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# Effects of Accelerated DLPFC-rTMS on Cognition, EEG Activity, and Blood Biomarkers in Alzheimer's Disease

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**Abstract**

Repetitive transcranial magnetic stimulation (rTMS) may offer a noninvasive intervention for Alzheimer's disease (AD), but optimal protocols and mechanisms remain uncertain. We assessed clinical outcomes, resting-state electroencephalography (EEG), and blood biomarkers after a brief accelerated-rTMS application targeting bilateral dorsolateral prefrontal cortex (DLPFC). Thirty-three patients with mild–moderate AD were randomized to accelerated rTMS (n = 19) or non-stimulated control (n = 14). The rTMS group received 20-Hz stimulation to each DLPFC twice daily for five days (10 sessions). At baseline and four weeks later, participants completed cognitive testing, neuropsychiatric evaluation, resting EEG, and blood assays of oxidative stress, inflammatory, and neurotrophic markers. Compared with controls, rTMS produced greater improvement in activities of daily living and neuropsychiatric symptoms, with global cognition remaining stable over post-treatment assessment. Exploratory EEG analyses indicated increased parietal beta-band power following rTMS, although between-group EEG effects did not remain significant after correction for multiple comparisons. Blood measures shifted toward a more neuroprotective profile, including higher neurotrophic signaling and more favorable oxidative and inflammatory indices. No serious adverse events were reported. A one-week accelerated rTMS

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protocol was feasible and well tolerated in AD, showing aligned improvements in function, EEG, and blood biomarkers, supporting accelerated-rTMS as a feasible and biologically promising intervention that warrants confirmation in sham-controlled trials.

**Keywords:** Alzheimer's disease; bilateral DLPFC; accelerated-rTMS; blood biomarkers; EEG

## 1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. According to recent global estimates, more than 57 million people were living with dementia in 2021, and this number is expected to nearly triple by 2050 due to aging populations. Beyond its devastating cognitive and functional consequences, AD imposes a substantial socioeconomic burden through increased healthcare expenditures, long-term care demands, disability, and caregiver stress worldwide [1–3]. This reality underscores the need to develop new therapeutic approaches [4,5]. Given the limited efficacy of pharmacological interventions, noninvasive neuromodulation techniques aimed at modulating neural networks have emerged as promising alternatives. Among these, repetitive transcranial magnetic stimulation (rTMS) has received particular attention. rTMS offers a noninvasive, generally well-tolerated, and target-focused form of brain stimulation [6–8]. Although it cannot reverse neuron loss due to cell-level atrophy, rTMS may attenuate disease progression by enhancing synaptic connectivity between neurons [9–11]. A large proportion of rTMS studies in individuals with AD report beneficial effects on cognitive functions [5,12–15]. These effects appear to depend on multiple parameters, including the targeted cortical region, total duration, session frequency, and the cumulative number of pulses. Despite numerous experimental studies and systematic reviews in the context of AD, there is still no consensus on the optimal rTMS protocols to enhance cognitive performance [13].

Since multiple brain regions are affected in AD, the dorsolateral prefrontal cortex (DLPFC), which is implicated in a wide range of functions, has become a frequent stimulation target [16,17]. The DLPFC plays a central role in higher-order cognitive processes such as decision-making, information processing, and working memory [18,19]. Prior work has shown that stimulating the DLPFC is suitable for modulating the default mode network (DMN) [20]. Findings from studies combining rTMS with PET imaging indicate that high-frequency rTMS (HF-rTMS) applied to the DLPFC increases cerebral blood flow not only within this region but also in connected areas, including the anterior cingulate cortex (ACC). Moreover, HF-rTMS may influence the dopaminergic system and modulate serotonergic activity within limbic structures such as the cingulate, insular, and parahippocampal cortices [21,22].

Among the critical parameters in neuromodulation protocols are total treatment duration and the number of sessions. Overall, accumulating evidence suggests that longer protocols with more sessions may yield greater therapeutic efficacy [7,8]. However, such intensive regimens can hinder adherence, particularly in older adults. As an alternative, Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) was proposed by Cole and colleagues (2020) for the treatment of depression. SAINT delivers a high dose of stimulation over a short period and has been described as a safe and feasible intervention [23]. Evidence indicates that SAINT achieves improvements comparable to standard, longer-duration protocols. This approach also holds promise for situations requiring rapid clinical response, such as inpatient settings or emergencies [24]. Within this framework, accelerated-rTMS protocols that shorten overall treatment duration and include multiple daily sessions have gained attention as more accessible and implementable

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neuromodulation strategies. To date, the potential therapeutic effects of such accelerated protocols have not been reported for AD.

Beyond symptomatic improvement, rTMS may exert neuroprotective effects. Some meta-analyses suggest that rTMS could have disease-modifying potential and may be better tolerated than currently available pharmacological treatments such as aducanumab, lecanemab, and donanemab [25]. In this context, electroencephalography (EEG) provides an important neurophysiological perspective for both diagnosis and disease monitoring in AD. A characteristic "EEG slowing" pattern has been described, marked by increased low-frequency delta (1-4 Hz) and theta (4-8 Hz) activity accompanied by reductions in alpha (8-12 Hz), beta (13-30 Hz), and gamma frequencies [26–30]. In particular, elevations in delta and theta bands (1-8 Hz) form part of the typical slowing pattern in AD and have been linked to deficits in attention, memory, and executive functions. Following rTMS, decreases in delta power and normalization trends in theta activity have been interpreted as reflecting reorganization of attentional systems and synaptic plasticity [31,32]. Changes in higher-frequency EEG components, namely alpha (8-12 Hz), beta (13-30 Hz), and gamma (30+ Hz), appear more complex yet therapeutically promising. Increases in alpha and gamma bands after rTMS have been associated with stronger cortical synchronization and improved network organization [31,33]. Experimental findings further suggest that rTMS may enhance synaptic plasticity, reduce amyloid-β burden, elevate neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF), and modulate oxidative stress and neuroinflammation [10,15]. Additional effects on exosome release, Glial Cell Line-Derived Neurotrophic Factor (GDNF) levels, thiol-disulfide balance, and neurotransmitter systems support the possibility that rTMS could serve as a disease-modifying tool in AD. Nevertheless, the extent and precise mechanisms of these effects in patients with AD remain to be fully elucidated.

In this study, we wanted to evaluate, for the first time, an accelerated-rTMS protocol delivered bilaterally to the DLPFC in AD. We hypothesized that this approach would yield measurable gains in cognition and behavior. To test this, we combined standardized cognitive and behavioral assessments with resting-state EEG to quantify network-level modulation, and we collected peripheral blood samples to explore putative neuroprotective mechanisms. Together, these multimodal measures allowed us to link clinical change with neural and biological readouts of treatment effect.

## 2. Methods

This study was a parallel-group, delayed-treatment-controlled, single-blind (participant-blinded) clinical trial. Eligible participants who met the inclusion criteria were randomly allocated (1:1) to either the active accelerated-rTMS group or the control (delayed-treatment) group using a computer-generated randomization procedure. Outcome assessments were conducted by experienced evaluators who were aware of group assignments but were not involved in administering TMS. Participants in the control group did not receive active stimulation during the trial period (Figure 1).

