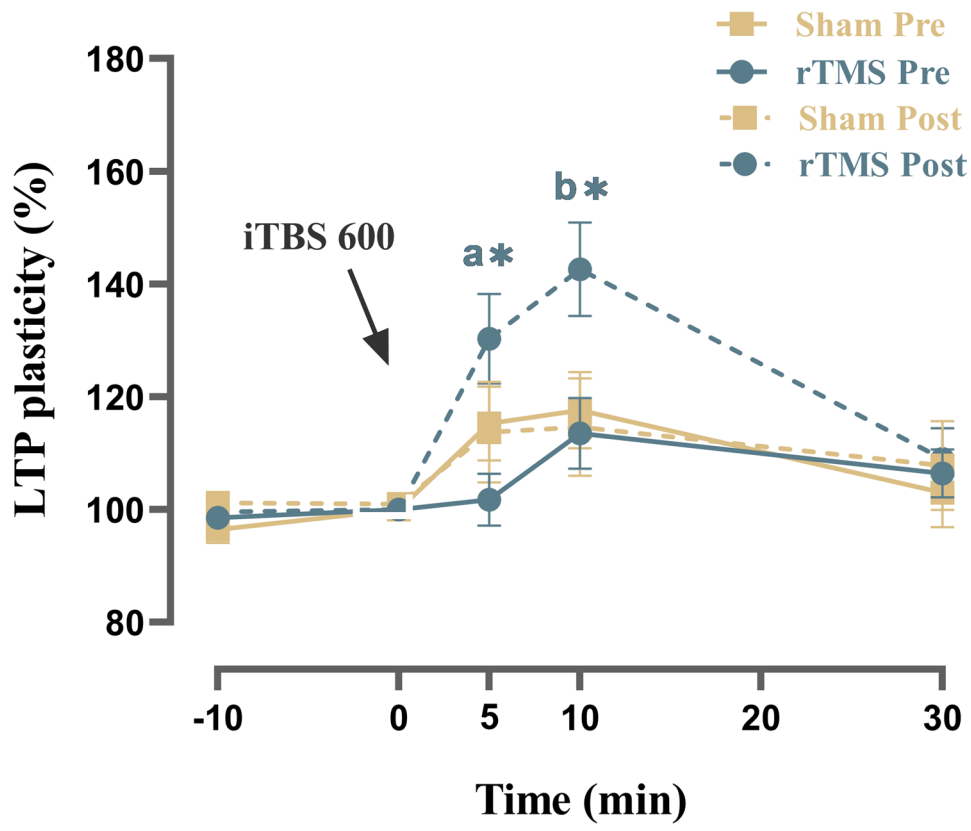

Fig. 3 Changes in LTP-like plasticity levels at the T_5, T_{10}, and T_{30} for the rTMS and sham groups before and after the intervention. a: comparison of normalized MEP amplitudes between T_0 and T_5 in the rTMS group after the intervention; b: comparison of normalized MEP amplitudes between T_0 and T_{10} in the rTMS group after the intervention; $^*P < 0.05$

observed in other cognitive domains such as language or executive function, consistent with prior studies reporting domain-specific benefits of rTMS in episodic memory without generalized cognitive enhancement [52, 54]. This selective effect may be attributed to the vulnerability of episodic memory in SCD, which is closely associated with the function integrity of the L-DLPFC.

Although our study revealed a significant improvement in AVLT-N5 for the rTMS group relative to the sham group, no between-group differences were found for other AVLT subtests or broader cognitive functions. The general improvement in episodic memory performance across both the rTMS and sham groups may reflect non-specific influences such as practice effects or increased familiarity with the testing procedures, which are likely to enhance performance on tasks requiring immediate recall (e.g., AVLT-H) [55]. However, the significant time-by-group interaction exclusively for AVLT-N5 (delayed recall following interference) suggests the involvement of a more specific neurobiological mechanism beyond generalized learning or expectancy effects [56]. Unlike immediate recall, delayed recall after interference places greater demands on executive control and resistance to proactive interference, processes that are critically supported by the integrity of the prefrontal-hippocampal network [57, 58]. HF-rTMS over the left DLPFC may enhance synaptic efficacy and strengthen functional connectivity within these circuits, thereby improving memory consolidation and retrieval under high interference conditions [59, 60]. In contrast, sham stimulation did not provide sufficient neuromodulatory influence to support delayed recall after interference, resulting in the absence of corresponding improvement. This task-specific dissociation underscores the role of L-DLPFC in mediating rTMS-induced cognitive benefits and highlights AVLT-N5 as a sensitive behavioral marker of plasticity following this neuromodulation.

