



Non-Invasive Brain Stimulation in Alzheimer's Disease

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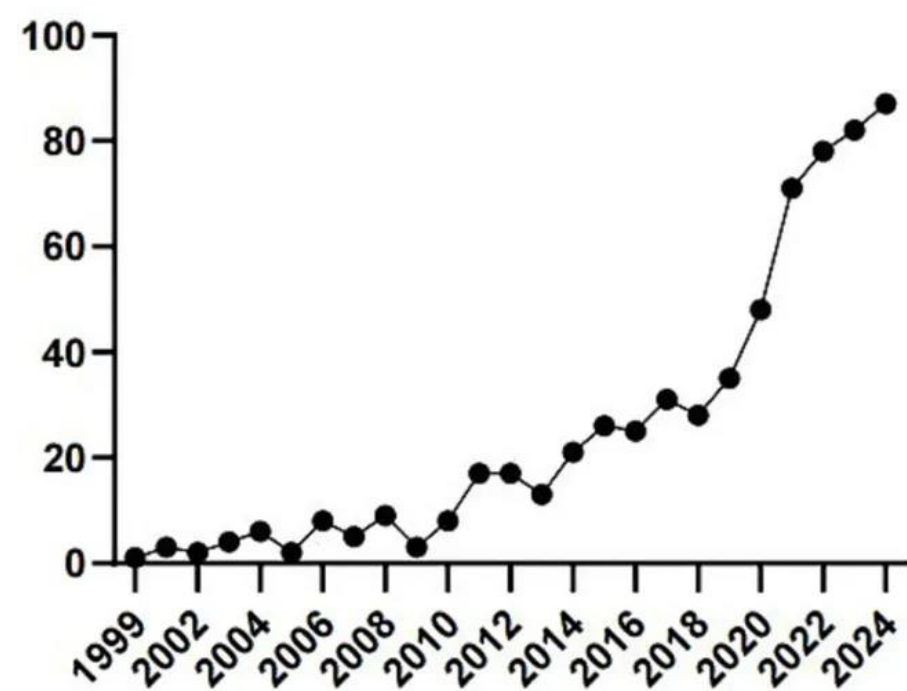
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Highlighted Conclusion: Momentum and the level of evidence to support non-invasive brain stimulation therapies for Alzheimer's Disease is steadily growing.

INTRODUCTION

Non-invasive brain stimulation (NIBS) is attracting increasing interest as a possible approach to treat cognitive and functional impairment in patients with neurodegenerative disorders. The field is rapidly evolving with novel techniques and protocols that offer the possibility to develop tailored interventions for AD. A recent bibliometric analysis identified a total of 632 NIBS-AD studies in the WOSCC database through November 27, 2024, demonstrating a recent surge in NIBS-AD publications as shown in Figure 1.¹

Figure 1. Bibliometric Analysis (Cong 2025) Publication Trend



Alzheimer's disease is increasingly recognized as a disorder characterized by early, progressive synaptic dysfunction preceding neuronal loss by years or decades. Pathological accumulation of amyloid- β (A β) and hyperphosphorylated tau disrupts glutamatergic and GABAergic transmission, impairs long-term potentiation (LTP), and desynchronizes neural oscillations, particularly in the gamma frequency band (30–100 Hz), across the default mode network (DMN). NIBS techniques are uniquely positioned to directly target these synaptic and oscillatory deficits, offering a mechanism of action that is fundamentally complementary to, and distinct from, current pharmacological approaches.²

The most popular NIBS methods include repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (tES) based on either direct (tDCS) or alternating (tACS) current. More recently, sensory (visual and/or auditory) stimulation in the gamma (γ) frequency (typically 30–100 Hz), photobiomodulation (PBM) and transcranial focused ultrasound (tFUS) have also drawn the attention of the scientific community.² It is important to emphasize that the different NIBS have different targets and mechanisms of action as shown in Table 1.

Across all modalities, NIBS techniques demonstrate a favorable safety profile; serious adverse events are rare, and the most common side effects, mild headache and transient scalp discomfort, are well-tolerated even in elderly and cognitively impaired populations receiving extended treatment courses.

