

rTMS renews long-tract myelination to improve AD cognitive function predicted by baseline myelin and E-field

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Abstract

Objective

Alzheimer's disease (AD) is more than a neuronal disease, as myelin damage actively drives its pathogenesis. Maintaining myelin integrity during aging may delay the progression of AD. Myelin repair is an emerging strategy for AD treatment; however, whether rTMS can drive myelin remodeling through neuronal excitation remains unclear.

Methods

AD patients received rTMS targeting the left DLPFC. Myelin-sensitive white matter measures were assessed pre- and post-treatment. Functional connectivity (FC) changes within and between the cognitive networks were evaluated. Baseline myelin characteristics and individualized E-field modeling were used to predict clinical response.

Results

rTMS increased myelin content (MyC) in several left-hemisphere white matter tracts, particularly the superior fronto-occipital fasciculus (SFOF), superior corona radiata, and cingulum (Cohen's $d = 0.59, 0.57, 0.59$, separately). These changes were associated with enhanced CEN-SN cross-network, interhemispheric CEN, and intra-CEN connectivity enhancements, contributing to clinical improvement (correlations between MOCA and MyC of SFOF_L ($R = 0.56, p < 0.01$)). Baseline MyC of SFOF-L and E-field jointly predicted post-treatment cognitive outcomes, with the strongest MoCA model explaining 44.4% of the adjusted variance and outperformed either metric alone. No direct correlation was found between myelin increase and E-field, highlighting the constraining role of structural reserve.

Conclusions

This study reveals a myelin-mediated mechanism of rTMS action in AD, demonstrating the potential of promoting myelination as a novel therapeutic strategy for alleviating AD-related cognitive impairment. These findings support individualized biological dosing combining E-field modeling and myelin features of key tracts to identify the E-field threshold that triggers myelin remodeling, replacing traditional physical dose measures.

1. Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized not only by cortical atrophy and amyloid pathology but also by extensive white matter (WM) microstructural damage [1–3]. Accumulating evidence indicates that myelin loss and microstructural disintegration of WM occur early

in AD and mild cognitive impairment (MCI) [4–6]. These WM tracts facilitate the interregional transmission of cognitive control signals over extended neural distances [7–10]. Consequently, their myelin integrity underpins efficient large-scale brain network communication, and their damage directly contributes to cognitive dysfunction, memory retrieval difficulties, and executive deficits in AD patients [11–13]. However, whether these WM pathways can be remodeled by non-invasive neuromodulation remains largely unknown [14, 15].

Repetitive transcranial magnetic stimulation (rTMS) targeting the left dorsolateral prefrontal cortex (DLPFC) has emerged as a promising therapeutic intervention for AD, with reported clinical benefits including cognitive improvement [16, 17]. Conventional models of rTMS action have focused primarily on cortical excitability and synaptic plasticity [18–21]. Recent evidence, however, suggests that rTMS may induce activity-dependent myelin plasticity, a process through which neuronal firing promotes oligodendrocyte proliferation and myelin remodeling along activated axonal pathways [22, 23]. Despite this, it remains unclear whether rTMS can produce tract-level, region-specific myelin changes in the human AD brain [24]. And if so, how such structural remodeling relates to alterations in large-scale functional network connectivity and clinical improvement has not been systematically investigated [25, 26].

A critical challenge in clinical rTMS application is the substantial inter-individual variability in treatment response [27, 28]. Traditional dosing parameters, such as the percentage of resting motor threshold (%RMT), fail to capture individual differences in cortical neuronal atrophy or WM integrity in AD patients [29–31]. Recent advances in computational modeling now allow patient-specific estimation of the induced electric field (E-field), providing a more direct measure of target engagement [30]. Nevertheless, whether baseline myelin characteristics and E-field exposure act to predict clinical response has not been explored [28, 32]. Moreover, the relationship between the induced E-field and subsequent myelin plasticity remains poorly understood, particularly in the context of AD where cortical atrophy and WM damage may be dissociated, each contributing unique sources of variability [33, 34].

To address these gaps, the present study had three primary objectives. First, we sought to determine whether rTMS treatment targeting the left DLPFC induces myelin-sensitive changes in WM tracts in AD patients. Second, we examined whether baseline myelin characteristics and baseline E-field engagement predict therapeutic response after treatment. Third, we assessed whether such myelin changes are associated with alterations in large-scale network connectivity. The findings provide novel evidence for a myelin-mediated mechanism underlying rTMS-induced network reorganization and may inform individualized biological dosing strategies for AD treatment.

2. Material and methods

2.1 Participants and neuropsychological assessment

This was a retrospective study which included 30 patients from Xuanwu Hospital, Capital Medical University, China. In this study, all patients underwent rTMS targeting the left DLPFC between May 2021 and July 2025. Four patients were excluded (3 for excessive head motion, 1 for age matching), leaving 26. This study was approved by the Medical Research Ethics Committee of Xuanwu Hospital, and all patients provided signed informed consent forms. The study was approved by the Medical Research Ethics Committee of Xuanwu Hospital, Capital Medical University, China and registered on the site Chinese Clinical Trial Registry (<https://www.chictr.org.cn/index.html>; ChiCTR2200062564, ChiCTR2500099162).