The L-DLPFC has been widely recognized as an optimal neuromodulatory target for interventions for improving cognitive functions in patients with MCI and AD [32], which is primarily due to its critical role in processing and recalling verbal information, working memory, and executive control [34]. Applying rTMS to the L-DLPFC has been proposed to enhance episodic memory by facilitating semantic processing and promoting memory reconsolidation [61]. In supporting of this hypothesis, Manenti et al. [62] found that anodal transcranial direct current stimulation (tDCS) applied to the

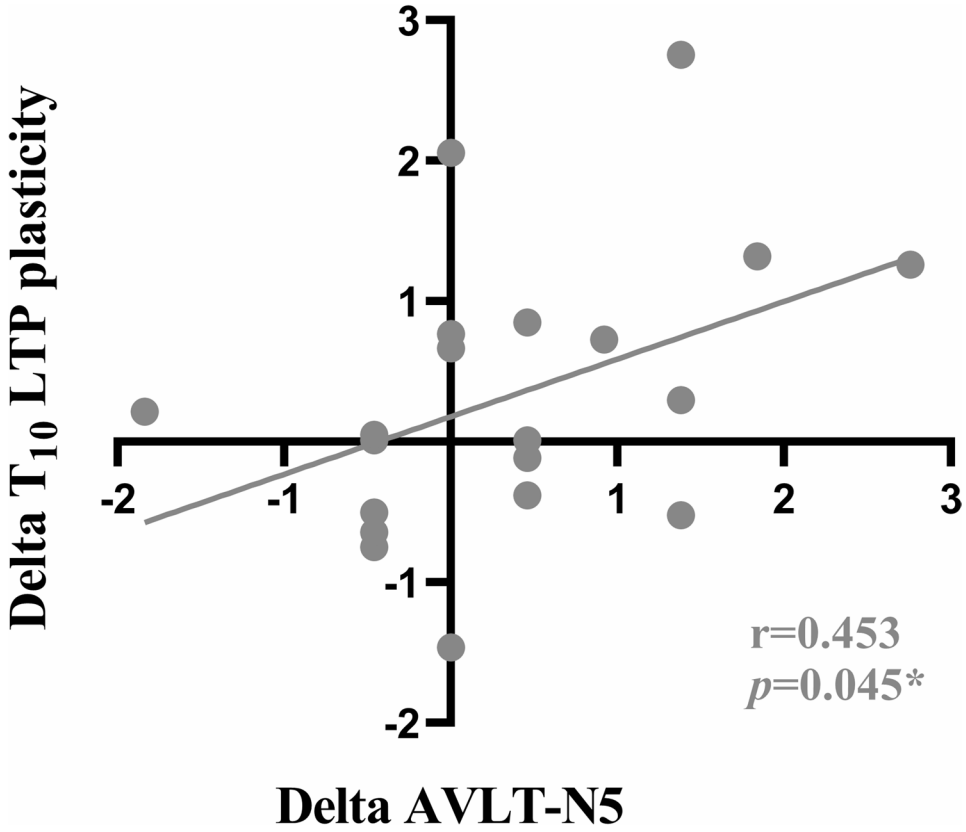

Fig. 4 Scatter plots showing significant correlations between post-pre changes in AVLT-N5 and iTBS-induced MEP at T_{10} in the rTMS group. AVLT-H: Auditory Verbal Learning Test-Huashan; *$P < 0.05$

left parietal cortex and L-DLPFC significantly improved verbal memory retrieval in older adults. Similarly, anodal tDCS over the left PFC in individuals with SCD enhanced delayed memory retrieval compared to sham stimulation, with effects persisting for up to 30 days [63]. Consistent with these findings, our results provide additional evidence that HF-rTMS over the L-DLPFC may enhance and consolidate verbal episodic memory in individuals with SCD.

Hyperactivation of the DLPFC has been consistently associated with compensatory responses to cognitive decline across the AD spectrum [64]. In MCI, increased DLPFC activation is thought to compensate for structural and functional deficits, enhancing performance across various cognitive domains like semantic retrieval [65]. A similar compensatory process may occur in SCD, where increased DLPFC activation may counterbalance reduced activation of the right hippocampus during the retrieval of episodic memory, enabling performance comparable to healthy individuals [66]. Notably, this compensatory hyperactivation is not confined to the DLPFC itself but extends to other cortical regions through distal clusters of neurons. For example, Solé-Padullé et al. [28] found that 5-Hz rTMS over the L-DLPFC in individuals with SCD enhanced the recruitment of the right PFC and bilateral posterior cortical regions during associative memory tasks. Similarly, Plas et al. [50] found that 1-Hz rTMS over the L-DLPFC in healthy individuals modulated beta power in the posterior brain regions to facilitate memory encoding. These findings suggest that rTMS over the L-DLPFC may not only enhance local cortical excitability but also modulate neural activity across connected networks, particularly involving parietal and posterior regions. Such network-level modulation highlights the potential of L-DLPFC neuromodulation as a circuit-based intervention strategy for mitigating early cognitive decline.