The study protocol was registered at ClinicalTrials.gov (https://clinicaltrials.gov/study/NCT05977088-ID: NCT05977088- registration date: 02/06/2023) and approved by the Ethics Committee of Istanbul Medipol University, Turkey (File number: E-66291034-772.02-1122), and the study was conducted in accordance with the Declaration of Helsinki. All participants received detailed written information about the study objectives, procedures, potential risks, and benefits, and provided written informed consent prior to

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enrollment. Participant confidentiality and anonymity were strictly maintained throughout the study.

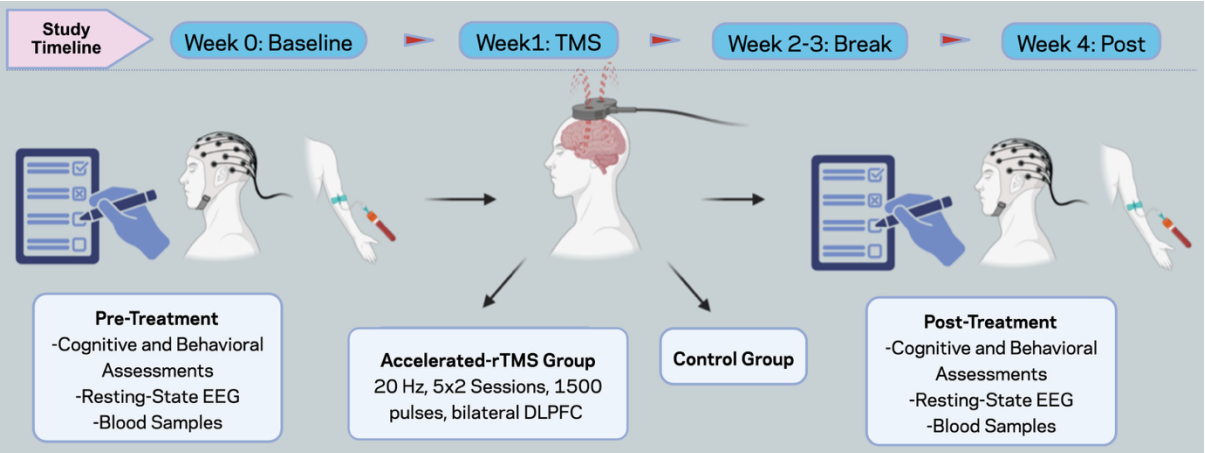



**Figure 1. Study flowchart:** Overview of the four-week experimental protocol comparing the accelerated-rTMS intervention group and the non-TMS control group. In Week 0 (baseline/pre-treatment), all participants completed cognitive and behavioral assessments, resting-state EEG recordings, and blood sampling. In Week 1, the accelerated-rTMS group received bilateral dorsolateral prefrontal cortex stimulation (20 Hz; 5×2 sessions; 1500 pulses per session), whereas the control group received no stimulation. Week 2-3 consisted of two-weeks break without intervention. In Week 4 (post-treatment), all participants again underwent cognitive and behavioral testing, resting-state EEG, and blood sampling to evaluate changes following the intervention. The figure was created using BioRender (https://biorender.com), and are published under a CC BY 4.0 license with permission from BioRender.

### *2.1 Participants*

Sample size was calculated using G*Power (version 3.1), assuming an effect size of 0.5, $\alpha = 0.05$, and 95% power ($1-\beta = 0.95$), yielding a required sample size of 30 participants. A total of 40 participants were enrolled and randomized into two groups: accelerated-rTMS and control. In the experimental group, one participant withdrew before completing the TMS protocol. In the control group, 6 participants discontinued the planned sessions due to personal and transportation-related issues. Thirty-three participants completed the study (accelerated-rTMS: n=19, 11 male; mean age 72.16 ± 3.85 years; control: n=14, 7 male; mean age 69.21 ± 7.52 years) (Table 1). The accelerated-rTMS group received the stimulation protocol, whereas the control group received no rTMS and continued their pre-existing pharmacotherapy at stable doses throughout the study.

The clinical diagnosis of AD was conducted by an experienced neurologist according to NINCDS-ADRDA criteria [34]. Clinical Dementia Rating (CDR) scores for enrolled patients ranged from 1 to 2. Inclusion criteria comprised: (1) adequate vision and hearing; (2) willingness to participate for the full duration of the study with caregiver accompaniment; and (3) absence of comorbid medical or psychiatric conditions known to affect cognitive functioning. Exclusion criteria included: (1) current or recent (within the past month) use of investigational pharmacological agents for AD or any neuromodulation therapy (transcranial Direct Current Stimulation (tDCS), TMS) in addition to, or outside of, standard symptomatic treatments (acetylcholinesterase inhibitors, memantine); (2) a history of any other neurological disorder; and (3) standard

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contraindications to TMS, such as intracranial metallic implants or the presence of a cardiac pacemaker.

**Table 1**: Baseline participant characteristics

| | Accelerated-rTMS Group (n = 19) | Control Group (n = 14) | p Value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| **Gender** | 8 F / 11 M | 7 F / 7 M | 0.653 |
| **Age** | 72.16 ± 3.85 | 69.21 ±7.52 | 0.151 |
| **Education** | 8.26 ± 4.57 | 8.14 ± 5.14 | 0.924 |
| **SMMSE** | 19.9 ± 5.13 | 19 ± 6.71 | 0.667 |

SMMSE: Standardized Mini-Mental State Examination, SD: Standart Deviation

### *2.2 Accelerated-rTMS Protocol and Application*

TMS was conducted using a PowerMAG Research stimulator (Mag & More) with a figure-of-eight coil. The treatment protocol comprised 10 sessions administered over 5 consecutive days, with two sessions per day. The coil was positioned tangential to the scalp at approximately a 45° angle. In each train, 75 pulses were delivered with a 45-second inter-train interval, yielding 1500 pulses to the bilateral DLPFC per session, for a total of 3000 pulses [5,12,35]. Each target region was stimulated for 15 minutes; total stimulation time per session was 30 minutes. There was a 30-minute break between daily sessions [36–38].

Resting motor threshold (RMT) was determined prior to treatment using single-pulse TMS over the left primary motor cortex while recording EMG from the contralateral abductor pollicis brevis at rest, and was defined as the minimum stimulator output that evoked motor-evoked potentials ≥50 μV in at least 5 of 10 consecutive trials. After identifying the motor hotspot, the DLPFC was localized as a point 5 cm anterior to this site and further refined using the international 10-20 EEG system to target F3 (left DLPFC) and F4 (right DLPFC) [39]. Stimulation intensity over the DLPFC was set to 100% of the individual RMT.

TMS safety was monitored at each session using a standardized TMS Safety and Adverse Effects Checklist based on the safety guidelines proposed by Rossi et al stimulation [40]. Participants were systematically queried about headache, dizziness, tinnitus, irritability, and sleep changes during and after stimulation [36,40]. No serious adverse events (seizures, persistent neurological deficits) were observed. Reported side effects were mild (predominantly transient headache) and resolved spontaneously within a few hours.