In patients with AD, rTMS is the most investigated NIBS technique. Critically, advances in neuroimaging and TMS-EEG now enable individualized target selection and protocol optimization based on each patient's functional connectivity profile, representing a shift toward precision neuromodulation in AD. Prior clinical trials have demonstrated the safety and feasibility of neuromodulation of the default mode network via the precuneus for the treatment of mild to moderate AD.^{3,4} These studies have shown promising early results on slowing cognitive and functional decline in AD patients as shown in Figure 3 in the Results section.

While no NIBS technique has currently been approved by the FDA for cognitive indications, this area of research is gaining momentum in the AD scientific community. Two devices have received FDA Breakthrough Device Designation (Sinaptica's SinaptiStim[®] system and Cognito's Spectris AD), providing regulatory momentum. Here we summarize the NIBS-AD landscape and highlight the TMS-EEG evidence.

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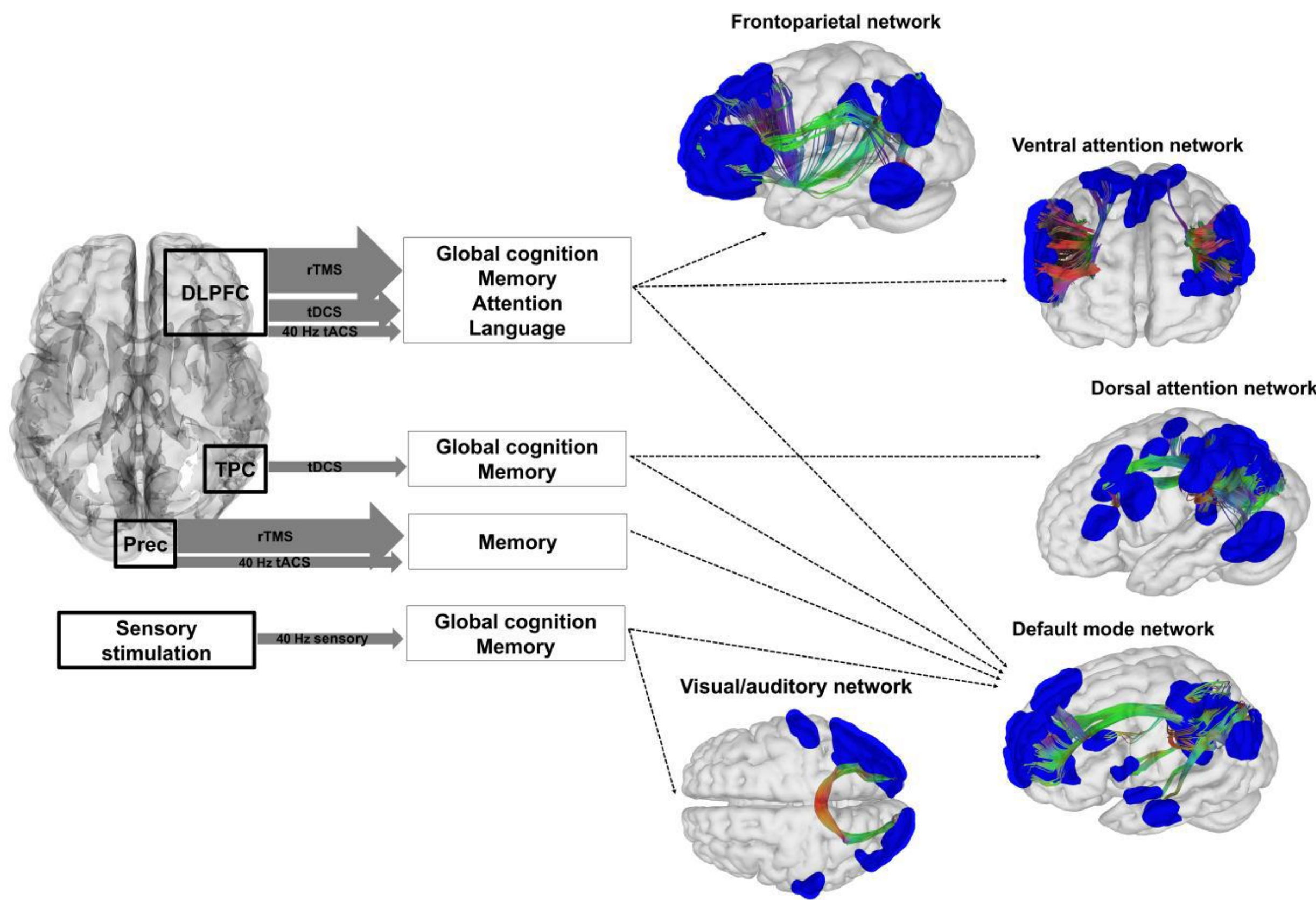
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METHODS