All patients were diagnosed by two trained senior neurologists. The inclusion criteria were as follows: (i) probable AD dementia, diagnosed according to the 2011 National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines; (ii) right-handed male or female patients aged 55–80 years; (iii) Clinical Dementia Rating (CDR) point of 0.5 or 1.0; (iv) Mini-mental State Examination (MMSE) ≤ 27 ; and (v) stabilized dose of donepezil at least 3 months prior to iTBS intervention until the completion of follow up. The exclusion criteria were as follows: (i) clinical features indicating an underlying pathology other than AD; (ii) non-magnetic resonance imaging (MRI) compatible metallic implantation, such as pacemakers, aneurysm clips, deep brain stimulators, or coronary stents; (iii) history of other neurological disorders, or complications with severe diseases of other systems; (iv) personal history of seizures or family history in first-degree relatives; (v) taking benzodiazepines or any history of substance abuse; and (vi) focal cerebral lesions on T1 or T2 images. Cognitive assessments of each patient were performed before and after treatment. All patients completed the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). The Geriatric Depression Scale (GDS), Face-word Stroop Task, Trail Making Test (TMT), Digit Span Test (DST) and Auditory Verbal Learning Test (AVLT) were performed [23]. The clinical characteristics, including sex, age and education, are presented in Table 1.

Table 1
Summary of the patients' clinical characteristic data

Gender (M: F)	PRE	POST	<i>p</i> value
	9:17	/	/
Age	69.8 ± 5.72	/	/
Education	12 ± 2.98	/	/
MMSE	23.73 ± 3.64	24.85 ± 3.39	0.003 ^a
MoCA	19.81 ± 3.96	20.96 ± 3.81	0 ^a
GDS	5.62 ± 3.91	5.77 ± 3.88	0.058 ^b
face-word	3.00 ± 3.27	3.96 ± 3.74	0.044 ^a
TMT-A	24.73 ± 1.19	24.5 ± 1.30	0 ^b
TMT-B	17.81 ± 7.06	18.15 ± 7.40	0 ^b
DS-Forward	8.35 ± 0.75	8.77 ± 0.77	0 ^b
DS-Backward	4.31 ± 1.12	4.85 ± 1.29	0.001 ^b
AVLT1	4.35 ± 1.72	5.31 ± 1.91	0.001 ^a
AVLT2	5.46 ± 1.88	6.65 ± 2.41	0.001 ^a
AVLT3	6.27 ± 2.39	7.62 ± 2.65	0.001 ^a
AVLT-Mean	5.36 ± 1.80	6.53 ± 2.16	0 ^a
AVLT-delay	2.38 ± 3.30	3.77 ± 4.15	0 ^b
AVLT-clue	5.31 ± 3.91	6.62 ± 3.93	0.015 ^a
AVLT-recognition	6.69 ± 3.52	7.54 ± 4.20	0.01 ^b

Note. Measurement data are described as the mean ± standard deviation. Statistical analyses before and after treatment were performed using the paired t-test (a) and Kolmogorov-Smirnov test (b).

Abbreviations: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; face-word, Face-Word Test; TMT, Trail Making Test; AVLT, Auditory Verbal Learning Test.

2.2 Protocol for rTMS therapy

The accelerated high-dose iTBS protocol was performed using a Magstim Rapid2 transcranial magnetic stimulator (Magstim, Co. Ltd, UK) with a figure-of-eight coil (70 mm diameter) [24]. The treatment regimen comprised 28 iTBS treatments over a 14-day period (twice daily at approximately 50 min intervals), with a total of 50,400 pulses [25]. Each iTBS session was composed of 1800 pulses for a total of 60 pulses strings, with a string duration of 2 s, a cyclic period of 8 s, and an intensity of 80 % of the resting motor threshold (Fig. 1A).

The stimulation site was the left DLPFC cortex at Montreal Neurological Institute (MNI) coordinates [-38,44,26] [27]. For each model, the TMS coil was kept parallel to the skull, with the handle pointing posterolaterally at a 45° angle to the midsagittal plane. The junction of the coil was positioned over the scalp location closest to the intracranial target [28].

2.3 Imaging acquisition and Image preprocessing

All resting-state functional MRI (rs-fMRI), T1-weighted data and T2-weighted data were acquired using a Siemens 3.0 T MRI system (Siemens, Erlangen, Germany). The participants were scanned before the first rTMS treatment and after the final treatment.

Rs-fMRI images were acquired using a single-shot gradient-echo echo planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, matrix size = 64 × 64, slice number = 32, slice thickness = 3.5 mm, voxel size = 3.5 × 3.5 × 4.75 mm³, volume number = 200. T1-weighted (T1w) images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR = 2530 ms, TE = 2.98 ms, inversion time (TI) = 1100 ms, FA = 7°, matrix size = 256 × 256, slice number = 192 and voxel size = 1 × 1 × 1 mm³. The specific parameters for T2w images are as follows: TR = 4000 ms, TE = 95 ms, matrix size = 512 × 512, slice number = 20, voxel size = 0.43 × 0.43 × 6.5 mm³.

All fMRI data were preprocessed using DPARSF version 5.3 (<http://rfmri.org/DPARSF>) [26]. Initially, the first 10 time points from the fMRI data. Secondly, slice timing and head motion corrections were performed. Subsequently, cerebrospinal fluid and WM were regressed as nuisance variables. Then, the images were aligned to T1w, and normalized to the Montreal Neurological Institute space. Finally, the images were smoothed with a 6 mm Gaussian kernel and band-pass filtered (0.01– 0.1 Hz). All T1w and T2w DICOM files were converted into 3D NIfTI (.nii) format using the built-in dcm2nii tool in SPM12.

2.4 E-field modeling

Head models were derived from T1-weighted MRI using SimNIBS v3.2.5 (www.simnibs.org). In this simulation platform, stimulation strength was quantified by the di/dt ; here, we set di/dt to 1 A/μs to define the stimulation strength. Subsequently, we ran the “mri2mesh” pipeline to generate individualized meshes with five tissue compartments: scalp, skull, cerebrospinal fluid (CSF), gray matter (GM), and WM (Fig. 1B). Conductivities followed SimNIBS defaults: scalp 0.465 S/m, skull 0.010 S/m, CSF 1.654 S/m, GM 0.275 S/m, and WM 0.126 S/m.

