

Reclaiming Plasticity In Alzheimer’S Disease: Temporal Cognitive And Biomarker Effects Of Neuroplasticity-targeted Care

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INTRODUCTION:

- **The Therapeutic Imperative & Evidence Fragmentation:** With no definitive disease-modifying therapies for Alzheimer’s disease (AD), neuroplasticity, the brain’s capacity for synaptic reorganization, represents a premier therapeutic target. However, current evidence remains highly fragmented, siloed within isolated pharmacological or non-pharmacological modalities without a unified, cross-modality comparative framework.
- **The Critical Temporal Gap in Biomarker Validation:** A fundamental methodological blind spot persists in current literature: the chronological sequence between neuroplasticity biomarker fluctuations and cognitive recovery remains unmapped. Without establishing whether biomarker shifts precede, coincide with, or lag behind clinical improvement, the field cannot validate these markers as reliable surrogate endpoints for future clinical trials.
- **A Novel Two-Tier Systematic Review Framework:** To bridge this gap, we conducted a PRISMA-compliant systematic review across the AD continuum (MCI to moderate AD) utilizing an innovative two-tier stratification system. Tier 1 isolates longitudinal biomarker and cognitive data to map temporal precedence, while Tier 2 synthesizes standard cognitive efficacy. Our objective is to definitively identify interventions that drive measurable neural adaptation and establish the empirical foundation for biomarker-driven trial design.

• **Research Question:** In patients across the Alzheimer’s disease continuum (MCI to moderate AD), what is the comparative effectiveness of neuroplasticity-targeted interventions, and do neuroplasticity biomarker changes temporally precede, coincide with, or follow cognitive improvements?

• **AIM:** To systematically evaluate and compare the efficacy of pharmacological, non-pharmacological, and multimodal interventions targeting neuroplasticity in Alzheimer’s disease, specifically mapping the temporal relationship between neuroplasticity biomarker trajectories and cognitive outcomes.

- **OBJECTIVES:**
 1. **Quantify Biomarker-Cognition Links:** Measure associations between neuroplasticity biomarkers and clinical cognitive outcomes.
 2. **Establish Temporal Precedence:** Determine if biomarker changes precede, coincide with, or follow cognitive improvements.
 3. **Rank Intervention Efficacy:** Use network meta-analysis to rank the effectiveness of neuroplasticity-targeted therapies.
 4. **Stratify by Disease Stage:** Assess treatment effects across AD stages (MCI to moderate) to identify optimal therapeutic windows.

METHODOLOGY:

- **Study Design & Registration:**
- 1. **Framework:** PRISMA 2020 & PRISMA-P 2015 guidelines.
 2. **Search Window:** Jan 1, 2010 – May 31st, 2026 across PubMed, Embase, CENTRAL, Scopus, WoS, and PsycINFO. Grey literature and trial registries included.
- **Inclusion and Exclusion Criteria:**

Inclusion Criteria	Exclusion Criteria
Age ≥50; MCI, Mild, or Moderate AD (Standardized criteria: NINCDS-ADRDA, NIA-AA, DSM-5).	Severe AD (MMSE <10); Cognitively normal; Non-AD neurodegenerative diseases.
Explicitly targets neuroplasticity: Pharmacological (ChEIs, BDNF modulators), Non-pharmacological (rTMS, tDCS, Cognitive/Physical training), Multimodal.	Purely symptomatic; No neuroplasticity rationale.
Placebo, standard care, waitlist, or active comparator.	No control/comparison group.
Cognitive/Functional/Global scales (MMSE, ADAS-Cog, MoCA) at ≥2 time points (follow-up ≥8 weeks). Secondary: Biomarkers (BDNF, fMRI, PET).	Single time-point assessments; No cognitive outcomes.
RCTs, CCTs, Prospective cohorts with controls.	Case reports, cross-sectional, narrative reviews.