LTP-like plasticity provides a fundamental neurophysiological basis for learning and memory by maintaining the integrity of distributed neural networks [67, 68]. Disruptions in LTP-like plasticity reflect synaptic dysfunction and reduced network stability [17], which has been observed in early AD [24]. In line with these findings, our results found that individuals with SCD exhibited no significant LTP-like plasticity before the intervention, suggesting the presence of early, subclinical deficits in synaptic responses. Importantly, following a four-week intervention of 10-Hz rTMS over the L-DLPFC, the rTMS group exhibited significantly increased MEP amplitudes at T_5 and T_{10}, whereas no such modulation

occurred in the sham group. These findings suggest that HF-rTMS may reinstate LTP-like plasticity, possibly via NMDA receptor-dependent mechanisms that recalibrate excitatory-inhibitory balance within compromised memory networks [69]. This interpretation is supported by Freedberg et al. [49], showing that rTMS over the inferior parietal cortex enhanced episodic memory performance while strengthening hippocampal-cortical connectivity. Similarly, rTMS over the precuneus in AD patients improved episodic memory and enhanced functional connectivity within the DMN, particularly between the precuneus and the medial frontal lobe [54]. These converging lines of evidence highlight the potential of rTMS to restore synaptic plasticity and functional integration within compromised memory networks.

Our study revealed a significant positive correlation between improvements in AVLT-N5 scores and increases in LTP-like plasticity at T_{10} in the rTMS group, suggesting a potential functional link between rTMS-induced synaptic plasticity and delayed episodic memory improvement. However, it is noteworthy that this association did not remain significant when baseline memory performance was controlled for using regression analysis, indicating that the observed relationship should be viewed as preliminary. Nevertheless, previous research has shown that disrupted LTP-like plasticity is associated with memory deficits and elevated cerebrospinal fluid (CSF) tau levels in AD [70]. However, other reports have reported an inverse relationship between LTP-like plasticity and memory function in amyloid-positive patients with MCI, where greater plastic responses may reflect maladaptive hyperexcitability or compensatory overactivation during prodromal stages [71]. These discrepancies highlight the complex and context-dependent nature of neuroplasticity in early cognitive decline. While cortical hyperexcitability and disrupted homeostatic regulation have been implicated in progressive memory dysfunction [72, 73], reduced LTP-like responses in MCI may alternatively represent an adaptive mechanism to limit excitotoxicity and preserve neural integrity [73]. Taken together, these findings suggest that LTP-like plasticity may serve as a neurophysiological correlate of treatment-induced cognitive improvements in SCD, warranting further investigation in larger and longitudinal cohorts to clarify the robustness and significance of this relationship.

This study has several limitations that should be addressed. First, the relatively small sample size with a predominantly female cohort may restrict the generalizability of our findings. Although the trial was preregistered with a larger target sample, unforeseen logistical challenges including COVID-19–related disruptions to recruitment and temporary closures of clinical research sites impeded our ability to achieve the planned recruitment. Second, we did not evaluate psychological or emotional states such as anxiety, depression, or stress, which are known to influence cognitive performance and could confound treatment effects. Third, the lack of neuroimaging assessments limits our ability to characterize prefrontal plasticity and its network-level contributions underlying the observed behavioral improvement. Future research should address these limitations by recruiting larger, demographically balanced cohorts, incorporating assessments of psychological well-being, and integrating neuroimaging approaches to elucidate the neural mechanisms underlying rTMS-induced cognitive benefits in individuals with SCD.

Conclusion

In summary, our study provides evidence that 10-Hz rTMS over the L-DLPFC can selectively enhance delayed episodic memory and promote LTP-like plasticity in individuals with SCD, as reflected by improved AVLT-N5 scores and increased MEP amplitudes at T_5 and T_{10}. A significant correlation was also found between improved AVLT-N5 and increased MEP amplitudes at T_{10}, although this relationship should be considered preliminary given its failure to reach significance after adjusting for baseline memory performance. These findings highlight the potential of HF-rTMS over the L-DLPFC for restoring synaptic plasticity and enhancing cognitive function in SCD, suggesting that LTP-like plasticity may provide important insights into the neurophysiological basis underlying treatment-induced cognitive benefits.