ROI was centered on the gyral crown at the target and defined as a 10-mm radius sphere on the cortical surface. Within each ROI, we computed three E-field summaries: (i) the mean field across all voxels in the ROI (E_{ROI}); (ii) the mean field restricted to GM voxels (E_{GM}); and (iii) the mean field restricted to WM voxels (E_{WM}).

2.5 Calculation of MyC

MyC was quantified using the MRTTool extension within SPM12. First, bias correction was performed on the T1w and T2w images to eliminate slow intensity variations associated not only with MRI hardware but also with the interaction between the hardware and the subject's skull tissue. Subsequently, intensity normalization was applied to the bias-corrected images, and the normalized T1w images were divided by the normalized T2w images to generate multimodal T1w/T2w images. These images can effectively eliminate MRI device-related intensity biases and serve as an indirect quantitative indicator of MyC. Finally, the myelin-wrapped nerve fibers in WM regions with significant differences were extracted as a mask, and the mean MyC within this mask was calculated for each subject [29,30] (Fig. 1C).

2.6 Calculation of Functional Connectivity

To observe the effects of treatment on the two networks (SN: Salience Network; CEN: Central Executive Network), we first calculated the FC between these networks using the Schaefer 400-parcels atlas. The FC before and after rTMS treatment was calculated using Pearson's correlation with Fisher's Z-transformation for FC matrix normalization. The mean FC was quantified within and between the SN and CEN by considering all possible hemispheric combinations, including: (1) intra-hemispheric connectivity within each network and their mutual interactions; (2) inter-hemispheric homotopic connectivity; and (3) inter-hemispheric heterotopic connectivity.

2.7 Statistical analyses

2.7.1 Statistical Analysis of Clinical Scales

Continuous clinical scale scores pre- and post-rTMS treatment were first subjected to the Kolmogorov-Smirnov test to evaluate data normality. For data conforming to a normal distribution, two-tailed paired t-tests were employed to contrast longitudinal clinical changes; otherwise, the non-parametric Wilcoxon signed-rank tests were implemented.

2.7.2 Comparison of MyC and FC before and after treatment

Paired t-tests and Wilcoxon signed-rank tests were employed for group-level comparisons of clinical scales. For MyC, paired t-tests were performed on pre- and post-treatment T1w/T2w images, with results subjected to Gaussian Random Field (GRF) correction (voxel $p < 0.05$, cluster $p < 0.05$). Significant clusters were localized using the JHU-ICBM-labels-1mm template. Similarly, the treatment-induced changes in the previously defined SN and CEN FC configurations were evaluated using paired t-tests at the group level.

2.7.3 Correlation Analysis

Correlation analyses were performed among MyC, FC and clinical scale scores both before and after treatment, as well as baseline E-field. Pearson or Spearman correlation was used as appropriate [31]. Statistical significance was set at $p < 0.05$.

2.7.4 Multiple Linear Regression

Multiple linear regression was applied to explore the predictive effects of baseline MyC, FC and E-field on post-treatment scale scores. To maintain model robustness and parsimony, univariate analysis was first used to filter out independent variables not significantly associated with the dependent variable. To further address severe collinearity [32], inter-correlations between independent variables were examined; if $|r| > 0.6$ [33] occurred between two independent variables, they were considered redundant, and only the one with superior clinical interpretability was retained. Model fit and significance were assessed using adjusted R^2 , standardized β , and p -values, with results further validated through 2000 bootstrap samples.

3. Results

3.1. Participants characteristics

Demographic information of the participants is shown in Table 1. The following scale scores showed a significant increase after treatment compared to before treatment: MMSE ($p = 0.003$), MoCA ($p < 0.001$), Face-Word ($p = 0.044$), TMT-B ($p < 0.001$), DS-Forward ($p < 0.001$), DS-Backward ($p = 0.001$), AVLT1 ($p = 0.001$), AVLT2 ($p = 0.001$), AVLT3 ($p = 0.001$), AVLT-Mean ($p < 0.001$), AVLT-Delay ($p < 0.001$), AVLT-Clue ($p = 0.015$), and AVLT-Recognition ($p = 0.01$). Although the P -value of GDS was greater than 0.05 ($p = 0.058$), it was marginally significant. For TMT-A, although the post-treatment scores were slightly lower than the pre-treatment scores, the mean scores all fell within the normal range.

3.2 Treatment-Induced enhancement of MyC and FC

We explored individual longitudinal profiles of MyC, E-field, and FC, alongside whole-brain significant MyC at the voxel level and network alterations. At the individual level, the subject demonstrated a localized increase in myelin content, with the spatial distribution of the E-field illustrated in the figure. Concurrently, although FC neighboring the DLPFC remained stable with no noticeable alterations, the patient exhibited a substantial elevation in post-treatment clinical scale scores (Fig. 2A). We observed a significant post-treatment increase in MyC across multiple whole-brain regions (Fig. 2B), namely the left cingulate gyrus (Cingulum_L, $p = 0.006$), left external capsule ($p < 0.001$), left posterior limb of internal capsule (PLIC_L, $p < 0.001$), left anterior limb of internal capsule (ALIC_L, $p < 0.001$), left superior corona radiata (SCR-L, $p = 0.008$), and left superior fronto-occipital fasciculus (could be a part of anterior internal capsule) (SFOF-L, $p = 0.006$). Concurrently, we identified significantly enhanced FC within and between several networks relative to baseline (Fig. 2C), namely between the left salience network and the left central executive

network (SN_L–CEN_L; $p = 0.038$), intra-connectivity within the left central executive network (CEN_L; $p = 0.022$), between the left salience network and the right central executive network (SN_L–CEN_R; $p = 0.030$), and between the left and right central executive networks (CEN_L–CEN_R; $p = 0.015$).