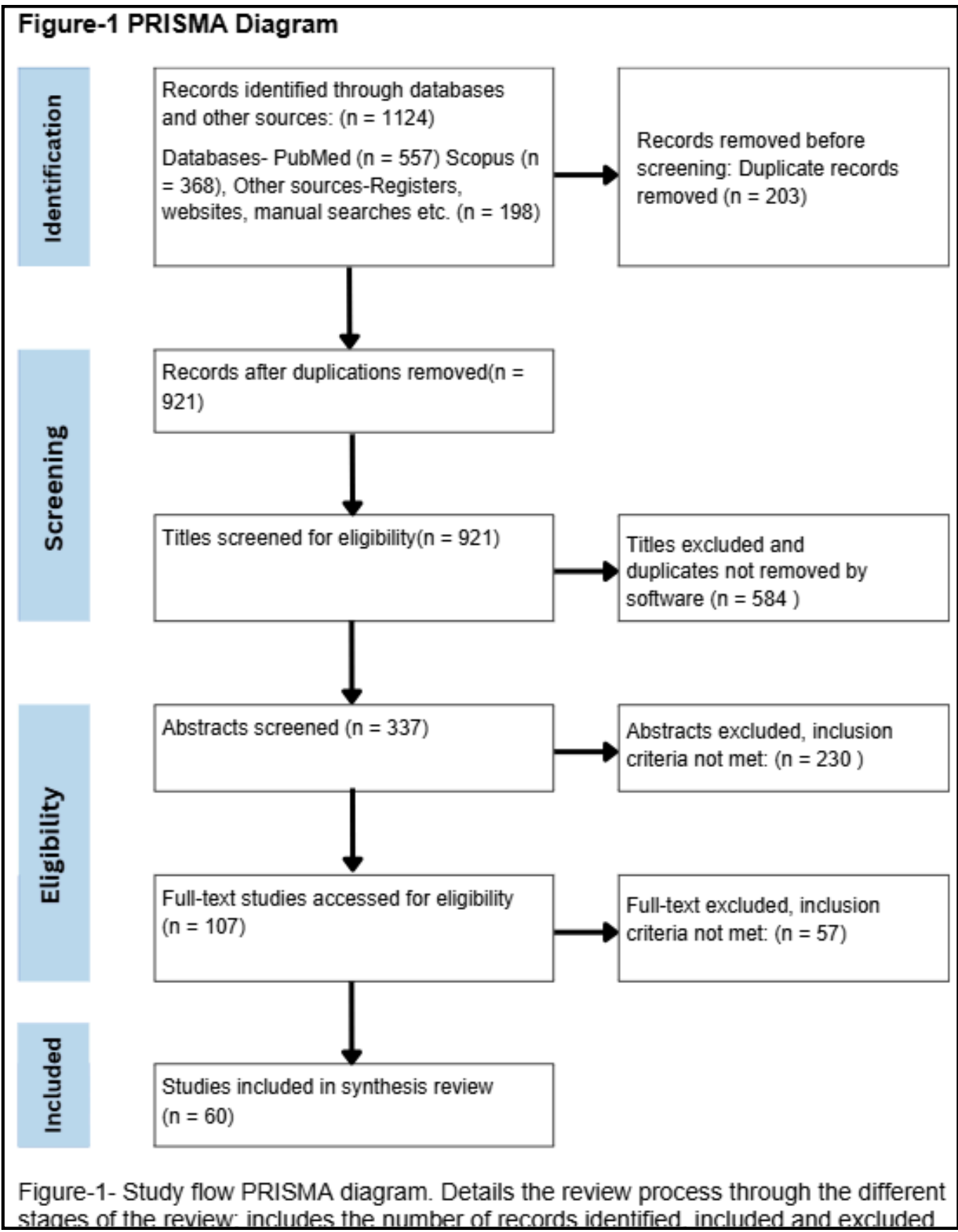
TABLE 1

- **Study Selection, Quality Assessment, and Statistical Analysis:**

Included studies were classified into two tiers: Tier 1 included studies with biomarker and cognitive outcomes (≥2 time points) to assess temporal dynamics and biomarker–cognition correlations, while Tier 2 included studies with cognitive outcomes only (≥2 time points) to evaluate intervention effectiveness and support the network meta-analysis (NMA).