Abbreviations

AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
AFT	Animal Fluency Test
APB	Abductor pollicis brevis
BNT-C	Boston Naming Test China version
CEN	Executive control network
CSF	Cerebrospinal fluid
DMN	Default mode network
EMG	Electromyography
HF-rTMS	High-frequency repetitive transcranial magnetic stimulation
iTBS	Intermittent theta burst stimulation
L-DLPFC	Left dorsolateral prefrontal cortex
LTP	Long-term potentiation
M1	Primary motor cortex
MCI	Mild cognitive impairment
MEP	Motor evoked potential
MMSE	Mini-Mental State Examination
NMDA	N-methyl-D-aspartate
PFC	Prefrontal cortex
PSQI	Pittsburgh Sleep Quality Index
RMT	Resting motor threshold
RM-ANOVA	Repeated-measures analysis of variance
SCD	Subjective cognitive decline
SPSS	Statistical Package for the Social Sciences
TMT	Trail Making Test
tDCS	Transcranial direct current stimulation

Author contributions

Authors' contributionsTianjiao Zhang contributed to the writing of the original draft, conducted formal analysis, and curated data. Qian Lu developed the

methodology and contributed to the software implementation. Jie Song, Manyu Dong, Han Yang and Yilun Qian performed the assessments and intervention for the patients. Chuan He and Zude Zhu provided resources and supervised the study. Hanjun Liu participated in writing, reviewing, and editing the manuscript. Tong Wang managed project administration. Ying Shen secured funding and contributed to the conceptualization of the study. All authors reviewed and approved the final manuscript.

Funding
This study was supported by the National Natural Science Foundation of China (No.82372582), the Competitive Project of Jiangsu Province's Key Research and Development Program (No. BE2023034), and the Jiangsu Province Hospital clinical diagnosis and treatment of technological innovation "Open bidding for selecting the best candidates" project (No. JBGS202414).

Data availability
The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Human Research Ethics Committee of The Affiliated Jiangsu Shengze Hospital (No. 2023-002-01). All the patients signed the written informed consent before enrollment.

Consent for publication
Consent for publication were given by all participants.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Rehabilitation Medicine, The First Affiliated Hospital with Nanjing Medical University, Nanjing 210029, China
[2]Department of Rehabilitation Science, Hong Kong Polytechnic University, Hong Kong SAR, China
[3]Department of Rehabilitation Medicine, The Affiliated Jiangsu Shengze Hospital of Nanjing Medical University, Suzhou, China
[4]School of Linguistic Sciences and Arts, Jiangsu Normal University, Xuzhou, China
[5]Department of Rehabilitation Medicine, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
[6]Guangdong Provincial Key Laboratory of Brain Function and Disease, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China

Received: 1 March 2025 / Accepted: 1 September 2025
Published online: 26 September 2025