3.3 Predicting Post-treatment Scales Based on Baseline Electric Field and Myelin

To identify candidate predictors for multivariable models, we first performed univariate regression analyses between baseline E-field/MyC metrics and post-treatment clinical scores. Several baseline E-field and tract-specific MyC measures were associated with post-treatment cognitive scales (Fig. S1). Representative univariate associations are shown in Fig. 3A. We predicted Post-MoCA scores using E_{ROI} and MyC of SFOF-L (Adjusted $R^2 = 0.444$, ANOVA $p < 0.001$), and further validated these findings through a bootstrap procedure (E_{ROI} : $\beta = 1.66$, $p = 0.047$, 95% CI [0.08, 3.14]; MyC of SFOF-L: $\beta = 7.32$, $p = 0.001$, 95% CI [4.46, 12.04]) (Fig. 3B). Similarly, Post-AVLT3 scores were successfully predicted by E_{ROI} and MyC of SFOF-L (Adjusted $R^2 = 0.281$, ANOVA $p = 0.009$), and further validated these findings through a bootstrap procedure (E_{ROI} : $\beta = 1.08$, $p = 0.045$, 95% CI [0.02, 2.16]; MyC of SFOF-L: $\beta = 4.49$, $p = 0.049$, 95% CI [1.71, 9.22]). Finally, we utilized Post-AVLT-clue scores using E_{WM} and MyC of SFOF-L (Adjusted $R^2 = 0.286$, ANOVA $p = 0.008$), and further validated these findings through a bootstrap procedure (E_{WM} : $\beta = 1.13$, $p = 0.026$, 95% CI [0.19, 2.30]; MyC of SFOF-L: $\beta = 6.47$, $p = 0.007$, 95% CI [2.67, 11.97]).

3.4 Closer Statistical Correlations Post-treatment Than at Baseline

We analyzed the correlations of pre-treatment scales with baseline E-field and MyC, as well as the correlations of post-treatment scales with baseline E-field and post-treatment MyC (Fig. S2). The correlations between clinical scale scores and MyC both before and after treatment are shown in Fig. 4A. Post-treatment clinical scale scores exhibited a closer correlation with MyC compared to pre-treatment correlations. Furthermore, we compared the associations between FC and MyC across the two timepoints (Fig. 4B), with the correlation after treatment being statistically significant: MyC of the External capsule L and FC of SN_L–CEN_L ($R = 0.427$, $p = 0.003$); MyC of ALIC_L and FC of SN_L–CEN_L ($R = 0.424$, $p = 0.031$); MyC of SCR_L and FC of SN_L–CEN_L ($R = 0.394$, $p = 0.047$); MyC of Cingulum_L and FC of SN_L–CEN_R ($R = 0.402$, $p = 0.042$); MyC of SCR_L and FC of SN_L–CEN_R ($R = 0.430$, $p = 0.028$); MyC of ALIC_L and FC of CEN_L–CEN_R ($R = 0.403$, $p = 0.041$); MyC of SCR_L and FC of CEN_L–CEN_R ($R = 0.479$, $p = 0.013$); MyC of SFOF_L and FC of CEN_L–CEN_R ($R = 0.411$, $p = 0.037$). Post-treatment FC demonstrated a closer correlation with MyC than pre-treatment correlations. Finally, we identified significant positive correlations (Fig. 4C), between MOCA and E_{ROI} ($R = 0.432$, $p = 0.028$), between MOCA and E_{GM} ($R = 0.409$, $p = 0.038$), and between AVLT3 and E_{ROI} ($R = 0.395$, $p = 0.046$). Post-treatment E-field showed a closer correlation with clinical scales than pre-treatment correlations.

4. Discussion

This study examined rTMS-induced myelin changes and their impact on network in AD, and the predictive value of baseline myelin and E-field for treatment response. The results indicate that rTMS intervention

over the left DLPFC specifically and significantly increases myelin content in long-range WM fiber tracts of the left hemisphere. These changes mediated both the increased CEN-SN cross-network FC and interhemispheric CEN connectivity, and also contributed to clinical improvements as measured by scale scores. Baseline myelin metrics combined with E-field parameters more effectively predict rTMS clinical response in AD patients. This study provides the first evidence that rTMS induces region-specific myelin plasticity in long-range WM tracts. These findings reveal a novel mechanism linking rTMS-induced myelin plasticity to network-level functional reorganization and clinical benefit in AD. Identifying a myelin-mediated mechanism of rTMS action advance clinical application to guide patient selection and individualized stimulation protocols for AD treatment.

This study innovatively finds that left DLPFC rTMS-induced region-specific myelin plasticity shows a significant spatial preference for long-range WM tracts. The results showed that rTMS treatment in AD patients markedly increases myelin content in three left-hemisphere tracts: the left superior fronto-occipital fasciculus (SFOF), superior corona radiata, and cingulum. We further analyzed the predictive efficacy of baseline indicators for treatment response. Importantly, baseline myelin features (particularly in long-range tracts like the SFOF) and E-field exposure acted synergistically to predict clinical response, with their combination yielding significantly greater predictive efficacy than either metric alone. Specifically, the combined model using EROI and baseline MyC of SFOF-L showed the highest predictive performance for post-treatment MoCA, explaining 44.4% of the adjusted variance, corresponding to an equivalent adjusted multiple R of approximately 0.67. This predictive strength was numerically higher than several previously reported single-domain predictors of rTMS response in AD. Liang et al. [28] showed that DLPFC cortical WM E-field predicted rTMS-related memory improvement in MCI due to AD, explaining approximately 37% of the variance. Chen et al. [46] reported that baseline dynamic functional network connectivity predicted memory improvement after rTMS in AD, with predictive correlations of $R = 0.58$ and $R = 0.54$.