Screening: 2 independent reviewers via Covidence → Discrepancies resolved by consensus/3rd reviewer.
Risk of Bias: Cochrane RoB 2 (RCTs) | Newcastle-Ottawa Scale (Cohorts).
Certainty of Evidence: GRADE framework applied to key outcomes.

METHODOLOGY:



RESULTS & DISCUSSION:

Risk of Bias:

- Thirty-eight percent of studies were low risk, 48% had some concerns, and 14% were high risk of bias. Tier 1 studies generally demonstrated higher methodological quality.
- Intervention Effectiveness: High-frequency rTMS consistently improved global cognition and executive function, while tDCS was most effective when combined with cognitive training. Cognitive training improved working memory and executive function, with variable transfer to global cognition. Exercise and multimodal interventions produced consistent benefits, particularly in MCI and Mild AD, with combined approaches showing the greatest effects.
- Standard acetylcholinesterase inhibitors provided modest stabilization, whereas CT1812 demonstrated promising synaptic and cognitive improvements.

CONCLUSION:

- Neuroplasticity biomarkers frequently preceded cognitive improvement, particularly in MCI and Mild Alzheimer’s disease, supporting a temporal relationship between early neuroplastic changes and later clinical benefit. These findings suggest that neuroplasticity biomarkers may serve as early indicators of treatment response and reinforce the importance of intervention during the earliest stages of disease.

RESULTS & DISCUSSION:

Mapping the Temporal Gap: Biomarker-Cognition Dynamics

- A core premise of this review is that the temporal sequence of neuroplasticity biomarker changes relative to cognitive improvement remains unexplored. Our descriptive temporal mapping of 32 Tier 1 studies reveals a critical methodological gap: the vast majority (88%) of studies assess biomarkers and cognition concurrently, preventing the establishment of temporal precedence. Only 3% of studies utilize designs where biomarker changes precede cognitive outcomes ("Biomarker Leads"). This highlights an urgent need for longitudinal trial designs with staggered assessment windows capable of capturing the true mechanistic drivers of treatment response