References

1. Yin X, Xie Q, Huang L, Liu L, Armstrong E, Zhen M, et al. Assessment of the psychological burden among family caregivers of people living with alzheimer's disease using the Zarit burden interview. J Alzheimers Dis. 2021;82(1):285–91. https://doi.org/10.3233/JAD-210025.
2. Wang X, Huang W, Su L, Xing Y, Jessen F, Sun Y, et al. Neuroimaging advances regarding subjective cognitive decline in preclinical alzheimer's disease. Mol Neurodegeneration. 2020;15(1):55. https://doi.org/10.1186/s13024-020-00395-3.
3. Rabin LA, Smart CM, Amariglio RE. Subjective cognitive decline in preclinical alzheimer's disease. Ann Rev Clin Psychol. 2017;13:369–96. https://doi.org/10.1146/annurev-clinpsy-032816-045136.
4. Liew TM. Trajectories of subjective cognitive decline, and the risk of mild cognitive impairment and dementia. Alzheimers Res Ther. 2020;12(1):135. https://doi.org/10.1186/s13195-020-00699-y.
5. Rosenberg PB, Lyketsos C. Mild cognitive impairment: searching for the prodrome of alzheimer's disease. World Psychiatry: Official J World Psychiatric Association (WPA). 2008;7(2):72–8. https://doi.org/10.1002/j.2051-5545.2008.tb00159.x.
6. Sperling RA, Donohue MC, Raman R, Sun CK, Yaari R, Holdridge K, et al. Association of factors with elevated amyloid burden in clinically normal older individuals. JAMA Neurol. 2020;77(6):735. https://doi.org/10.1001/jamaneurol.2020.0387.
7. Si T, Xing G, Han Y. Subjective cognitive decline and related cognitive deficits. Front Neurol. 2020;11:247. https://doi.org/10.3389/fneur.2020.00247.
8. Sheng C, Yang K, Wang X, Li H, Li T, Lin L, et al. Advances in Non-Pharmacological interventions for subjective cognitive decline: A systematic review and Meta-Analysis. J Alzheimers Dis. 2020;77(2):903–20. https://doi.org/10.3233/jad-191295.
9. Tromp D, Dufour A, Lithfous S, Pebayle T, Després O. Episodic memory in normal aging and alzheimer disease: insights from imaging and behavioral studies. Ageing Res Rev. 2015;24(Pt B):232–62. https://doi.org/10.1016/j.arr.2015.08.006.
10. Xue G. The neural representations underlying human episodic memory. Trends Cogn Sci. 2018;22(6):544–61. https://doi.org/10.1016/j.tics.2018.03.004.
11. Yu Q, Cheval B, Becker B, Herold F, Chan CCH, Delevoye-Turrell YN, et al. Episodic memory encoding and retrieval in Face-Name paired paradigm: an fNIRS study. Brain Sci. 2021;11(7). https://doi.org/10.3390/brainsci11070951.
12. Torres-Morales C, Cansino S. Brain representations of space and time in episodic memory: A systematic review and meta-analysis. Cogn Affect Behav Neurosci. 2024;24(1):1–18. https://doi.org/10.3758/s13415-023-01140-1.
13. Ergis AM, Eusop-Roussel E. [Early episodic memory impairments in alzheimer's disease]. Rev Neurol. 2008;164(Suppl 3):S96–s. https://doi.org/10.1016/s0035-3787(08)73298-3.
14. Takehara-Nishiuchi K. Prefrontal-hippocampal interaction during the encoding of new memories. Brain Neurosci Adv. 2020;4:2398212820925580. https://doi.org/10.1177/2398212820925580.
15. Zhu Y, Zang F, Wang Q, Zhang Q, Tan C, Zhang S, et al. Connectome-based model predicts episodic memory performance in individuals with subjective cognitive decline and amnestic mild cognitive impairment. Behav Brain Res. 2021;411:113387. https://doi.org/10.1016/j.bbr.2021.113387.
16. Vidal-Piñeiro D, Martin-Trias P, Arenaza-Urquijo EM, Sala-Llonch R, Clemente IC, Mena-Sánchez I, et al. Task-dependent activity and connectivity predict episodic memory network-based responses to brain stimulation in healthy aging. Brain Stimul. 2014;7(2):287–96. https://doi.org/10.1016/j.brs.2013.12.016.
17. Wichmann C, Kuner T. Heterogeneity of glutamatergic synapses: cellular mechanisms and network consequences. Physiol Rev. 2022;102(1):269–318. https://doi.org/10.1152/physrev.00039.2020.
18. Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, et al. Amyloid-beta protein dimers isolated directly from alzheimer's brains impair synaptic plasticity and memory. Nat Med. 2008;14(8):837–42. https://doi.org/10.1038/nm1782.
19. Walsh DM, Selkoe DJ. Deciphering the molecular basis of memory failure in alzheimer's disease. Neuron. 2004;44(1):181–93. https://doi.org/10.1016/j.neuron.2004.09.010.
20. Motta C, Di Lorenzo F, Ponzo V, Pellicciari MC, Bonnì S, Picazio S, et al. Transcranial magnetic stimulation predicts cognitive decline in patients with alzheimer's disease. J Neurol Neurosurg Psychiatry. 2018;89(12):1237–42. https://doi.org/10.1136/jnnp-2017-317879.
21. Di Lorenzo F, Motta C, Casula EP, Bonnì S, Assogna M, Caltagirone C, et al. LTP-like cortical plasticity predicts conversion to dementia in patients with memory impairment. Brain Stimul. 2020;13(5):1175–82. https://doi.org/10.1016/j.brs.2020.05.013.
22. Di Lazzaro V, Bella R, Benussi A, Bologna M, Borroni B, Capone F, et al. Diagnostic contribution and therapeutic perspectives of transcranial magnetic stimulation in dementia. Clin Neurophysiology: Official J Int Federation Clin Neurophysiol. 2021;132(10):2568–607. https://doi.org/10.1016/j.clinph.2021.05.035.
23. Tian Y, Margulies DS, Breakspear M, Zalesky A. Topographic organization of the human subcortex unveiled with functional connectivity gradients. Nat Neurosci. 2020;23(11):1421–32. https://doi.org/10.1038/s41593-020-00711-6.
24. Di Lorenzo F, Ponzo V, Bonnì S, Motta C, Negrão Serra PC, Bozzali M, et al. Long-term potentiation-like cortical plasticity is disrupted in alzheimer's disease patients independently from age of onset. Ann Neurol. 2016;80(2):202–10. https://doi.org/10.1002/ana.24695.
25. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018).