As structural substrates for DLPFC communication with areas, these three fiber tracts are longitudinally oriented long-range pathways connecting the prefrontal cortex to posterior parietal, occipital, or limbic regions [47,48]. They are responsible for the long-distance transmission of cognitive control signals, and their myelin integrity underpins efficient large-scale network communication [49,50]. In AD and mild cognitive impairment, these fiber tracts all exhibit early myelin loss or microstructural damage, which directly leads to executive dysfunction, memory retrieval difficulties, and visuospatial deficits in patients [29,51]. Notably, we discovered that these fiber tracts were strengthened by rTMS, mediating a triple enhancement comprising CEN-SN cross-network coupling, interhemispheric CEN integration, and intra-CEN connectivity. Their overlapping functions collectively support executive functions (working memory, attentional switching), and emotional processing [47,52,53].

The synergistic prediction of baseline myelin and the local E-field points to a key insight. Baseline WM microstructural integrity is a critical factor. It determines both the brain's response to neuromodulation and its ability to undergo activity-dependent myelin plasticity [34,51]. In AD patients, cortical neuronal atrophy and WM microstructural damage may be dissociated, generating two dimensions of inter-

individual variability: (i) the induced E-field (dependent on neuronal atrophy) and (ii) WM responsiveness to the E-field (dependent on myelin integrity) [54,55]. These interactions rendered the relationship between E-field exposure and myelin plasticity more complex than simple causality or linear correlation [55]. In line with this, no significant correlation was found between myelin content increase and induced E-field. This negative result precisely supports the core novel finding that E-field exposure alone is insufficient to directly drive myelin plasticity, which instead requires the constraint of “structural reserve” (i.e., baseline WM integrity). Therefore, individualized rTMS “biological dosing” should be based on a combination of baseline E-field modeling and myelin features of key tracts (e.g., SFOF). This strategy helps identify the E-field threshold that triggers myelin plasticity, moving beyond traditional “physical dose” measures like RMT%.

Several limitations should be acknowledged. First, while our cohort represents a relatively large sample for individualized E-field research in AD to our knowledge, the findings originate from a single center. Future multi-center studies with larger, diverse populations are necessary to validate these results across different imaging parameters and ethnicities. Second, the current longitudinal follow-up is limited to one or two post-intervention time points. We intend to extend this follow-up to four or five time points to determine whether the observed WM remodeling persists or evolves over a more prolonged period [57]. Finally, the underlying cellular and molecular mechanisms remain to be fully elucidated. Future research employing non-human primate models will be crucial to bridge this gap, allowing for a deeper exploration of the specific cellular pathways and microscopic processes that govern stimulation-induced circuit reconfiguration [58,59].

5. Conclusion

In conclusion, this study provides new evidence that the role of WM in TMS neuromodulation for AD may have been underestimated. Our findings suggest that prefrontal iTBS may induce myelin-sensitive white-matter plasticity, promote the rewiring of long-range white-matter pathways, and thereby support functional network remodeling and cognitive improvement. Importantly, effective rewiring appears to depend on both sufficient individualized E-field engagement and relatively preserved baseline myelin integrity, indicating that stimulation effects are jointly shaped by target engagement and the plastic potential of the white-matter substrate. Clinically, these findings suggest that individualized E-field modeling and baseline myelin assessment may help identify patients who are more likely to benefit from rTMS, guide stimulation optimization, and provide imaging-based indicators for predicting therapeutic response in AD.

Declarations

Ethics approval and consent to participate

The study protocols were approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University. The ethics approval numbers were 000[2022]0810-001 (Amendment 1) and 000[2024]0040-002,

approved on July 9, 2022, and April 8, 2024, respectively. The studies were conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before enrollment. The studies were registered in the Chinese Clinical Trial Registry under the registration numbers ChiCTR2200062564, registered on August 11, 2022, and ChiCTR2500095949, registered on January 15, 2025.

Consent for publication

Not applicable.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing financial interests or personal relationships that could be perceived to have influenced the work reported in this paper.

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Author contributions

ZZ, investigation, writing original draft, writing-review and editing; JX, data curation, visualization, writing original draft, writing-review and editing; NW, data curation, visualization, writing original draft; QS, investigation, writing-review and editing; SZ, data curation, visualization, writing-review and editing; JJ, supervision, writing-review and editing; GZ, supervision, writing-review and editing; LW, formal analysis, methodology, supervision, writing-review and editing; HL, conceptualization, project administration, supervision, writing-review and editing. All authors have approved the final manuscript.