### *2.3 Cognitive, Behavioral Assesments and Analysis*

All participants in the accelerated-rTMS and control groups completed baseline and post-treatment assessments separated by three weeks. Cognitive status was assessed using the Standardized Mini-Mental State Examination (SMMSE) to index global cognition and disease severity [41], the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), [42] and Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) [43]. Behavioral status was assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q) [44], and the Geriatric Depression Scale (GDS) [45]. Validated Turkish versions of all tests were used.

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Baseline differences between groups were examined with independent-samples t tests (two-tailed, $\alpha = 0.05$). To estimate the effect of TMS on behavioral outcomes while adjusting for any initial group differences, we conducted analyses of covariance (ANCOVA) in which the corresponding pretest score was included as a covariate. In these models, post-test scores were the dependent variables and group (accelerated-rTMS vs control) was the between-subjects factor; assumptions of normality, homogeneity of variance, and homogeneity of regression slopes were evaluated and satisfied. In addition, the Benjamini–Hochberg False Discovery Rate (FDR-BH) correction was applied to control for Type I error due to multiple comparisons. Statistical analyses for the behavioral measures were performed in Jamovi (version 2.3.12; https://www.jamovi.org).

### *2.4 EEG Recordings Procedure and Analysis*

Resting-state EEG was recorded before and after treatment using BrainVision Recorder (version 1.21.0102) software (Brain Products GmbH, Gilching, Germany; https://www.brainproducts.com ) with a 0.01-500 Hz bandpass. Electrode placement followed the 10/10 EEG system [46]. Signals were acquired from 64 channels using Ag/AgCl ring electrodes with an EasyCap. EEG preprocessing and analysis were performed using BrainVision Analyzer (version 2.2.2; Brain Products GmbH, Gilching, Germany; https://www.brainproducts.com). Signals were band-pass filtered at 0.1-60 Hz and notch-filtered at 50 Hz to remove line noise, then re-referenced to the average. Ocular, muscular, and environmental artifacts were identified and removed using independent component analysis (ICA) and the Clean Raw Data plug-in, with both automated and manual procedures. Artifact-free data were segmented into 1-s epochs. Remaining artifacts were rejected manually to ensure comparable epoch counts across pre- and post-treatment recordings. Power spectral density was computed via Fast Fourier Transform (FFT) with 0.5-Hz frequency resolution. Band-limited power was extracted beta (15-28 Hz) and then averaged within band. Peak-to-peak amplitudes were measured for each participant, the derived metrics were exported for statistical analysis.

Baseline differences between groups were examined with independent-samples t tests (two-tailed, $\alpha = 0.05$). To examine between-group differences in post-treatment EEG beta power, separate analyses of covariance (ANCOVAs) were conducted for each predefined region of interest (ROI). Post-treatment beta power values were entered as the dependent variables, group (accelerated-rTMS vs. control) was included as the fixed factor, and the corresponding pre-treatment beta power values were included as covariates to adjust for baseline differences. Effect sizes were reported using eta squared ($\eta^2$). To control for Type I error associated with multiple regional comparisons, p-values for the group effects were adjusted using the Benjamini–Hochberg False Discovery Rate (FDR-BH) procedure. Statistical significance was set at $p < 0.05$. Statistical analyses for the EEG measures were performed in Jamovi (version 2.3.12; https://www.jamovi.org).

### *2.5 Blood Sample Collection and Biochemical Analyses*

Pre- and post-treatment blood samples were collected to analyze BDNF, GDNF, total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), total thiol (TT), native thiol (NT), disulfide (DS), exosome marker (EXOSC9), and inflammatory biomarkers [interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and nuclear factor-kappa B (NF-κB)]. For each participant, one 9-mL gel-separator tube of venous blood was drawn from the cubital vein. Samples were centrifuged at 3000

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rpm for 10 minutes, and the resulting serum was aliquoted into Eppendorf tubes and stored at -80 °C until all participants' samples had been collected.

Human ELISA kits specific to each parameter were used to quantify biomarker levels in serum. BDNF (ng/mL) was measured with the BTLab kit E1302Hu; GDNF (ng/mL) with BTLab E0122Hu; EXOSC9 (ng/L) with BTLab E5269Hu; IL-1β (pg/mL) with BTLab E0143Hu; IL-6 (ng/L) with BTLab E0090Hu; TNF-α (ng/L) with BTLab E0082Hu; IFN-γ (ng/mL) with BTLab E0105Hu; and NF-κB (ng/mL) with BTLab E0690Hu. All assays were performed strictly according to the manufacturers' protocols.

Oxidative stress indices were assessed using both photometric and spectrophotometric methods described by Erel (2004, 2005) [47,48]. TAS, TOS, and OSI (the ratio of TOS to TAS) were determined to provide a comprehensive evaluation of oxidative balance in serum. Thiol-disulfide homeostasis, a dynamic indicator of cellular redox status, was evaluated as follows: TT and NT concentrations were measured spectrophotometrically using the method of Erel and Neselioglu (2014) [49], and DS levels were calculated mathematically. These metrics reflect the oxidation of thiol groups to disulfides and were used to characterize biochemical effects of oxidative stress. Serum albumin and globulin concentrations and their ratio (Alb/Glob) were determined using electrophoresis and automated analyzers. Omega-3 and Omega-6 fatty acids were quantified by gas chromatography-mass spectrometry (GC-MS) on an Agilent 7890B GC-EI-MS operating in selected ion monitoring (SIM) mode to ensure high sensitivity and selectivity. Statistical analyses of the biochemical data were performed using jamovi (version 2.3.12; https://www.jamovi.org).

## 3. Results

Within-group analyses showed no significant pre-to-post change in the accelerated-rTMS group on GDS ($p = 0.086$) or SMMSE total ($p = 0.213$), whereas significant improvements were observed on ADAS-Cog total ($p < 0.001$), ADCS-ADL ($p = 0.007$), and NPI-Q total and severity scores ($p = 0.025$ and $p < 0.001$, respectively). In the control group, SMMSE changed significantly from baseline to post-treatment ($p = 0.020$), while ADAS-Cog, GDS, ADCS-ADL, and NPI-Q showed no significant change (all $p > 0.05$; Table 2). Between-group ANCOVAs adjusting for the corresponding pretest scores indicated effects favoring rTMS on ADCS-ADL ($F(1,31) = 9.08$, $p = 0.005$, $\eta^2 = 0.072$), NPI-Q total ($F(1,31) = 6.98$, $p = 0.013$, $\eta^2 = 0.124$), NPI-Q severity ($F(1,31) = 9.81$, $p = 0.004$, $\eta^2 = 0.122$), SMMSE ($F(1,31) = 10.09$, $p = 0.004$, $\eta^2 = 0.027$), and ADAS-Cog ($F(1,31) = 4.54$, $p = 0.041$, $\eta^2 = 0.021$), with no significant group difference on GDS ($F(1,31) = 1.10$, $p = 0.302$, $\eta^2 = 0.016$ (Table 2).