Clin Neurophysiology: Official J Int Federation Clin Neurophysiol. 2020;131(2):474–528. https://doi.org/10.1016/j.clinph.2019.11.002.
26. Suppa A, Li Voti P, Rocchi L, Papazachariadis O, Berardelli A. Early visuomotor integration processes induce LTP/LTD-like plasticity in the human motor cortex. Cerebral cortex (New York, NY: 1991). 2015;25(3):703-12. https://doi.org/10.1093/cercor/bht264.
27. Cirillo G, Di Pino G, Capone F, Ranieri F, Florio L, Todisco V, et al. Neurobiological after-effects of non-invasive brain stimulation. Brain Stimul. 2017;10(1):1–18. https://doi.org/10.1016/j.brs.2016.11.009.
28. Solé-Padullés C, Bartrés-Faz D, Junqué C, Clemente IC, Molinuevo JL, Bargalló N et al. Repetitive transcranial magnetic stimulation effects on brain function and cognition among elders with memory dysfunction. A randomized sham-controlled study. Cerebral cortex (New York, NY: 1991). 2006;16(10):1487-93. https://doi.org/10.1093/cercor/bhj083.
29. Liu M, Nie ZY, Li RR, Zhang W, Huang LH, Wang JQ, et al. Neural mechanism of repeated transcranial magnetic stimulation to enhance visual working memory in elderly individuals with subjective cognitive decline. Front Neurol. 2021;12:665218. https://doi.org/10.3389/fneur.2021.665218.
30. Liang X, Xue C, Zheng D, Yuan Q, Qi W, Ruan Y, et al. Repetitive transcranial magnetic stimulation regulates effective connectivity patterns of brain networks in the spectrum of preclinical alzheimer's disease. Front Aging Neurosci. 2024;16:1343926. https://doi.org/10.3389/fnagi.2024.1343926.
31. Lin Y, Jiang WJ, Shan PY, Lu M, Wang T, Li RH, et al. The role of repetitive transcranial magnetic stimulation (rTMS) in the treatment of cognitive impairment in patients with alzheimer's disease: A systematic review and meta-analysis. J Neurol Sci. 2019;398:184–91. https://doi.org/10.1016/j.jns.2019.01.038.
32. Zhang T, Sui Y, Lu Q, Xu X, Zhu Y, Dai W, et al. Effects of rTMS treatment on global cognitive function in alzheimer's disease: A systematic review and meta-analysis. Front Aging Neurosci. 2022;14:984708. https://doi.org/10.3389/fnagi.2022.984708.
33. Hauer L, Sellner J, Brigo F, Trinka E, Sebastianelli L, Saltuari L, et al. Effects of repetitive transcranial magnetic stimulation over prefrontal cortex on attention in psychiatric disorders: A systematic review. J Clin Med. 2019;8(4). https://doi.org/10.3390/jcm8040416.
34. Balconi M. Dorsolateral prefrontal cortex, working memory and episodic memory processes: insight through transcranial magnetic stimulation techniques. Neurosci Bull. 2013;29(3):381–9. https://doi.org/10.1007/s12264-013-1309-z.
35. Li Y, Wang L, Jia M, Guo J, Wang H, Wang M. The effects of high-frequency rTMS over the left DLPFC on cognitive control in young healthy participants. PLoS ONE. 2017;12(6):e0179430. https://doi.org/10.1371/journal.pone.0179430.
36. Davis SW, Luber B, Murphy DLK, Lisanby SH, Cabeza R. Frequency-specific neuromodulation of local and distant connectivity in aging and episodic memory function. Hum Brain Mapp. 2017;38(12):5987–6004. https://doi.org/10.1002/hbm.23803.
37. Li X, Qi G, Yu C, Lian G, Zheng H, Wu S, et al. Cortical plasticity is correlated with cognitive improvement in alzheimer's disease patients after rTMS treatment. Brain Stimul. 2021;14(3):503–10. https://doi.org/10.1016/j.brs.2021.01.012.
38. Wu Q, Xu X, Zhai C, Zhao Z, Dai W, Wang T, et al. High-frequency repetitive transcranial magnetic stimulation improves Spatial episodic learning and memory performance by regulating brain plasticity in healthy rats. Front NeuroSci. 2022;16:974940. https://doi.org/10.3389/fnins.2022.974940.
39. Zhang T, Huang S, Lu Q, Song J, Teng J, Wang T, et al. Effects of repetitive transcranial magnetic stimulation on episodic memory in patients with subjective cognitive decline: study protocol for a randomized clinical trial. Front Psychol. 2023;14:1298065. https://doi.org/10.3389/fpsyg.2023.1298065.
40. Zhong Q, Ali N, Gao Y, Wu H, Wu X, Sun C, et al. Gait kinematic and kinetic characteristics of older adults with mild cognitive impairment and subjective cognitive decline: A Cross-Sectional study. Front Aging Neurosci. 2021;13:664558. https://doi.org/10.3389/fnagi.2021.664558.
41. Shen Y, Lu Q, Zhang T, Yan H, Mansouri N, Osipowicz K, et al. Use of machine learning to identify functional connectivity changes in a clinical cohort of patients at risk for dementia. Front Aging Neurosci. 2022;14:962319. https://doi.org/10.3389/fnagi.2022.962319.
42. Jia Y, Xu L, Yang K, Zhang Y, Lv X, Zhu Z, et al. Precision repetitive transcranial magnetic stimulation over the left parietal cortex improves memory in alzheimer's disease: A randomized, Double-Blind, Sham-Controlled study. Front Aging Neurosci. 2021;13:693611. https://doi.org/10.3389/fnagi.2021.693611.
43. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul. 2009;2(1):50–4. https://doi.org/10.1016/j.brs.2008.09.006.
44. Li Q, MIAO Y, ZHONG Y. Auditory verbal learning test-HuaShan version in the diagnosis of amnestic mild cognitive impairment. Geriatr Health Care. 2016;22(5):282–5.
45. Z Q, G Y. Application of auditory verbal learning test-Huashan version in patients with subjective cognitive decline and mild cognitive impairment. Chin J Rehabilitation Med. 2024;39(2):191–5.
46. Yu F, Tang X, Hu R, Liang S, Wang W, Tian S, et al. The After-Effect of accelerated intermittent theta burst stimulation at different session intervals. Front NeuroSci. 2020;14:576. https://doi.org/10.3389/fnins.2020.00576.
47. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005;45(2):201. https://doi.org/10.1016/j.neuron.2004.12.033.
48. Kensara OA, Helal OF, El-Kafy EMA, Ghafouri KJ, Ghaith MM, Alsolami FJ, et al. The combined effect of vitamin D deficiency and hyperparathyroidism on postural stability among healthy adult males. Pakistan J Biol Sciences: PJBS. 2019;22(9):406–11. https://doi.org/10.3923/pjbs.2019.406.411.
49. Freedberg MV, Reeves JA, Fioriti CM, Murillo J, Wassermann EM. Reproducing the effect of hippocampal network-targeted transcranial magnetic stimulation on episodic memory. Behav Brain Res. 2022;419:113707. https://doi.org/10.1016/j.bbr.2021.113707.
50. van der Plas M, Braun V, Stauch BJ, Hanslmayr S. Stimulation of the left dorsolateral prefrontal cortex with slow rTMS enhances verbal memory formation. PLoS Biol. 2021;19(9):e3001363. https://doi.org/10.1371/journal.pbio.3001363.
51. Traikapi A, Kalli I, Kyriakou A, Stylianou E, Symeou RT, Kardama A, et al. Episodic memory effects of gamma frequency precuneus transcranial magnetic stimulation in alzheimer's disease: A randomized multiple baseline study. J Neuropsychol. 2023;17(2):279–301. https://doi.org/10.1111/jnp.12299.
52. Hoy KE, Emonson MRL, Bailey NW, Rogers C, Coyle H, Stockman F, et al. Gamma connectivity predicts response to intermittent theta burst stimulation in alzheimer's disease: a randomized controlled trial. Neurobiol Aging. 2023;132:13–23. https://doi.org/10.1016/j.neurobiolaging.2023.08.006.
53. Canas PM, Simões AP, Rodrigues RJ, Cunha RA. Predominant loss of glutamatergic terminal markers in a β-amyloid peptide model of Alzheimer's disease. Neuropharmacol 2014;76 Pt A:51–610.1016/j.neuropharm.2013.08.026
54. Koch G, Bonnì S, Pellicciari MC, Casula EP, Mancini M, Esposito R, et al. Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal alzheimer's disease. NeuroImage. 2018;169:302–11. https://doi.org/10.1016/j.neuroimage.2017.12.048.
55. Cui X, Ren W, Zheng Z, Li J. Repetitive transcranial magnetic stimulation improved source memory and modulated Recollection-Based retrieval in healthy older adults. Front Psychol. 2020;11:1137. https://doi.org/10.3389/fpsyg.2020.01137.
56. Zhao Q, Lv Y, Zhou Y, Hong Z, Guo Q. Short-term delayed recall of auditory verbal learning test is equivalent to long-term delayed recall for identifying amnestic mild cognitive impairment. PLoS ONE. 2012;7(12):e51157. https://doi.org/10.1371/journal.pone.0051157.
57. Ma J, Zheng MX, Wu JJ, Xing XX, Xiang YT, Wei D, et al. Mapping the long-term delayed recall-based cortex-hippocampus network constrained by the structural and functional connectome: a case-control multimodal MRI study. Alzheimers Res Ther. 2023;15(1):61. https://doi.org/10.1186/s13195-023-01197-7.
58. Jin J, Maren S. Prefrontal-Hippocampal interactions in memory and emotion. Front Syst Neurosci. 2015;9:170. https://doi.org/10.3389/fnsys.2015.00170.
59. Ye Z, Shi L, Li A, Chen C, Xue G. Retrieval practice facilitates memory updating by enhancing and differentiating medial prefrontal cortex representations. eLife. 2020;9. https://doi.org/10.7554/eLife.57023.
60. Kluen LM, Dandolo LC, Jocham G, Schwabe L. Dorsolateral Prefrontal Cortex Enables Updating of Established Memories. Cerebral cortex (New York, NY: 1991). 2019;29(10):4154-68. https://doi.org/10.1093/cercor/bhy298
61. Higo T, Mars RB, Boorman ED, Buch ER, Rushworth MF. Distributed and causal influence of frontal operculum in task control. Proc Natl Acad Sci USA. 2011;108(10):4230–5. https://doi.org/10.1073/pnas.1013361108.
62. Manenti R, Brambilla M, Petesi M, Ferrari C, Cotelli M. Enhancing verbal episodic memory in older and young subjects after non-invasive brain stimulation. Front Aging Neurosci. 2013;5:49. https://doi.org/10.3389/fnagi.2013.00049.
63. Manenti R, Sandrini M, Gobbi E, Cobelli C, Brambilla M, Binetti G, et al. Strengthening of existing episodic memories through Non-invasive