Table 1. Summary of NIBS Methods for AD

Modality	Primary Mechanism	Best Target	Key AD Trial / Status
rTMS	LTP-like synaptic plasticity; restores E/I balance (Glu/GABA); $\downarrow$ A β ($\downarrow$ BACE1, $\uparrow$ IDE); $\downarrow$ phospho-tau; $\uparrow$ BDNF; $\downarrow$ neuroinflammation (IL-6, TNF- α , microglia); enhances glymphatic clearance; macroscale DMN network reorganization ⁵	Precuneus (earliest A β -depositing DMN hub)	Koch et al., Brain 2022 (24-wk Phase 2, n=50, NCT03778151); Koch et al., Alzheimers Res Ther 2025 (52-wk Phase 2, n=48, NCT05454540); FDA Breakthrough Device Designation (SinaptiStim System); pivotal RETAIN trial starting soon
tDCS	Subthreshold membrane potential modulation; anodal stimulation increases, cathodal decreases cortical excitability; modulates GABA and glutamate receptor activity	DLPFC; temporal cortex	Multiple meta-analyses; weaker effect size vs. rTMS (non-significant in several RCTs); home-based protocols in development
γ -tACS (40 Hz)	Entraines endogenous gamma oscillations (30–100 Hz) disrupted in AD; frequency-specific oscillatory drive; PET evidence of $\downarrow$ tau burden in medial temporal cortex; distinct from rTMS — no significant A β effect	Temporal cortex; precuneus	Multiple RCTs in MCI showing episodic/associative memory improvement; τ -PET evidence; ongoing home-based RCTs; evidence more preliminary than rTMS; ongoing P2 3-arm randomized trial iTBS+ γ -tACS (NCT07075770)
γ -Sensory Stimulation (40 Hz AV)	Synchronized 40 Hz visual + auditory entrainment of gamma oscillations; mouse: $\downarrow$ A β , $\downarrow$ tau, $\uparrow$ microglia phagocytosis; preserves white matter and myelin integrity on MRI	Visual cortex $\rightarrow$ widespread network entrainment	OVERTURE trial (Cognito Therapeutics); 4.83 months of preserved daily activities; OLE at AAIC 2025: 9.93 months MMSE preservation; pivotal HOPE trial (NCT05637801) nearing completion 2026; FDA Breakthrough Device Designation (Spectris AD)
tFUS / TIS (Temporal Interference)	Transcranial focused ultrasound modulates deep structure excitability; temporal interference stimulation uses two high-frequency carrier waves to deliver low-frequency target to hippocampus non-invasively; may enhance BBB permeability	Hippocampus (deep target)	First-in-human TIS hippocampal stimulation published in Nature Neuroscience; Early study results for tFUS in 9 patients published in early 2026.
Photobiomodulation (PBM)	Primary target: mitochondrial cytochrome c oxidase $\rightarrow$ $\uparrow$ ATP production; $\downarrow$ oxidative stress (ROS modulation); $\downarrow$ neuroinflammation (IL-6, TNF- α); $\uparrow$ cerebral blood flow; $\uparrow$ neurogenesis and synaptogenesis; $\downarrow$ A β accumulation and microglial proliferation; $\uparrow$ BDNF and NGF. Red (600–700 nm) or near-infrared (780–1100 nm) light delivered transcranially at low	Frontal cortex (transcranial); intranasal delivery also used to reach deeper structures	Multiple small RCTs and pilot studies safe, positive cognitive improvements in dementia; RCT (REGENLIFE RGN600 NCT05926011). Evidence currently exploratory; consistent safety profile.