Resting-state, eyes-open EEG power was analyzed across the beta frequency band in six scalp regions (frontal, frontocentral, parietal, occipital, temporoparietal, and parieto-occipital) in both groups. Primary between-group comparisons were conducted using ANCOVA controlling for baseline beta power; corresponding repeated-measures ANOVA results are provided in Supplementary Table S1 for reference. ANCOVA analyses revealed no significant group effects in the frontal ($F(1,31) = 2.96$, $p = .096$, $\eta^2p = .046$), frontocentral ($F(1,31) = 1.77$, $p = .194$, $\eta^2p = .039$), parietal ($F(1,31) = 0.003$, $p = .960$, $\eta^2p < .001$), occipital ($F(1,31) = 0.09$, $p = .767$, $\eta^2p = .002$), temporoparietal ($F(1,31) = 2.89$, $p = .100$, $\eta^2p = .056$), or parieto-occipital ($F(1,31) = 0.11$, $p = .748$, $\eta^2p = .002$) regions, and none of these findings remained significant after false discovery rate (FDR) correction. Post-hoc comparisons based on estimated marginal means similarly indicated no significant between-group differences in frontal ($p = .453$), frontocentral ($p = .247$), parietal ($p = .221$), occipital ($p = .063$), or parieto-occipital ($p = .125$) beta power. Although the

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temporoparietal region showed a nominally significant post-hoc difference ($p = .027$, Cohen's $d = 0.84$), the corresponding overall ANCOVA group effect was not significant; this finding should therefore be interpreted cautiously and considered exploratory rather than confirmatory (Figure 2; Table 3).

In the accelerated-rTMS group, several biomarkers exhibited statistically significant changes relative to controls. Serum BDNF increased from 5.13 ± 1.33 to 5.68 ± 1.32 ng/mL ($p = 0.010$). Oxidative stress indices improved markedly, with TOS decreasing (14.6 ± 2.44 to 12.2 ± 1.73; $p < 0.001$), TAS rising (0.88 ± 0.10 to 0.99 ± 0.17; $p < 0.001$), and OSI reducing (16.84 ± 3.34 to 12.56 ± 2.12; $p < 0.001$). Thiol/disulfide homeostasis also shifted significantly: total thiols increased from 452.53 ± 35.91 to 476.07 ± 43.91 µmol/L and native thiols from 258.73 ± 31.02 to 270.79 ± 23.90 µmol/L ($p < 0.001$ for both), with corresponding changes in %NT/TT ($p = 0.007$), %DIS/TT ($p = 0.007$), and %DIS/NT ($p = 0.013$). EXOSC9 levels rose from 484.75 ± 82.73 to 519.33 ± 70.42 pg/mL ($p < 0.001$), and pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and IFN-γ all declined significantly (all $p < 0.001$), with NF-κB also decreasing ($p = 0.018$). Finally, fatty acid profiles were altered: omega-3 increased ($p = 0.035$), omega-6 decreased ($p = 0.001$), and the omega-6/omega-3 ratio shifted significantly ($p = 0.004$) (Table 4).

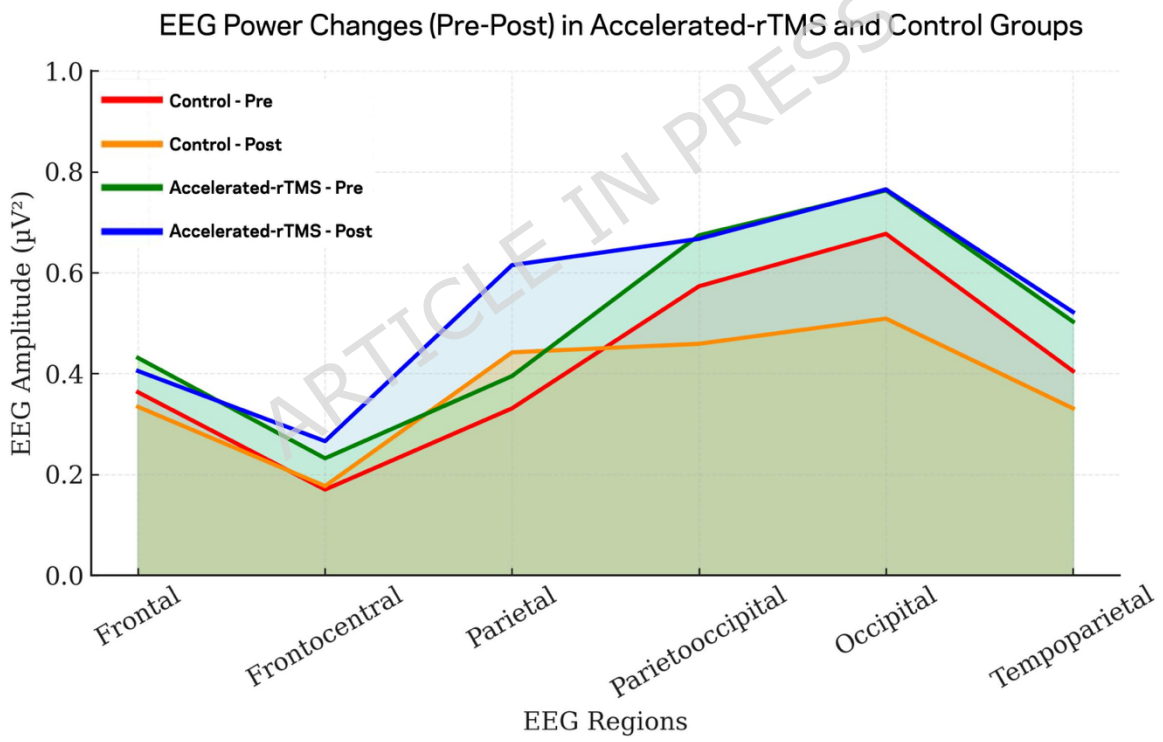



**Figure 2. EEG Line plots:** Plots show mean EEG beta power (µV²) across six scalp regions (Frontal, Frontocentral, Parietal, Parietooccipital, Occipital, Temporoparietal) for both the accelerated-rTMS and control groups, measured before and after the intervention. The largest pre–post difference was observed in the parietal region within the accelerated-rTMS group. Shaded areas represent the difference between pre- and post-treatment amplitudes within each group.

**Table 2.** Cognitive and Behavioral Assessments Results

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| | Accelerated-rTMS Group (n= 19) | | | | | Control Group (n= 14) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | T Test | | | | | T Test | | | | | |
| | Pre-evaluation | Post-evaluation | Cohen'd | intra group | | Pre-evaluation | Post-evaluation | Cohen'd | intra group | | *F(* |
| | Mean ± SD | Mean ± SD | | p Value | FDR BH p value | Mean ± SD | Mean ± SD | | p Value | FDR BH p value | |
| **GDS** | 5.05 ± 3.91 | 3.68 ± 3.06 | 0.416 | 0.086 | 0.103 | 7.43 ± 6.17 | 6.36 ± 5.69 | 0.302 | 0.278 | 0.500 | |
| **ADCS-ADL** | 58.74 ± 14.27 | 64.26 ± 10.05 | -0.701 | 0.007 | 0.014 | 52.71 ± 15.15 | 52.79 ± 15.43 | -0.01 | 0.42 | 0.504 | 9 |
| **NPI-Q** | 8.32 ± 7.49 | 4.37 ± 5.56 | 0.561 | 0.025 | 0.038 | 10.71 ± 10 | 14.57 ± 15.83 | -0.355 | 0.206 | 0.500 | 6 |
| **NPI-Q - Severity** | 5.26 ± 4.96 | 2.79 ± 3.46 | 0.947 | < . 001 | <0.003 | 7.07± 6.11 | 8.64 ± 8.15 | -0.295 | 0.405 | 0.504 | 9 |
| **SMMSE** | 19.89 ± 5.13 | 20.42 ± 4.49 | -0.296 | 0.213 | 0.213 | 19 ± 6.71 | 17.79 ± 6.80 | 0.794 | 0.02 | 0.120 | 1 |
| **ADAS-Cog** | 23.03 ± 10.62 | 20.21 ± 10.91 | 1.008 | < . 001 | <0.003 | 27.81 ± 12.11 | 28.67 ± 14.05 | -0.134 | 0.622 | 0.622 | 4 |