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Figures

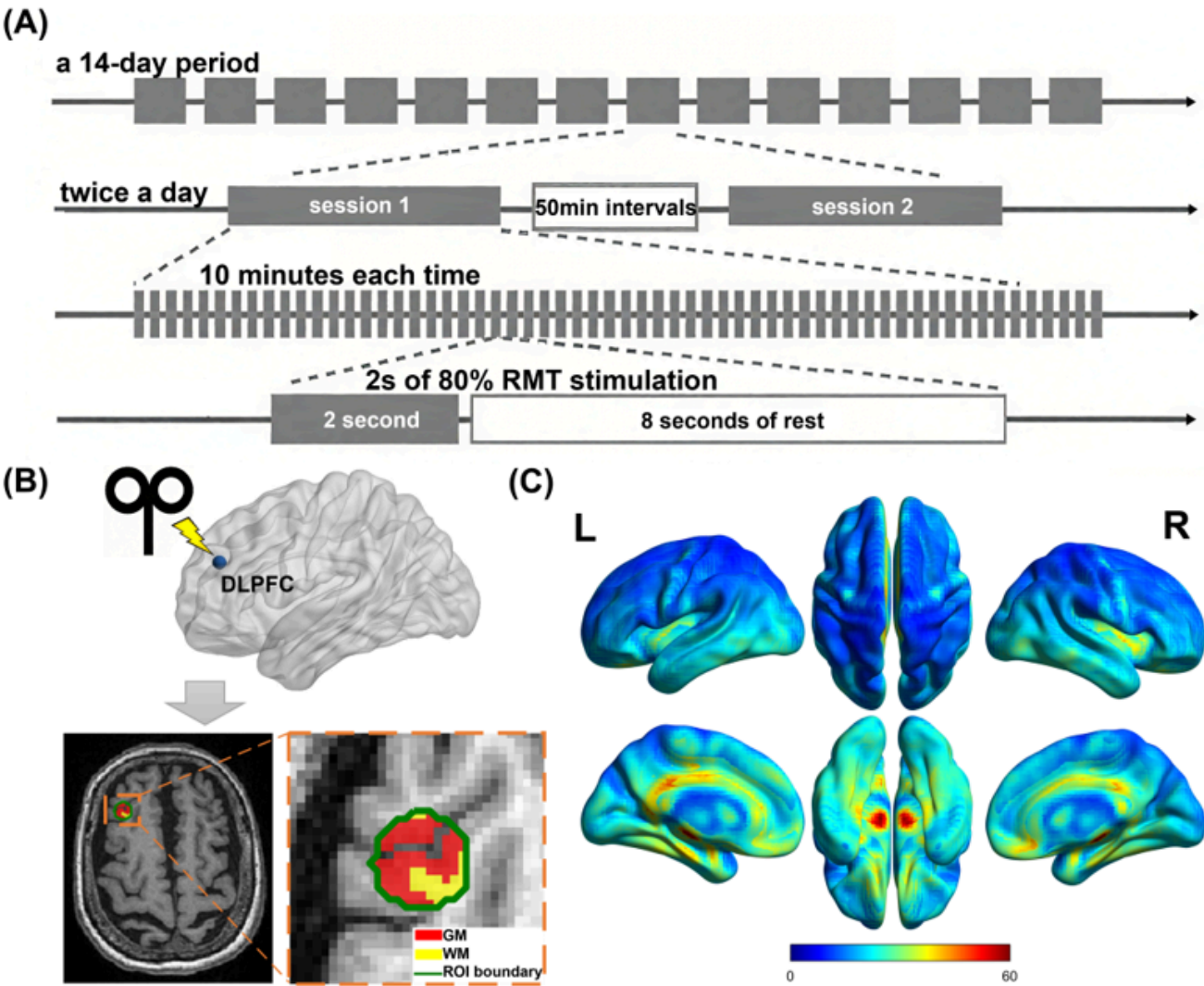


Figure 1

Schematic overview of the rTMS treatment protocol, myelin mapping, and regional region of interest (ROI) characterization. (A) Protocol for rTMS therapy. (B). Within the ROI, red and yellow segments represent gray matter (GM) and white matter (WM), respectively. The outline of the ROI is delineated by a green line. (C) Schematic diagram of myelin content.

