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Personalized high-dose accelerated intermittent theta-burst stimulation improves cognitive function in mild Alzheimer's disease: A randomized sham-controlled trial

Dear Editor,

Alzheimer's disease (AD) is characterized by dysfunction of large-scale brain networks, particularly the default mode network (DMN) and working memory network (WMN), with pathology, atrophy, and disconnection in these networks closely associated with cognitive decline [1]. Disease progression has been proposed to involve cascading dysfunction across these networks [2], with posterior DMN regions affected early and prefrontal DMN and WMN regions increasingly involved over time. Given their pivotal roles, these hub regions may represent promising targets for circuit-based AD therapies. Repetitive transcranial magnetic stimulation (rTMS) can modulate disease-relevant circuits, but clinical effects in AD have been inconsistent, potentially due to non-personalized targeting strategies that fail to account for patient-specific brain network organization and insufficient optimization of stimulation dose and schedule [3,4]. Building on emerging evidence for personalized network-targeted stimulation [5] and accelerated intermittent theta-burst stimulation (aiTBS) [6] in AD, we tested whether a high-dose personalized aiTBS protocol targeting DMN or WMN nodes could improve cognition in mild AD.

We conducted a single-center, randomized, sham-controlled trial at Xuanwu Hospital, Capital Medical University, China (ClinicalTrials.gov, NCT05872243). Eligible participants had probable AD supported by amyloid PET or cerebrospinal fluid biomarkers, MMSE scores of 20-26, CDR score of 1, stable AD medications for at least 3 months, and no MRI or TMS contraindications. Participants were randomized in an intended 2:2:1:1 ratio to personalized DMN-targeted aiTBS, personalized WMN-targeted aiTBS, sham DMN-targeted stimulation, or sham WMN-targeted stimulation; the two sham conditions were pooled as a single sham group for analyses. The intervention was delivered over 15 consecutive days, with assessments at baseline, after the 15-day treatment, and at 3-month follow-up. Randomization was stratified by age and education, and allocation was concealed. Participants, caregivers, outcome assessors, TMS operators, and data analysts were blinded to group assignment, as detailed in the Supplementary Methods. The study was approved by the institutional ethics committee, and all participants or legal representatives provided written informed consent.

The personalized targeting procedure is shown in Fig. 1A. A fine-grained functional parcellation was generated for each participant using structural MRI and 30-min resting-state fMRI [7]. DMN and WMN targets were selected from individualized network parcels within the left dorsomedial and dorsolateral prefrontal cortices, respectively, based on network relevance and TMS accessibility. Participants received four aiTBS or sham sessions per day for 15 consecutive days. Active aiTBS was delivered at 100% resting motor threshold, totaling 7200 pulses per day. Each aiTBS session consisted of 2-s burst trains repeated every 10 s, with three-pulse 50-Hz bursts repeated at 5 Hz. Treatments were delivered with neuronavigated TMS stimulators (MT20A, Neural Galaxy Inc, Beijing) equipped with double-sided coils. Sham stimulation followed the same schedule and used the sham side of the coil, which was identical to the active side in appearance and acoustic characteristics.

The primary outcome was change in Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) after the 15-day treatment. Secondary outcomes included 3-month ADAS-Cog change, post-treatment and 3-month changes in MMSE, other cognitive measures, and neuropsychiatric outcomes. Safety was evaluated by monitoring adverse events (AEs) throughout the trial. Efficacy analyses were conducted in the modified intention-to-treat (mITT) population, excluding participants who did not receive treatment after randomization or were found ineligible post-randomization. Outcomes were analyzed using linear mixed models with group, time, and group-by-time interaction as fixed effects and participant as a random effect. Pairwise comparisons were Bonferroni corrected. A reduction of at least 3 points on ADAS-Cog was considered clinically meaningful [8].

Between September 2023 and March 2025, 87 individuals were screened and 46 were randomized to DMN aiTBS (n = 15), WMN aiTBS (n = 17), or sham (n = 14). One DMN participant withdrew before treatment, and one was later found to violate a key eligibility criterion. Thus, 44 participants were included in the mITT analysis and 45 in the safety population (see CONSORT in Fig. S1). Baseline characteristics are provided in Table S1.

At the primary endpoint, both active groups showed significantly greater ADAS-Cog improvement than sham after the 15-day treatment. The estimated treatment advantage versus sham was −3.06 points for DMN aiTBS (95% CI, −4.84 to −1.28; Bonferroni-adjusted $p = 0.0020$) and −2.63 points for WMN aiTBS (95% CI, −4.29 to −0.96; Bonferroni-adjusted $p = 0.0048$) (Fig. 1B). Clinically meaningful improvement, defined as a ≥3-point ADAS-Cog reduction, occurred in 38.46% and 47.06% of participants in the DMN and WMN groups, respectively, compared with 0% in sham (Fig. 1C). At 3 months, within-group ADAS-Cog improvements remained significant in both active groups, but treatment advantages versus sham were no longer statistically significant (Fig. 1B). Detailed tests of score changes and group comparisons are provided in Table S2.