SMMSE: Standardized Mini-Mental State Examination; GDS: Geriatric Depression Scale; ADAS-Cog: The Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; NPI-Q: Neuropsychiatric Inventory Questionnaire; SD: Standart Deviation, *: Statistically significant at $p < 0.05$.

**Table 3:** Regional changes in beta power following accelerated-rTMS. A statistically significant effect was observed only in the parietal region

| | Accelerated-rTMS Group (n= 19) | | | | | Control Group (n= 14) | | | | | Accelerated-rTMS vs C | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T Test | | | | | T Test | | | | | ANCOV | | |
| **Region** | Pre-evaluation | Post-evaluation | Cohen'd | p | FDR BH p | Pre-evaluation | Post-evaluation | Cohen'd | p | FDR BH p | F(1,31) | P | |
| | Mean ± SD | Mean ± SD | | | | Mean ± SD | Mean ± SD | | | | | | |
| **Frontal** | 0.43 ± 0.30 | 0.40 ± 0.32 | 0.14 | 0.559 | 0.923 | 0.36 ± 0.34 | 0.31 ± 0.22 | 0.14 | 0.609 | 0.731 | 2.96 | 0.096 | 0 |
| **Fronto-central** | 0.23 ± 0.15 | 0.26 ± 0.20 | -0.27 | 0.257 | 0.771 | 0.17 ± 0.12 | 0.17 ± 0.16 | 0.02 | 0.942 | 0.942 | 1.77 | 0.194 | 0 |
| **Parietal** | 0.39 ± 0.28 | 0.61± 0.43 | -0.66 | **.010*** | 0.06 | 0.32 ± 0.16 | 0.43 ± 0.18 | -0.65 | 0.03 | 0.461 | 0.003 | 0.96 | 0 |
| **Occipital** | 0.76 ± 0.46 | 0.76 ± 0.49 | -0.01 | 0.983 | 0.983 | 0.68 ± 0.37 | 0.51 ± 0.23 | 0.59 | 0.044 | 0.533 | 0.09 | 0.767 | 0 |
| **Tempo-roparietal** | 0.50± 0.31 | 0.52 ± 0.34 | -0.09 | 0.694 | 0.923 | 0.39 ± 0.22 | 0.32 ± 0.13 | 0.28 | 0.307 | 0.461 | 2.89 | 0.1 | 0 |
| **Parieto-occipital** | 0.67 ± 0.43 | 0.66 ± 0.44 | 0.02 | 0.923 | 0.983 | 0.57 ± 0.29 | 0.45± 0.20 | 0.46 | 0.111 | 0.461 | 0.11 | 0.748 | 0 |

**Table 4**: Biochemical results of the accelerated-rTMS and Control groups.

| | Accelerated-rTMS Group (n=19) | Control Group (n=14) | Accelerated-rTMS vs Control |
|---|---|---|---|
| | T Test | T Test | ANCOVA |

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| Biomarkers | Pre-evaluation | Post-evaluation | Pre-evaluation | Post-evaluation | F *F(1,31)* | p Value | FDR-BH p value | $\eta^2$ |
|---|---|---|---|---|---|---|---|---|
| | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | | | | |
| **BDNF** | 5.13 ± 1.33 | 5.68 ± 1.32 | 5.79 ± 2.9 | 5.61 ± 2.55 | *7.588* | *0.01** | *0.015* | 0.202 |
| **GDNF** | 1.3 ± 0.56 | 1.4 ± 0.41 | 1.74 ± 0.68 | 1.68 ± 0.69 | *2.251* | *0.144* | *0.174* | 0.07 |
| **TOS** | 14.6 ± 2.44 | 12.2 ± 1.73 | 14.59 ± 2.66 | 16.86 ± 1.96 | *98.074* | *<0.001** | *0.002* | 0.766 |
| **TAS** | 0.88 ± 0.1 | 0.99 ± 0.17 | 0.8 ± 0.1 | 0.7 ± 0.15 | *18* | *<0.001* | *0.002* | 0.375 |
| **OSI** | 16.84 ± 3.34 | 12.56 ± 2.12 | 18.51 ± 3.96 | 25.3 ± 6.76 | *54.052* | *<0.001** | *0.002* | 0.643 |
| **TT** | 452.53 ± 35.91 | 476.07 ± 43.91 | 448.15 ± 29.87 | 423.91 ± 21.36 | *30.943* | *<0.001** | *0.002* | 0.508 |
| **NT** | 258.73 ± 31.02 | 270.79 ± 23.9 | 252.85 ± 27.98 | 215.82 ± 37.98 | *45.849* | *<0.001** | *0.002* | 0.604 |
| **DIS** | 96.9 ± 23.8 | 102.64 ± 23.08 | 97.65 ± 16.1 | 104.05 ± 15.85 | *0.028* | *0.868* | *0.868* | 0.001 |
| **% NT/TT** | 57.53 ± 8.46 | 57.27 ± 6.9 | 56.5 ± 5.92 | 50.81 ± 7.97 | *8.284* | *0.007** | *0.013* | 0.216 |
| **% DIS/TT** | 21.23 ± 4.23 | 21.36 ± 3.45 | 21.75 ± 2.96 | 24.6 ± 3.98 | *8.284* | *0.007** | *0.013* | 0.216 |
| **%DIS/NT** | 38.65 ± 12.65 | 38.42 ± 9.87 | 39.39 ± 9.28 | 51.18 ± 19.48 | *6.924* | *0.013** | *0.02* | 0.188 |
| **EXOSC9** | 484.75 ± 82.73 | 519.33 ± 70.42 | 464.3 ± 145.81 | 439.37 ± 103.78 | *33.357* | *<0.001** | *0.002* | 0.526 |
| **IL-1β** | 2458.17 ± 246.65 | 2219.35 ± 332.77 | 2701.18 ± 384.66 | 2799.35 ± 339.23 | *19.526* | *<0.001** | *0.002* | 0.394 |
| **IL-6** | 288.39 ± 81.07 | 252.06 ± 62.56 | 276.34 ± 73.67 | 299.24 ± 69.35 | *32.636* | *<0.001** | *0.002* | 0.521 |
| **TNF-α** | 370.95 ± 91.61 | 331.12 ± 63.55 | 375.14 ± 134.69 | 388.43 ± 125.13 | *16.188* | *<0.001** | *0.002* | 0.35 |
| **IFNy** | 155.35 ± 29.85 | 141.54 ± 23.61 | 137.25 ± 31.39 | 146.86 ± 34.84 | *25.213* | *<0.001** | *0.002* | 0.457 |
| **NF-κβ** | 3.14 ± 1.83 | 3 ± 1.85 | 3.81 ± 0.95 | 3.98 ± 0.97 | *6.324* | *0.018** | *0.024* | 0.174 |
| **Albümin** | 4.22 ± 0.27 | 4.26 ± 0.27 | 4.28 ± 0.25 | 4.29 ± 0.24 | *0.459* | *0.503* | *0.503* | 0.015 |
| **Globulin** | 3.59 ± 0.29 | 3.6 ± 0.31 | 3.52 ± 0.25 | 3.5 ± 0.29 | *1.557* | *0.222* | *0.268* | 0.049 |
| **Alb/Glo** | 1.18 ± 0.12 | 1.19 ± 0.11 | 1.22 ± 0.11 | 1.23 ± 0.11 | *1.175* | *0.287* | *0.316* | 0.038 |
| **Omega-3** | 141.88 ± 30.77 | 150.08 ± 28.77 | 152.97 ± 36.2 | 142.39 ± 29.14 | *4.87* | *0.035** | *0.039* | 0.064 |
| **Omega-6** | 6424.18 ± 300.89 | 6282.91 ± 236.04 | 6337.61 ± 198.32 | 6365.79 ± 222.97 | *13.23* | *0.001** | *0.002* | 0.306 |
| **Omega3/ omega 6** | 47.39 ± 10.91 | 43.14 ± 7.4 | 43.94 ± 11.62 | 46.48 ± 9.66 | *9.892* | *0.004** | *0.008* | 0.248 |