Figure 2. Effect of non-invasive brain stimulation on cognition in persons at high risk of Alzheimer's disease or with AD. (Koch 2024)



CONCLUSIONS

- NIBS is a rapidly maturing therapeutic frontier for AD:** with 632 published studies identified in a recent bibliometric analysis, two FDA Breakthrough Device Designations granted, and a citation burst accelerating from 2022 onward signaling the field has crossed from exploratory to translational
- Across all modalities, NIBS carries a highly favorable safety profile:** serious adverse events are rare, seizure risk is extremely low and protocol-dependent, and the most common side effects — mild headache and transient scalp discomfort — are well-tolerated in elderly and cognitively impaired populations across multi-month treatment courses
- The neurobiological rationale for rTMS in AD is mechanistically robust:** a single intervention simultaneously restores LTP-like synaptic plasticity, corrects excitation/inhibition balance, reduces A β and phospho-tau burden, elevates BDNF, suppresses neuroinflammation, and enhances glymphatic clearance — targeting the core pathophysiology of AD at multiple levels
- Among NIBS techniques, precuneus-targeted rTMS has accumulated the most robust Phase 2 clinical evidence in AD.** A 52-week double-blind RCT demonstrated statistically significant reductions in cognitive decline (CDR-SB), preservation of activities of daily living (ADCS-ADL), and improvement in behavioral symptoms compared to sham stimulation, supporting further evaluation in a pivotal trial
- Shift to precision neuromodulation:** advances in neuroimaging and TMS-EEG now enable individualized target selection and protocol optimization based on each patient's functional connectivity profile
- Pivotal trials are imminent:** Sinaptica's RETAIN pivotal is ready to begin enrollment and Cognito's HOPE trial will have topline data in 2026 making the next 3–5 years a critical window for the NIBS-AD field
- CTAD 2026:** We look forward to sharing more with you all at CTAD 2026 in Boston.

RESULTS

Figure 3. Time saved analyses from Koch 2025 study (Hendrix CTAD 2024)