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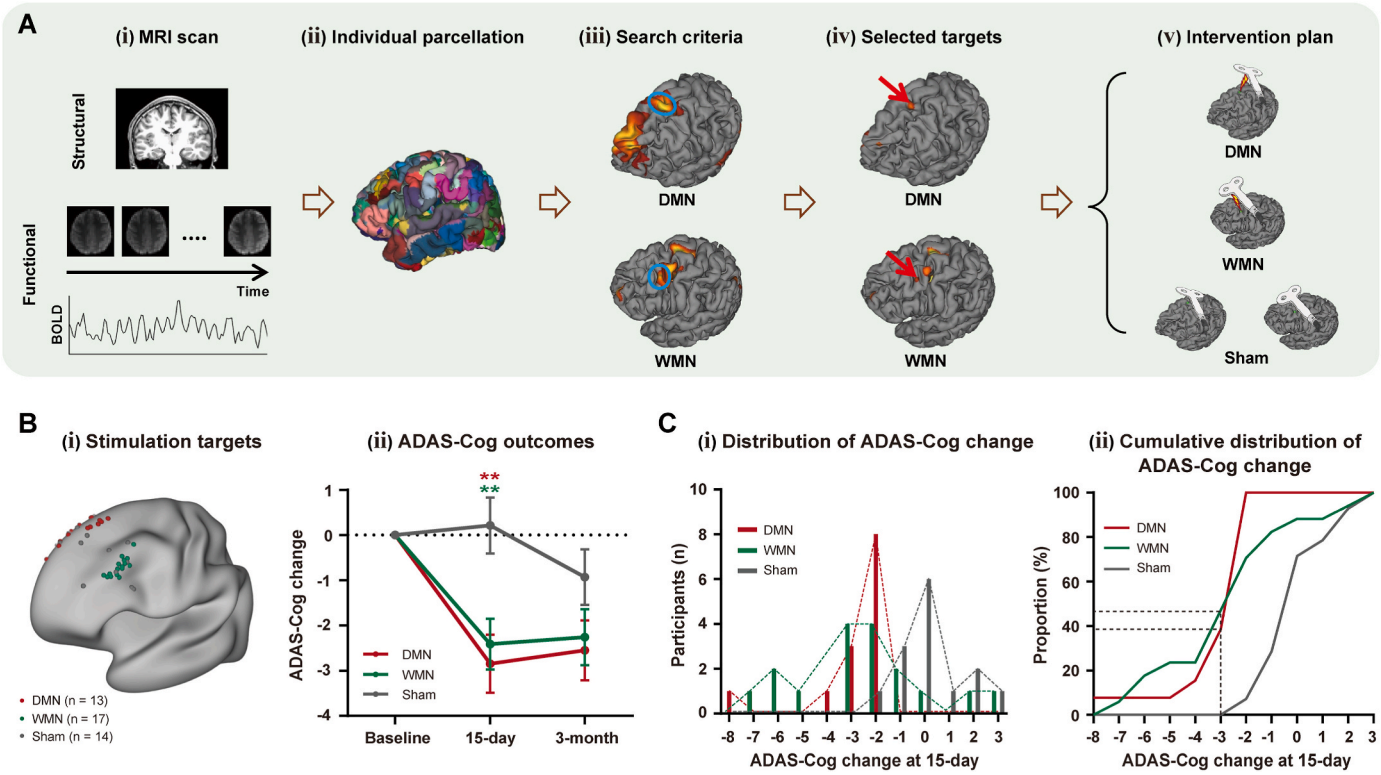

Fig. 1. Personalized network-guided aiTBS improves ADAS-Cog outcomes in mild AD. A Personalized target identification procedure. (i) For each participant, baseline structural and 30-min resting-state functional MRI data were acquired. (ii) Individual functional parcellation was generated using a previously reported iterative approach. (iii) Candidate stimulation sites were selected by integrating network functional connectivity and structural accessibility. (iv) The personalized target (marked by red arrows) were designated as the optimal stimulation site. (v) participants were randomized, with allocation concealed, to receive aiTBS targeting either the DMN or WMN, or sham stimulation. **B** Personalized stimulation targets and ADAS-Cog changes. (i) Personalized DMN targets (red, n = 13), WMN targets (green, n = 17) and sham stimulation sites (grey, n = 14) are displayed on a standard left hemisphere surface. (ii) Mean ADAS-Cog changes from baseline are shown at post-treatment and 3-month follow-up for the DMN (red), WMN (green) and sham (grey) groups. Negative values indicate cognitive improvement; error bars represent the standard error. **C** Distribution and cumulative profile of post-treatment ADAS-Cog changes. Individual ADAS-Cog changes (i) and cumulative proportions of participants with ADAS-Cog changes at or below each indicated threshold (ii) are shown for the DMN (red), WMN (green), and sham (grey) groups. In (ii), the dashed vertical line marks the threshold for clinically meaningful improvement, defined as a ≥3-point reduction in ADAS-Cog, and the dashed horizontal lines indicate the corresponding cumulative proportions of participants in the DMN and WMN groups achieving this threshold or greater improvement; no participant in the sham group reached this threshold.