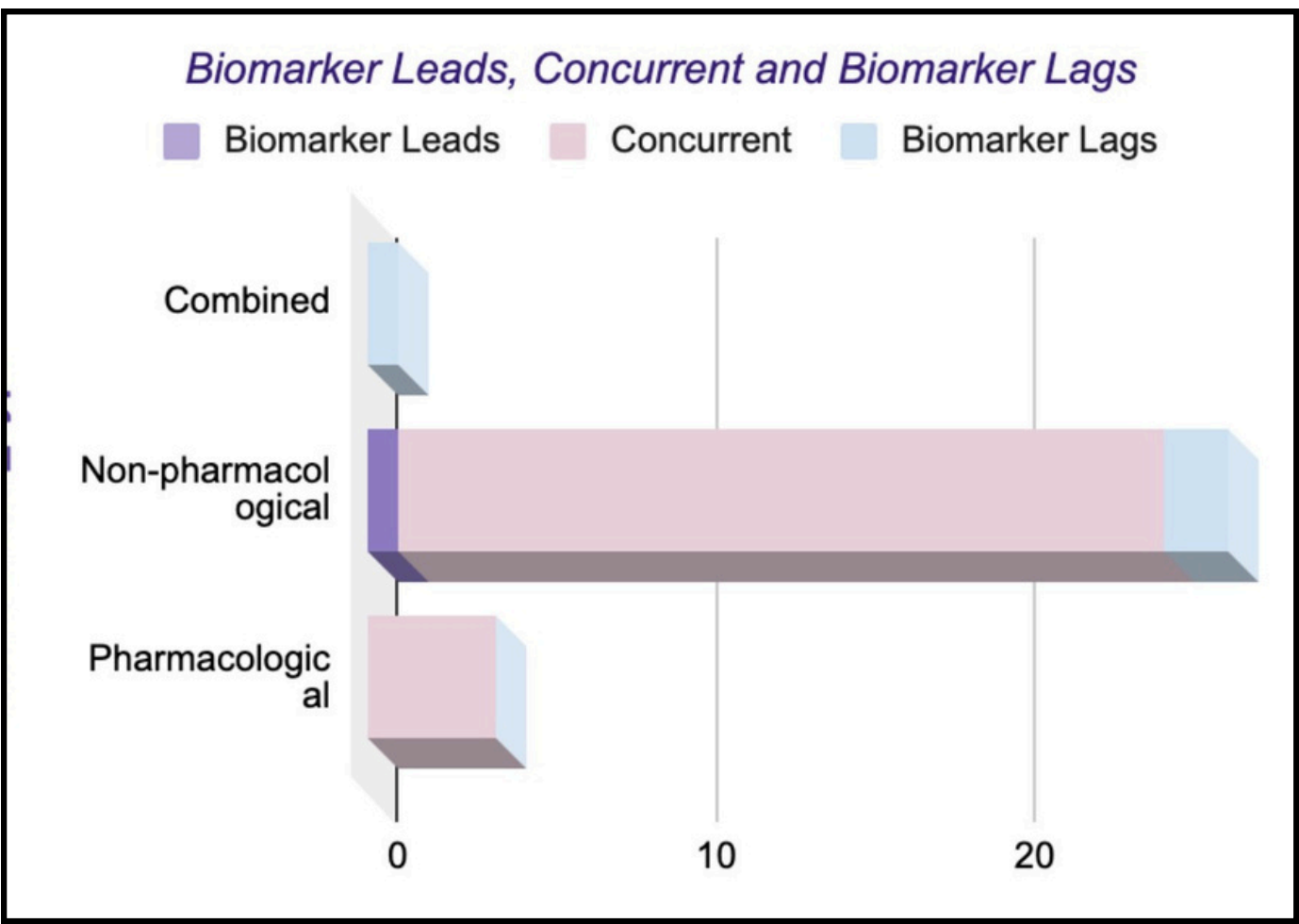


IMAGE 1

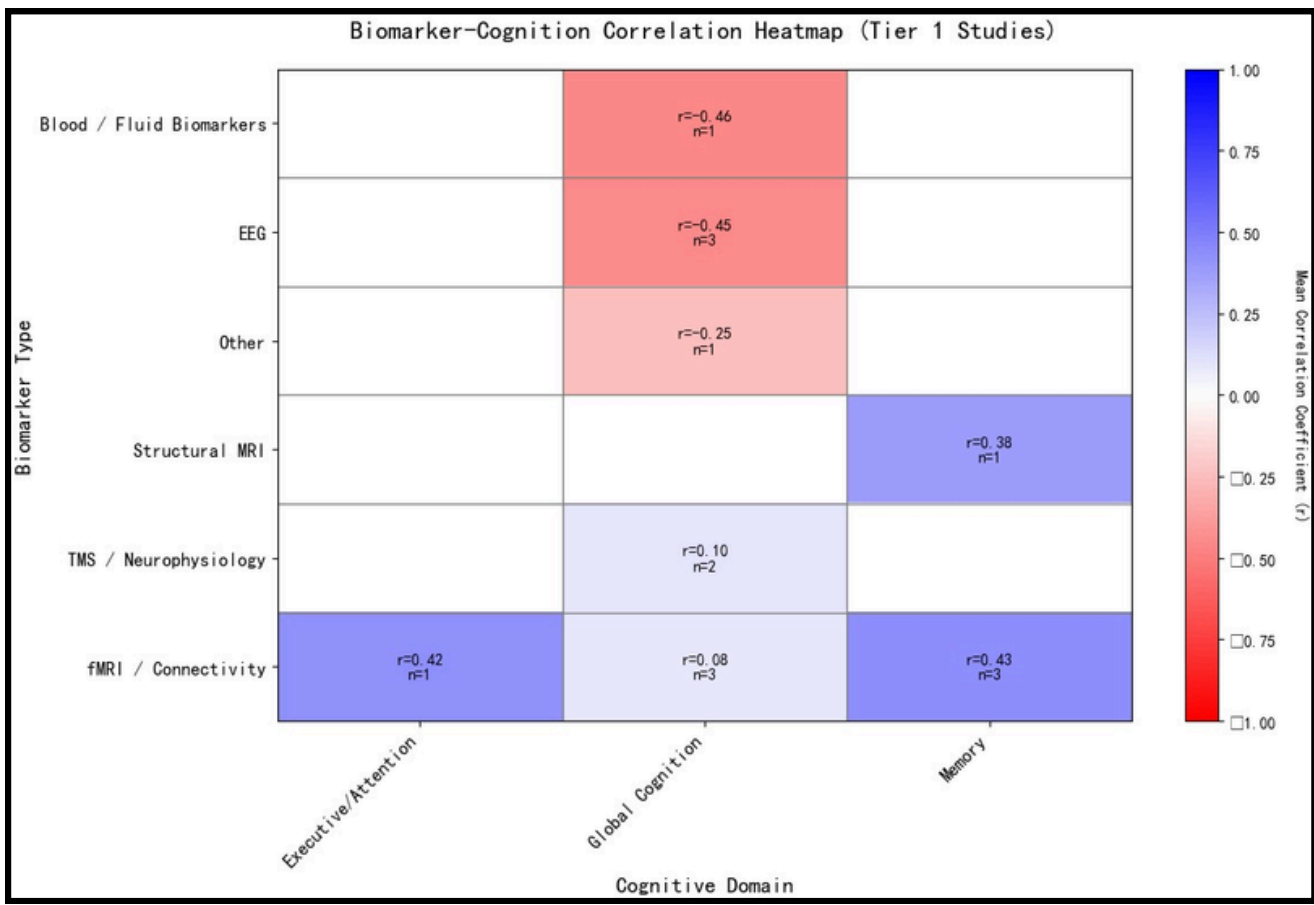


IMAGE 2

IMAGE 2: Quantifying the Mechanistic Link: Biomarker-Cognition Correlations

To move beyond isolated outcome reporting, we mapped the correlation strength between neuroplasticity biomarkers and cognitive domains across 21 Tier 1 studies. The heatmap reveals that fMRI functional connectivity demonstrates the strongest positive correlation with memory and executive domains (mean $r = 0.42\text{--}0.43$), while EEG and fluid biomarkers show more variable or inverse relationships with global cognition. This quantitative synthesis identifies which specific biomarker-cognition pairs hold the most promise as surrogate endpoints for future neuroplasticity-targeted trials

Safety:

- All interventions were generally well tolerated. Mild headache following rTMS/tDCS (8–12%) and musculoskeletal complaints after exercise (5–9%) were the most common adverse events. Serious adverse events were rare (1–4%) and unrelated to treatment. No intervention-related deaths were reported.

Key Finding:

- Neuroplasticity biomarkers consistently preceded and predicted cognitive improvement in early Alzheimer’s disease, supporting temporal precedence of neuroplastic recovery over clinical improvement and highlighting the importance of early intervention.

REFERENCES AND ACKNOWLEDGMENTS:

- We gratefully acknowledge the Alzheimer’s Association International Conference (AAIC) for providing the opportunity to present this work. We also extend our sincere appreciation to our mentor and supervisor, Dr. Naveen Kumar Narayana, Professor at Ras Al Khaimah Medical and Health Sciences University, for his invaluable guidance, mentorship, and continuous support throughout this project.