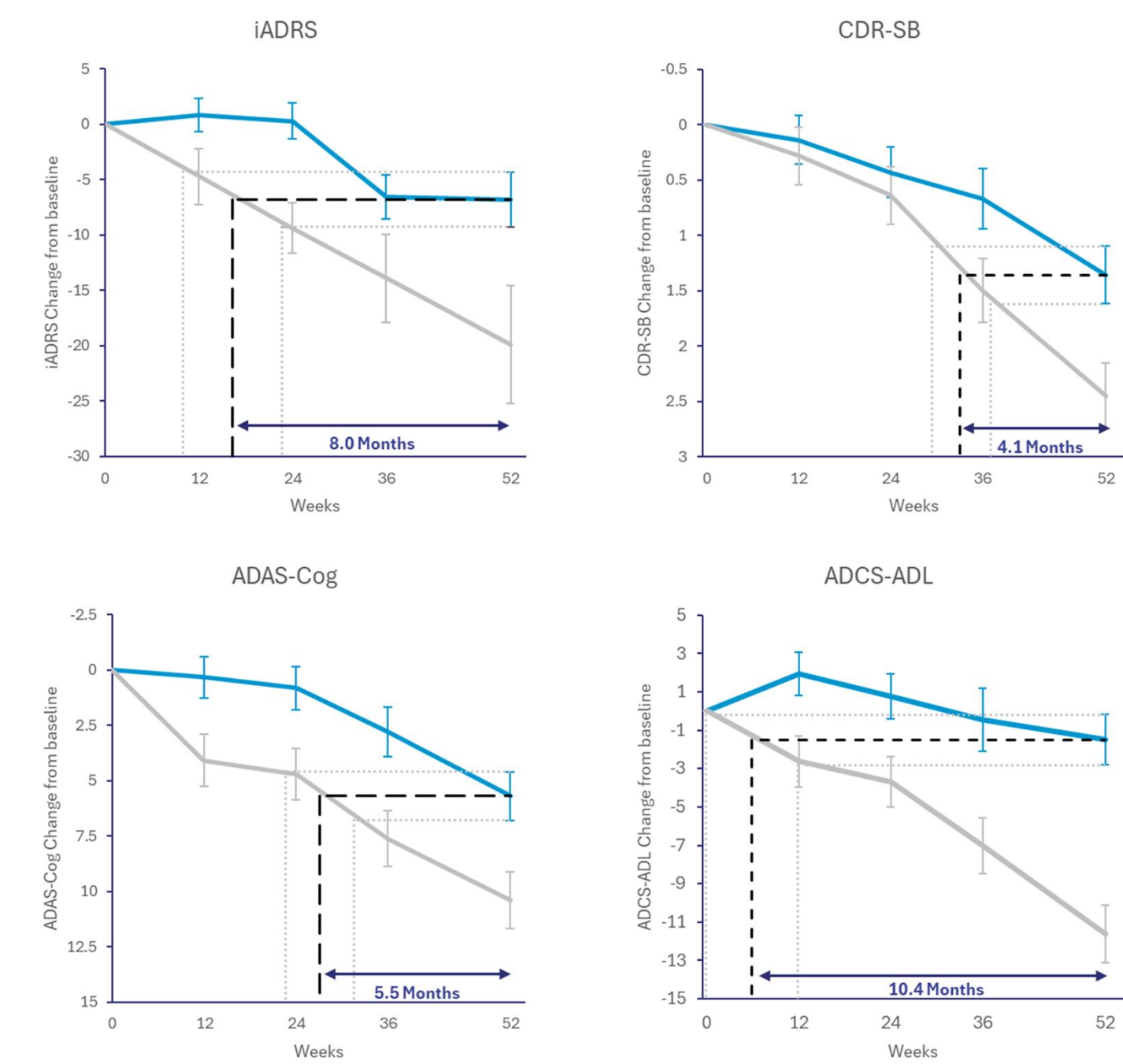


Table 2. Safety summary from Koch 2025 study

Adverse events	rTMS (number of patients/%)	Sham (number of patients/%)
Mild headache	3 (11.1%)	1 (4.8%)
Skin discomfort	2 (7.4%)	2 (9.5%)
Scalp discomfort	4 (14.8%)	2 (9.5%)
Neck pain	1 (3.7%)	2 (9.5%)
Stiffness	0 (0%)	1 (4.8%)

Figure 4. Mechanisms of rTMS-induced neuroplasticity and therapeutic effects in AD (Antonioni 2025)