The protocol was feasible and generally well tolerated, with all 45 treated participants completing the 15-day intervention. Safety findings included one serious adverse event (SAE) unrelated to treatment (inguinal hernia requiring surgery during follow-up), transient scalp discomfort in 6 participants, and single cases of dizziness and fatigue. The proportion of participants with AEs did not differ significantly across groups (DMN: 2/14; WMN: 6/17; Sham: 1/14; Fisher's exact test, $p = 0.146$). Complete AE data are provided in Table S3.

These preliminary findings suggest that 15 days of high-dose personalized aiTBS targeting prefrontal DMN or WMN nodes may produce rapid cognitive improvement in mild AD, with favorable tolerability. The day-15 ADAS-Cog advantage over sham was comparable to effects reported in prior AD rTMS studies [9,10]. At 3 months, within-group improvements persisted in both active groups, whereas treatment advantages versus sham were no longer significant, underscoring the need for larger trials to evaluate the persistence of treatment effects. Despite these promising results, this study has several limitations, including the relatively small sample size and potential population heterogeneity introduced by amyloid confirmation using either PET or CSF biomarkers. Together, these findings support further evaluation of the DMN and WMN as network-level neuromodulation targets for AD in larger multicenter trials.

Consent statement

All human subjects provided informed consent.

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CRediT authorship contribution statement

Na Xu: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Yi Xing:** Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. **Aonan Li:** Conceptualization, Data curation, Investigation, Project administration. **Shuaicheng Liu:** Investigation. **Jing Gao:** Investigation. **Xinyu Liu:** Investigation. **Wuxiang Xie:** Methodology, Resources. **Ning Guo:** Investigation. **Yue Chen:** Investigation. **Xiaoyue Sun:** Investigation. **Jilin Wu:** Investigation. **Weijun Gong:** Methodology. **Danhong Wang:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Yi Tang:** Conceptualization, Methodology, Supervision. **Hesheng Liu:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hesheng Liu reports a relationship with Neural Galaxy Inc. and Galaxy Brain Scientific that includes: consulting or advisory and equity or stocks. Danhong Wang reports a relationship with Neural Galaxy Inc. and Galaxy Brain Scientific that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2026.103142.

References

[1] Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. Neuron 2009;62(1):42–52. https://doi.org/10.1016/j.neuron.2009.03.024.

[2] Jones DT, Knopman DS, Gunter JL, Graff-Radford J, Vemuri P, Boeve BF, et al. Cascading network failure across the Alzheimer's disease spectrum. Brain 2016;139 (Pt 2):547–62. https://doi.org/10.1093/brain/awv338.

[3] Li S, Lan X, Liu Y, Zhou J, Pei Z, Su X, et al. Unlocking the potential of repetitive transcranial magnetic stimulation in Alzheimer's Disease: a meta-analysis of randomized clinical trials to optimize intervention strategies. J Alzheimers Dis 2024; 98(2):481–503. https://doi.org/10.3233/JAD-231031.

[4] Menardi A, Dotti L, Ambrosini E, Vallesi A. Transcranial magnetic stimulation treatment in Alzheimer's disease: a meta-analysis of its efficacy as a function of protocol characteristics and degree of personalization. J Neurol 2022;269(10): 5283–301. https://doi.org/10.1007/s00415-022-11236-2.

[5] Jung YH, Jang H, Park S, Kim HJ, Seo SW, Kim GB, et al. Effectiveness of personalized hippocampal network-targeted stimulation in alzheimer disease: a randomized clinical trial. JAMA Netw Open 2024;7(5):e249220. https://doi.org/10.1001/jamanetworkopen.2024.9220.

[6] Wu X, Ji GJ, Geng Z, Wang L, Yan Y, Wu Y, et al. Accelerated intermittent theta-burst stimulation broadly ameliorates symptoms and cognition in Alzheimer's disease: a randomized controlled trial. Brain Stimul 2022;15(1):35–45. https://doi.org/10.1016/j.brs.2021.11.007.

[7] Wang D, Buckner RL, Fox MD, Holt DJ, Holmes AJ, Stoecklein S, et al. Parcellating cortical functional networks in individuals. Nat Neurosci 2015;18(12):1853–60. https://doi.org/10.1038/nn.4164.

[8] Muir RT, Hill MD, Black SE, Smith EE. Minimal clinically important difference in Alzheimer's disease: rapid review. Alzheimer's Dement 2024;20(5):3352–63. https://doi.org/10.1002/alz.13770.

[9] Liu G, Xue B, Guan Y, Luo X. Effects of repetitive transcranial magnetic stimulation combined with cognitive training on cognitive function in patients with Alzheimer's disease: a systematic review and meta-analysis. Front Aging Neurosci 2023;15:1254523. https://doi.org/10.3389/fnagi.2023.1254523.

[10] Sabbagh M, Sadowsky C, Tousi B, Agronin ME, Alva G, Armon C, et al. Effects of a combined transcranial magnetic stimulation (TMS) and cognitive training intervention in patients with Alzheimer's disease. Alzheimer's Dement 2020;16(4): 641–50. https://doi.org/10.1016/j.jalz.2019.08.197.

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