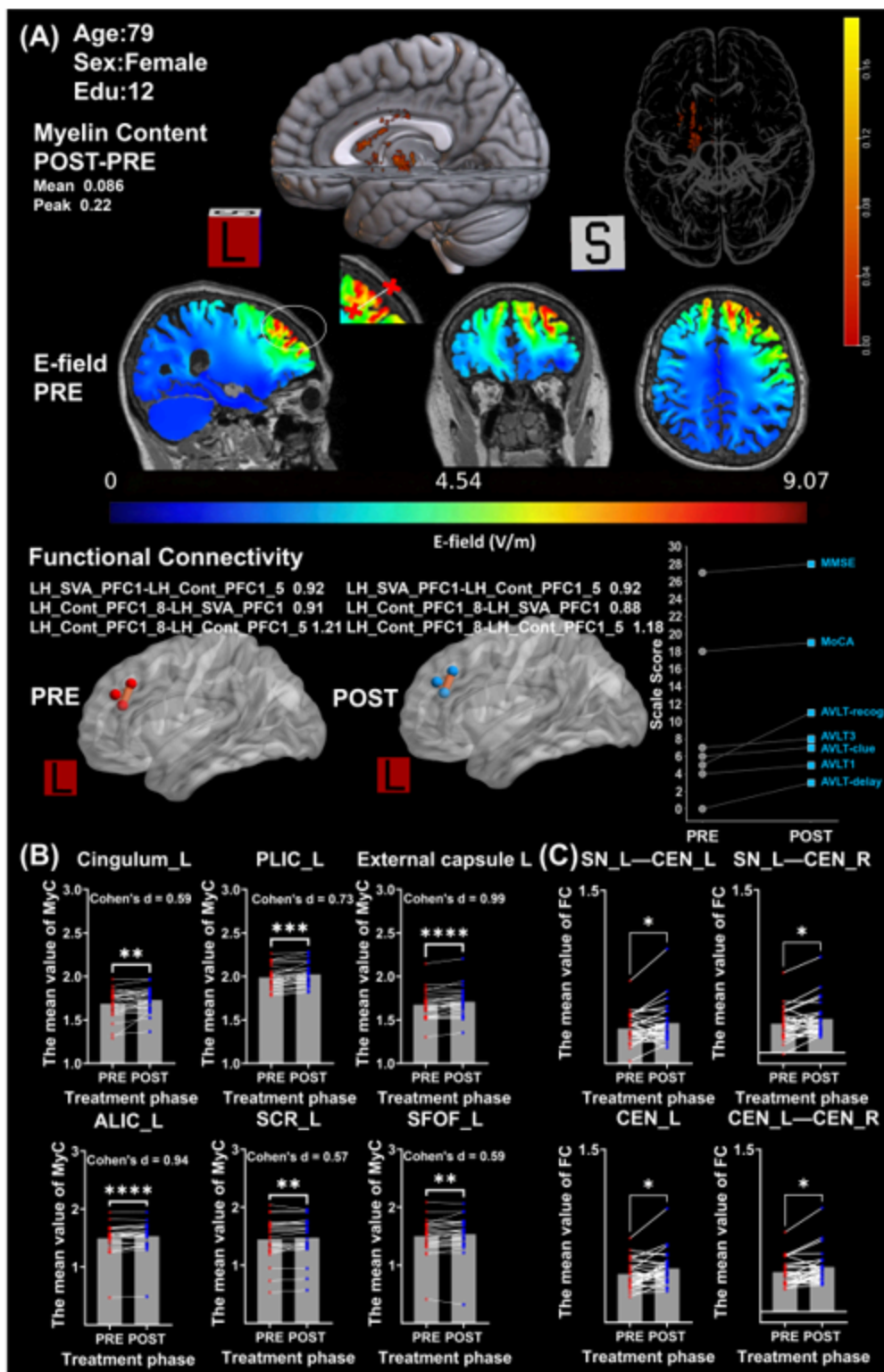


Figure 2

An individual case showing myelin, E-field, and FC, and whole-brain significant brain regions of myelin and networks. (A) An individual case demonstrating increased myelin (post- versus pre-treatment) and pre-treatment E-field, FC neighboring the DLPFC with no noticeable changes, and elevated post-treatment clinical scale scores. (B) Whole-brain significant brain regions of myelin across the left

hemispheres. (C) Whole-brain significant brain regions of networks. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, ****: $p < 0.0001$.

Abbreviations Cingulum_L: left cingulum (cingulate gyrus; PLIC_L: left posterior limb of internal capsule; SFOF_L: left superior fronto-occipital fasciculus (could be a part of anterior internal capsule; SCR_L: left superior corona radiat; ALIC_L: left anterior limb of internal capsule; SN_L–CEN_L: between the left salience network and the left central executive network; CEN_L: intra-connectivity within the left central executive network; SN_L–CEN_R: between the left and right central executive networks; CEN_L–CEN_R: between the left and right central executive networks.