stimulation of prefrontal cortex in older adults with subjective memory complaints. Front Aging Neurosci. 2017;9:401. https://doi.org/10.3389/fnagi.2017.00401.
64. Scarmeas N, Stern Y. fMRI evidence of compensatory mechanisms in older adults at genetic risk for alzheimer disease. Neurology. 2005;65(9):1514–5. https://doi.org/10.1212/wnl.65.9.1514-a. author reply – 5.
65. Gigi A, Babai R, Penker A, Hendler T, Korczyn AD. Prefrontal compensatory mechanism May enable normal semantic memory performance in mild cognitive impairment (MCI). J Neuroimaging: Official J Am Soc Neuroimaging. 2010;20(2):163–8. https://doi.org/10.1111/j.1552-6569.2009.00386.x.
66. Erk S, Spottke A, Meisen A, Wagner M, Walter H, Jessen F. Evidence of neuronal compensation during episodic memory in subjective memory impairment. Arch Gen Psychiatry. 2011;68(8):845–52. https://doi.org/10.1001/archgenpsychiatry.2011.80.
67. Haley MS, Maffei A. Versatility and flexibility of cortical circuits. The neuroscientist: a review journal bringing neurobiology. Neurol Psychiatry. 2018;24(5):456–70. https://doi.org/10.1177/1073858417733720.
68. Mansvelder HD, Verhoog MB, Goriounova NA. Synaptic plasticity in human cortical circuits: cellular mechanisms of learning and memory in the human brain? Current opinion in neurobiology. 2019;54:186–9310.1016/j.conb.2018.06.013
69. Stampanoni Bassi M, Iezzi E, Gilio L, Centonze D, Buttari F. Synaptic plasticity shapes brain connectivity: implications for network topology. Int J Mol Sci. 2019;20(24). https://doi.org/10.3390/ijms20246193.
70. Francesco DL, Koch G. Synaptic impairment: the new battlefield of alzheimer's disease. Alzheimer's Dement J Alzheimer's Assoc. 2021;17(2):314. https://doi.org/10.1002/alz.12189.
71. Buss SS, Press DZ, McDonald K, Kitchener E, O'Connor M, Donohoe K, et al. LTP-like plasticity is impaired in amyloid-positive amnestic MCI but independent of PET-amyloid burden. Neurobiol Aging. 2020;96:109–16. https://doi.org/10.1016/j.neurobiolaging.2020.08.021.
72. Vossel KA, Ranasinghe KG, Beagle AJ, Mizuiri D, Honma SM, Dowling AF, et al. Incidence and impact of subclinical epileptiform activity in alzheimer's disease. Ann Neurol. 2016;80(6):858–70. https://doi.org/10.1002/ana.24794.
73. Styr B, Slutsky I. Imbalance between firing homeostasis and synaptic plasticity drives early-phase alzheimer's disease. Nat Neurosci. 2018;21(4):463–73. https://doi.org/10.1038/s41593-018-0080-x.

Publisher's note