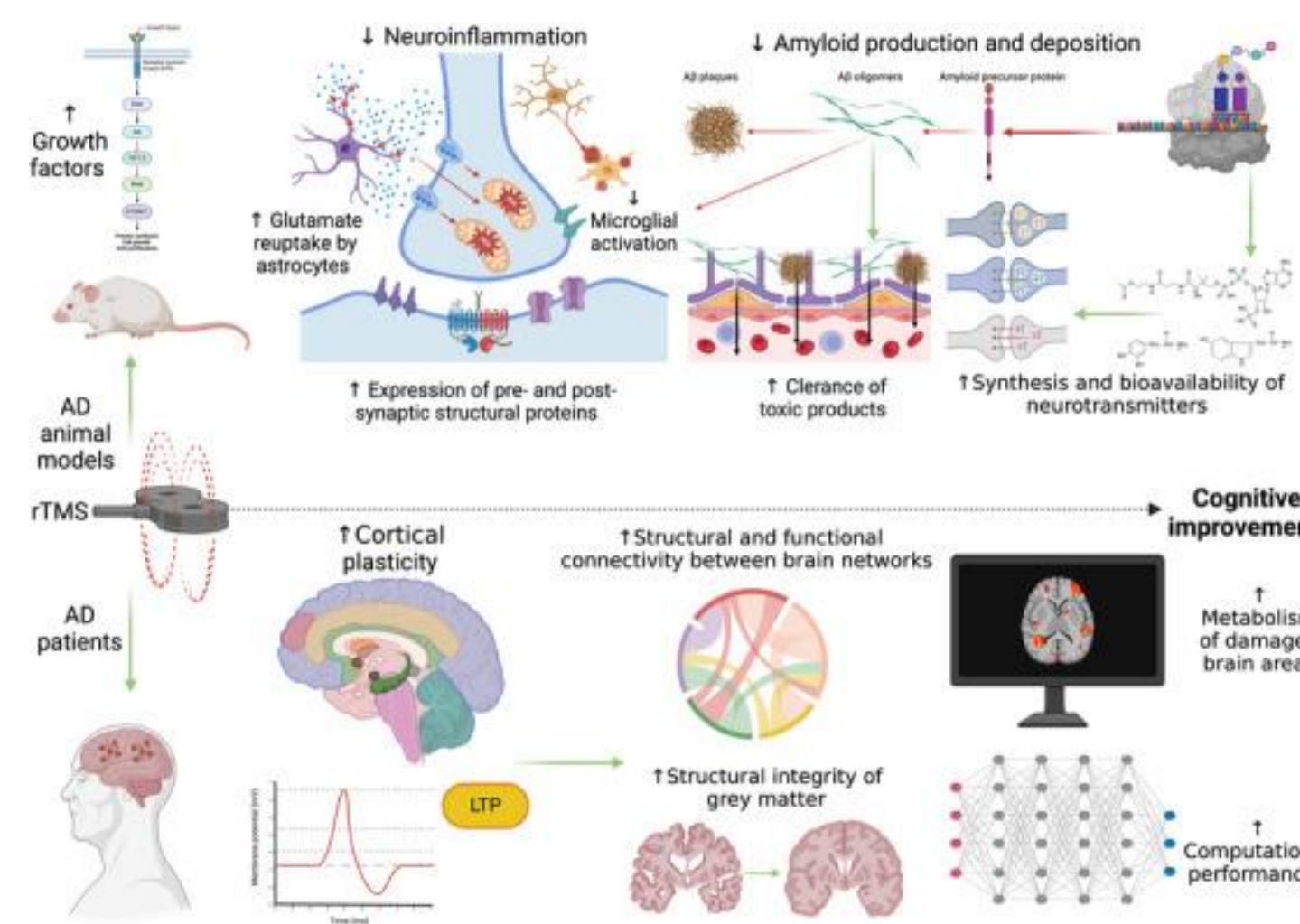
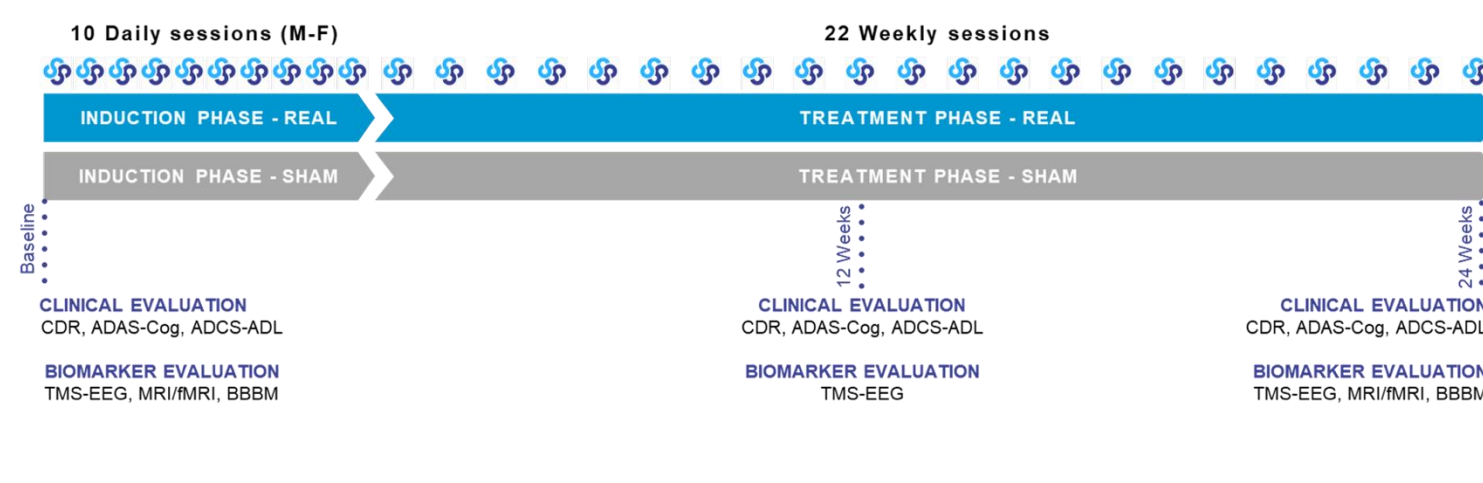


Figure 5. RETAIN Pivotal Study Design (Fosdick AAIC 2025)



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