BDNF: Brain-Derived Neurotrophic Factor; GDNF: Glial Cell Line–Derived Neurotrophic Factor; TOS: Total Oxidant Status; TAS: Total Antioxidant Status; OSI: Oxidative Stress Index; TT: Total Thiol; NT: Native Thiol; DIS: Disulfide; %NT/TT: Percentage of Native Thiol to Total Thiol; %DIS/TT: Percentage of Disulfide to Total Thiol; %DIS/NT: Percentage of Disulfide to Native Thiol; EXOSC9: Exosome Component 9; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-alpha; IFN-γ: Interferon-gamma; NF-κB: Nuclear Factor kappa B; Albumin: Serum Albumin; Globulin: Serum Globulin; Alb/Glo: Albumin-to-Globulin Ratio; Omega-3: Omega-3 Polyunsaturated Fatty Acids; Omega-6: Omega-6 Polyunsaturated Fatty Acids; Omega-3/Omega-6: Omega-3 to Omega-6 Ratio; *: Statistically significant at $p < 0.05$

Correlation analyses were performed using change scores (Δ), calculated as post-treatment minus pre-treatment values (Δ = Post − Pre), for all clinical, EEG, and biochemical variables. Thus, the reported Spearman correlation coefficients reflect associations between treatment-related changes

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rather than absolute measurements. Spearman rank-order correlation analyses were conducted separately within each study group to examine the relationships among changes in clinical, electrophysiological, and biochemical parameters.

**Table 5.** Significant Spearman Correlations in the Accelerated-rTMS Group

| Variable 1 | Variable 2 | ρ (rho) | p |
|---|---|---|---|
| ΔNPI | ΔTNF-α | .704 | < .001 |
| ΔNPI Distress | ΔFrontocentral Beta | .597 | .007 |
| ΔADAS-Cog | ΔGDNF | -.586 | .008 |
| ΔIFN-γ | ΔFrontocentral Beta | .491 | .034 |
| ΔIL-1β | ΔParieto-Occipital Beta | -.468 | .045 |

In the accelerated-rTMS group, significant correlations were observed between changes in neuropsychiatric symptoms and several biological markers. Specifically, changes in NPI scores were positively associated with changes in TNF-α levels ($\rho = .704$, $p < .001$). Furthermore, changes in NPI Distress scores were positively correlated with changes in frontocentral beta power ($\rho = .597$, $p = .007$). A significant negative correlation was identified between changes in ADAS-Cog scores and GDNF levels ($\rho = -.586$, $p = .008$). Additional significant associations were observed between changes in IFN-γ levels and frontocentral beta activity ($\rho = .491$, $p = .034$), as well as between changes in IL-1β levels and parieto-occipital beta power ($\rho = -.468$, $p = .045$).

**Table 6.** Significant Spearman Correlations in the Control Group

| Variable 1 | Variable 2 | ρ (rho) | p |
|---|---|---|---|
| ΔADAS-Cog | ΔOmega-3 | -.859 | < .001 |
| ΔFrontocentral Beta | ΔEXOSC9 | -.626 | .019 |
| ΔTT | ΔGDS | -.606 | .022 |
| ΔAlb/Glo | ΔNPI | -.596 | .025 |
| ΔIL-1β | ΔNPI | .567 | .034 |
| ΔBDNF | ΔADAS-Cog | .618 | .021 |
| ΔGDNF | ΔTemporoparietal Beta | -.542 | .045 |

In the control group, significant correlations were also detected between clinical outcomes and biochemical markers. The strongest association was observed between changes in ADAS-Cog scores and Omega-3 levels ($\rho = -.859$, $p < .001$). Changes in EXOSC9 were negatively correlated with frontocentral beta power ($\rho = -.626$, $p = .019$), while changes in TT levels were negatively associated with GDS scores ($\rho = -.606$, $p = .022$). Significant correlations were also observed between changes in the albumin/globulin ratio and NPI scores ($\rho = -.596$, $p = .025$), changes in IL-1β and NPI scores ($\rho = .567$, $p = .034$), changes in BDNF and ADAS-Cog scores ($\rho = .618$, $p = .021$), and changes in GDNF and temporoparietal beta power ($\rho = -.542$, $p = .045$). Overall, these exploratory findings suggest that changes in inflammatory, neurotrophic, oxidative stress, lipid-related, and electrophysiological markers were associated with concurrent changes in cognitive and behavioral outcomes; however, these associations should not be interpreted as causal or treatment-specific.

## 4. Discussion

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This study demonstrates that a short, accelerated bilateral DLPFC accelerated-rTMS protocol produces meaningful multidomain effects in AD. Clinically, patients showed improvements in daily functioning and behavioral symptoms, accompanied by stable global cognition over the brief treatment window. Electrophysiologically, accelerated-rTMS induced increased beta-band activity in parietal regions, suggesting enhanced cortical synchronization. Biochemically, the intervention was associated with elevated BDNF levels, improved oxidative stress markers, modulation of thiol-disulfide homeostasis, reductions in key pro-inflammatory cytokines, and shifts in omega-3/omega-6 profiles, together indicating engagement of neuroplastic, antioxidant, and anti-inflammatory mechanisms. These converging clinical, electrophysiological, and biochemical findings provide preliminary evidence that accelerated-rTMS may modulate biological processes relevant to AD; however, the exploratory nature of the study precludes definitive conclusions regarding causal mechanistic relationships.