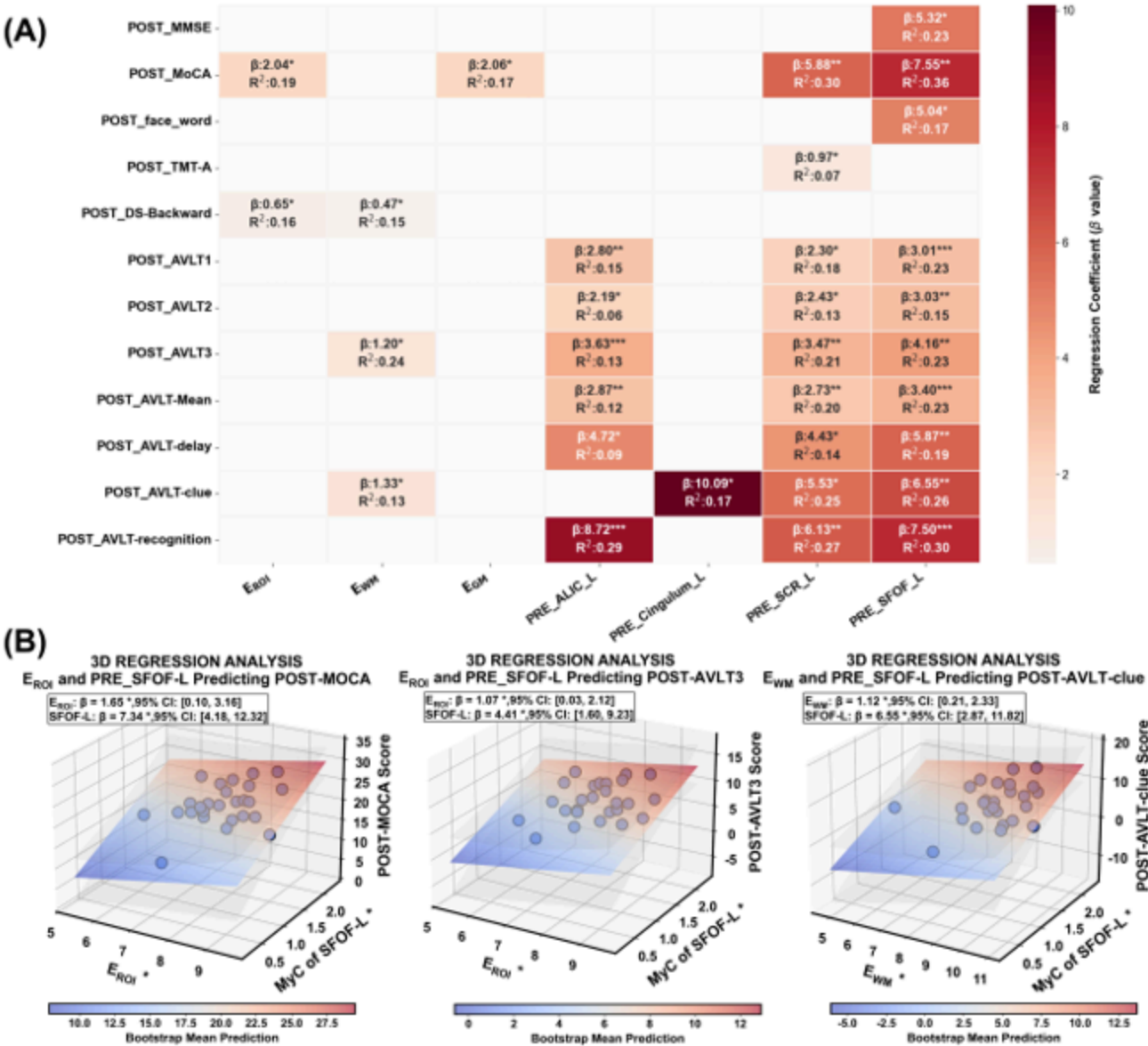


Figure 3

Multiple Linear Regression Analysis for Predicting Post-treatment Cognitive Scores. (A) Univariate Linear Regression for Predicting Post-treatment Cognitive Scores. (B) Multivariable Linear Regression for Predicting Post-treatment Cognitive Scores. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Abbreviations—Cingulum_L: left cingulum (cingulate gyrus; SFOF_L: left superior fronto-occipital fasciculus (could be a part of anterior internal capsule; SCR_L: left superior corona radiat; ALIC_L: left anterior limb of internal capsule.

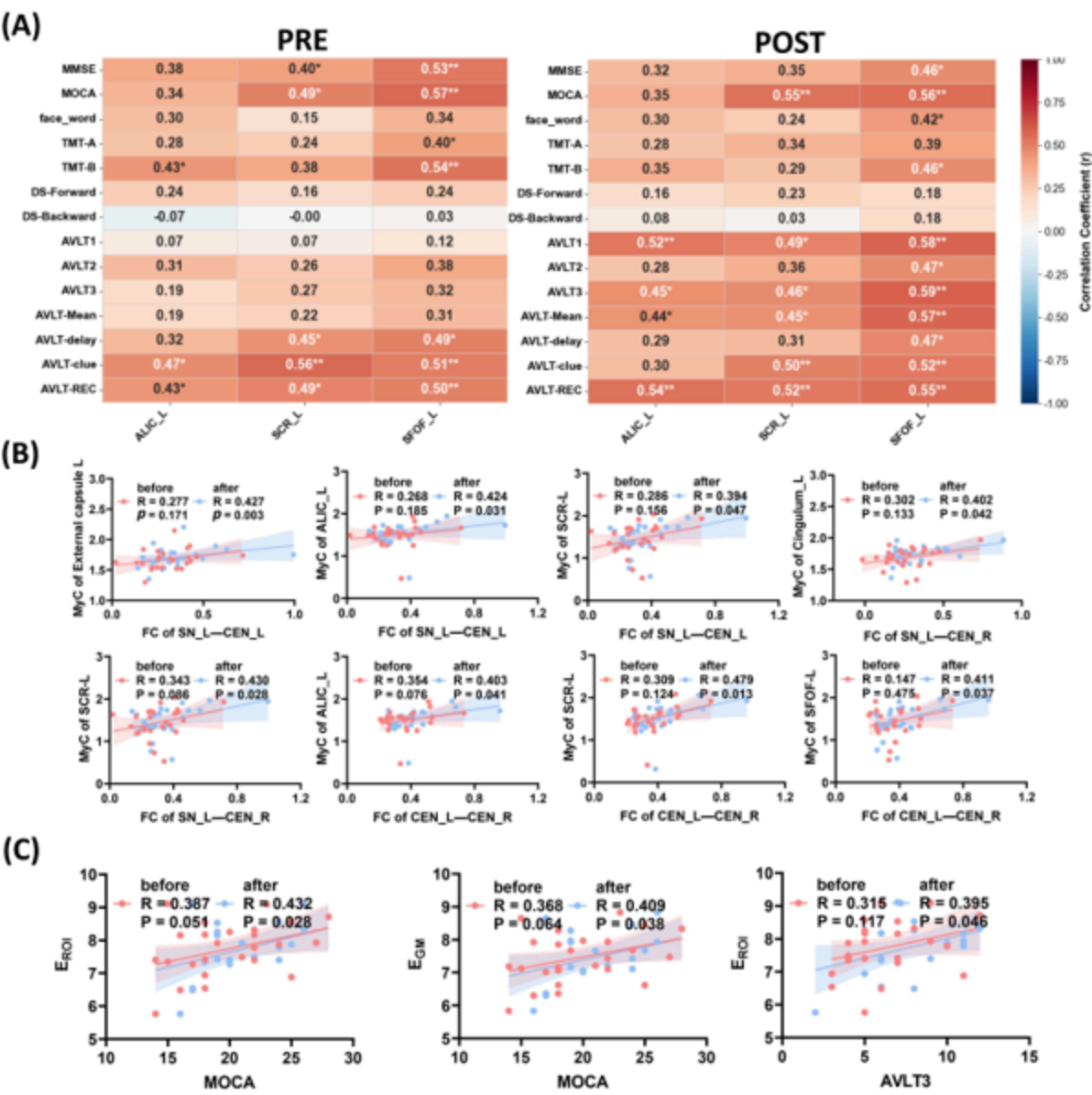


Figure 4

Correlations between the two networks, scales, myelin, and baseline E-field before and after treatment. (A) shows the correlations between pre-treatment scales and pre-treatment FC networks, as well as the correlations between post-treatment scales and post-treatment FC networks. (B) shows the comparison

of correlations between MyC and FC networks before and after treatment. (C) shows the comparison of correlations between E-field and clinical scales before and after treatment. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Abbreviations: Cingulum_L: Cingulum (cingulate gyrus) L; SFOF_L: Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) L; SCR_L: Superior corona radiata L; ALIC_L: Anterior limb of internal capsule L; SN_L–CEN_L: between the left salience network and the left central executive network; SN_L–CEN_R: between the left and right central executive networks; CEN_L–CEN_R: between the left and right central executive networks.

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