In the present study, accelerated bilateral DLPFC rTMS was associated with stabilization of global cognition (SMMSE) and a between-group advantage on ADAS-Cog relative to the non-stimulated control condition. These findings are in line with prior rTMS work in AD showing improvements on global cognitive scales particularly with high-frequency DLPFC stimulation and multi-session protocols and with trials combining rTMS with cognitive training that report ADAS-Cog/SMMSE benefits compared with sham. [50–52]. More broadly, recent meta-analyses support small-to-moderate improvements in global cognition and memory in AD following rTMS, while also highlighting substantial heterogeneity across targets, dosing parameters, and study designs [8,53]. At the same time, large multisite sham-controlled data underscore that nonspecific factors (expectancy/retest effects or sham-related currents) may contribute to apparent cognitive gains, reinforcing the need for larger, rigorously blinded studies to refine dosing and establish clinical efficacy [13]. Overall, our cognitive pattern (maintenance of SMMSE and improvement in ADAS-Cog relative to controls) is consistent with the direction of effects reported across the rTMS-in-AD literature, supporting further sham-controlled evaluation of accelerated schedules.

EEG alterations in AD are thought to reflect disease progression. The most frequently reported pattern is "EEG slowing," characterized by increased low-frequency power and reduced higher-frequency activity [26,27,29]. Within this context, EEG has emerged as a sensitive neurophysiological tool for quantifying brain effects of neuromodulatory interventions such as rTMS. Following rTMS in AD, increases in delta and theta power (1-8 Hz) have been reported and linked to impairments in attention, memory, and executive function; these changes are often interpreted as markers of attentional reorganization and synaptic plasticity [31,32]. Post-treatment increases in alpha and gamma bands have also been associated with stronger cortical synchronization and improved network organization [31,33]. Notably, greater gamma connectivity has shown positive correlations with episodic memory performance, suggesting that rTMS may influence not only superficial cortices but also functional integrity at deeper network levels [33]. Although beta rhythm is traditionally linked to motor and sensorimotor functions, recent work demonstrates a critical role in connectivity between frontal and parietal regions and in cognitive processes such as attention and short-term memory. In AD, reductions in beta activity may index loss of cortical synchronization and inhibitory imbalance, particularly over posterior regions, and have been proposed as electrophysiological markers of pathology [26,54,55]. In our study, we observed a significant increase in parietal beta power, indicating that accelerated-rTMS may strengthen synchronization within cortical networks. Given the association of beta activity with attention, inhibition, and cognitive stability [56], this increase may represent a neurophysiological mechanism paralleling behavioral improvements. Some studies have explored potential confounds

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and mechanisms. For example, Ding et al. (2021) suggested that auditory aspects of TMS delivery can modulate cerebral blood flow in sensorimotor cortex; nevertheless, converging evidence indicates that beta-band changes following high-frequency rTMS relate to clinical response [57]. Beta oscillations support functional integration between frontal and parietal, temporal, and occipital cortices and are closely tied to GABAergic inhibitory tone. Guo et al. (2021) reported that high-frequency rTMS enhances beta synchronization, which correlated with treatment response [58]. Koch et al. (2018) demonstrated that rTMS applied to the posterior cingulate gyrus was associated with memory improvement in early AD, increased neural activity within the posterior cingulate, enhanced beta-band oscillations, and altered functional connectivity between the posterior cingulate and medial frontal areas within the default mode network, consistent with network-level modulation accompanying clinical benefit [59].

Beyond clinical and electrophysiological effects, rTMS may exert neurobiological and neuroplastic influences at synaptic and cellular levels, raising the possibility of disease-modifying action [11]. Animal studies indicate that repeated TMS can reverse hippocampal depletion of nerve growth factor and BDNF, enhance hippocampal long-term potentiation, and reduce β-amyloid aggregation [60]. In AD, rTMS has been reported to influence synaptic plasticity, promote lasting structural changes, and reorganize large-scale functional and structural connectivity; it may also rebalance excitation-inhibition by engaging glutamatergic and GABAergic pathways, increase neurotrophic factors, counter amyloid and tau accumulation, and attenuate neuroinflammation by reducing microglial activation and pro-inflammatory cytokine release [61]. Given that impaired neuroplasticity, inflammation, and oxidative stress contribute alongside core amyloid/tau pathology, treatments acting on these processes could plausibly affect disease course. Among neurotrophic markers, BDNF is of particular interest due to its roles in synaptic plasticity, neuronal growth, and cell survival. In our experimental group, BDNF levels increased significantly after accelerated-rTMS, whereas no significant change was detected in the control group, supporting the potential of accelerated-rTMS to elevate BDNF. Prior literature is mixed but includes reports of rTMS-associated increases in BDNF in major depression and other conditions [14,62,63], alongside meta-analytic evidence of inconsistency [64]. In AD specifically, increased BDNF and reduced oxidative stress markers after rTMS have also been reported [15].

Considered together, our study supports the hypothesis that accelerated-rTMS may support neuroplastic processes. GDNF, which is critical for the development and survival of dopaminergic neurons, represents another neuroprotective biomarker [65]. Evidence on rTMS effects on GDNF in AD is limited. GDNF appears relevant to AD pathophysiology [66], with reports of reduced serum and elevated CSF levels in early AD [67]. In major depression, lower GDNF relative to controls and post-rTMS increases have been observed [62]. These findings suggest that rTMS may exert GDNF-mediated neuroprotective effects in neurodegenerative settings, though larger AD samples are needed. The inflammatory component of AD has long been recognized [68]. In our accelerated-rTMS group, we observed significant reductions in IL-1β, IL-6, TNF-α, and IFN-γ, indicating a potential for rTMS to modulate central inflammatory mechanisms. Prior studies have reported elevated IL-1β expression in AD relative to controls[69,70] and decreases in IL-1β and TNF-α after rTMS in depression, with mixed findings for IL-6 [71]. Decreases in IFN-γ following rTMS have also been described [72]. Collectively, these results suggest that rTMS may contribute favorably to AD by dampening inflammation-mediated mechanisms. Exosomes are implicated in regulating inflammatory and oxidative processes in AD [73,74]. We observed a significant post-rTMS increase in EXOSC9, consistent with effects on exosomal pathways and raising the possibility that rTMS influences exosome-mediated regulation of inflammation.

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Correlation analyses conducted within each group using change scores (Δpost − Δpre) revealed biologically coherent associations between treatment-related changes in clinical, electrophysiological, and biochemical parameters. In the accelerated-rTMS group, changes in neuropsychiatric symptom severity (ΔNPI) were strongly and positively correlated with changes in TNF-α levels ($\rho = .704$, $p < .001$). This finding is consistent with prior evidence demonstrating that elevated inflammatory cytokines including TNF-α are positively associated with neuropsychiatric symptom burden and NPI scores in Alzheimer's disease, suggesting that attenuation of pro-inflammatory signaling may parallel behavioral improvement following stimulation [75]. Furthermore, changes in cognitive performance (ΔADAS-Cog) were negatively associated with changes in GDNF levels ($\rho = -.586$, $p = .008$). This pattern is conceptually consistent with observations that neurotrophic factor modulation accompanies cognitive trajectories in AD; prior work has demonstrated that treatment-induced changes in BDNF are accompanied by significant reductions in ADAS-Cog scores, and that GDNF concentrations in CSF are dynamically modulated in response to neuroprotective interventions in early AD [67,76]. In the accelerated-rTMS group, changes in frontocentral beta power were correlated with changes in both NPI Distress and IFN-γ levels, pointing to a potential link between electrophysiological reorganization and neuroinflammatory-behavioral dimensions of treatment response. This is consistent with evidence that frontal high-beta oscillatory activity, particularly within fronto-parietal circuits, is causally associated with attentional modulation and cognitive performance, and can be entrained by TMS [77]. In the control group, the strongest association was between ΔADAS-Cog and ΔOmega-3 levels ($\rho = -.859$, $p < .001$). This observation is in line with the established relationship between omega-3 fatty acid levels and cognitive trajectory in AD, though randomized trial evidence suggests that omega-3 supplementation alone does not significantly modify ADAS-Cog scores, underscoring that the correlation observed in our control group may reflect naturally occurring biological covariation rather than a treatment effect [78,79]. Collectively, these exploratory correlational findings suggest that the multimodal changes observed following accelerated-rTMS are not isolated phenomena but may reflect partially interrelated biological processes; however, given the small sample size and the number of comparisons performed, these associations should be considered hypothesis-generating and require replication in larger, adequately powered studies.

Oxidative stress findings in the literature are heterogeneous. Özkan et al. reported increases in TAS, TT, and NT alongside decreases in TOS, OSI, and disulfide levels,[62] whereas Durmaz et al. noted reductions in TT and NT with no differences in disulfide or OSI [45]. In our study, bilateral DLPFC accelerated-rTMS was followed by decreases in TOS and OSI and increases in TAS, TT, NT, and disulfide, consistent with an enhanced systemic antioxidant response and reduced oxidative stress.

Nutritional and biochemical factors are increasingly recognized in neurodegenerative disease [80]. Decreases in omega-3 and omega-6 fatty acids have been linked to heightened inflammation and oxidative stress. In our experimental group, we observed a decrease in omega-3 ($p = 0.041$), an increase in omega-6 ($p = 0.0001$), and a significant reduction in the omega-6/omega-3 ratio ($p = 0.003$), suggesting a regulatory effect of accelerated-rTMS on fatty-acid metabolism. Taken together, our findings indicate that accelerated-rTMS in AD may support neuroplasticity and exert anti-inflammatory and antioxidant effects, with corresponding favorable changes in biochemical parameters. However, relationships between these biomarkers and clinical or cognitive outcomes require confirmation in larger samples.

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Several limitations of the present study should be acknowledged. First, the modest sample size limits statistical power and may compromise the detection of smaller treatment effects. Second, the absence of a sham-controlled and double-blind design limits the ability to definitively attribute the observed clinical improvements solely to accelerated-rTMS. In particular, caregiver-reported measures such as the ADCS-ADL and NPI-Q may be vulnerable to expectancy and reporting biases. Furthermore, non-specific factors associated with the treatment procedure itself including participant and caregiver expectations, the therapeutic environment, repeated interaction with clinical staff, device-related sounds, scalp sensations associated with stimulation, and caregiver judgment may have contributed to the observed outcomes. This limitation is particularly relevant when interpreting changes in subjective clinical measures. Third, the post-treatment period was limited to the immediate assessment phase, precluding conclusions regarding long-term durability and sustainability of treatment effects in Alzheimer's disease. In addition, inter-individual variability in response to stimulation may have influenced treatment outcomes. Despite these limitations, the multimodal nature of the present findings including convergent electrophysiological, biochemical, and clinical observations provides supportive evidence consistent with biological effects of accelerated bilateral DLPFC-rTMS in Alzheimer's disease. However, these findings should not be interpreted as definitive evidence against placebo, expectancy, or other non-specific treatment mechanisms.

An additional limitation is the potential influence of learning or practice effects associated with repeated cognitive testing. Given the relatively high baseline SMMSE scores, the mild degree of cognitive impairment, and the short interval between assessments, improvements observed in cognitive measures such as the SMMSE and ADAS-Cog may have been partially influenced by test–retest effects. Therefore, cognitive outcomes should be interpreted with caution, and future studies should incorporate sham-controlled designs and longer follow-up intervals to better distinguish treatment-related effects from practice-related improvements.

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## 5. Conclusion

In summary, in this study, a one-week high-frequency accelerated-rTMS protocol delivered twice daily (total 30,000 pulses) produced significant clinical improvements in activities of daily living and behavioral functioning in patients with AD. These findings warrant confirmation and optimization in larger, sham-controlled trials. EEG analyses demonstrated increased beta-band power, consistent with the possibility that DLPFC-targeted stimulation supports neuroplasticity. In the treatment group, accelerated-rTMS was associated with significant increases in BDNF and GDNF, elevations in exosomal markers, and reductions in inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ, and NF-κB). We also observed improvements in oxidative-stress indices and favorable shifts in omega-3 and omega-6 fatty-acid measures. Taken together, these findings may reflect potential neuroplastic and neuroprotective effects associated with accelerated-rTMS; however, the underlying mechanisms require confirmation in larger mechanistic and sham-controlled studies.While the present results indicate that accelerated-rTMS may influence not only cognitive and behavioral outcomes but also underlying biochemical processes with potential to slow disease progression, future work should examine longer-term effects across disease stages and refine individualized protocols by optimizing stimulation frequency, target localization, and session scheduling.

**Data availability**

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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to [restrictions e.g. their containing information that could compromise the privacy of research participants].

**Code Availability**

No custom code, novel computational tool, or bespoke analysis pipeline was developed for this study. All analyses were performed using commercially available or open-source software as described in the Methods section.

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**Competing interests**

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**Figure Legends**

**Figure 1. Study flowchart:** Overview of the four-week experimental protocol comparing the accelerated-rTMS intervention group and the non-TMS control group. In Week 0 (baseline/pre-treatment), all participants completed cognitive and behavioral assessments, resting-state EEG recordings, and blood sampling. In Week 1, the accelerated-rTMS group received bilateral dorsolateral prefrontal cortex stimulation (20 Hz; 5×2 sessions; 1500 pulses per session), whereas the control group received no stimulation. Week 2-3 consisted of two-weeks break without intervention. In Week 4 (post-treatment), all participants again underwent cognitive and behavioral

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testing, resting-state EEG, and blood sampling to evaluate changes following the intervention. The figure was created using BioRender (https://biorender.com), and are published under a CC BY 4.0 license with permission from BioRender

**Figure 2. EEG Line plots:** Plots show mean EEG beta power ($\mu V^2$) across six scalp regions (Frontal, Frontocentral, Parietal, Parietooccipital, Occipital, Temporoparietal) for both the accelerated-rTMS and control groups, measured before and after the intervention. The largest pre–post difference was observed in the parietal region within the accelerated-rTMS group. Shaded areas represent the difference between pre- and post-treatment amplitudes within each group.

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