

Neuropsychological and Neurobiological Effects of Gamma-tACS in MCI-AD: a case series

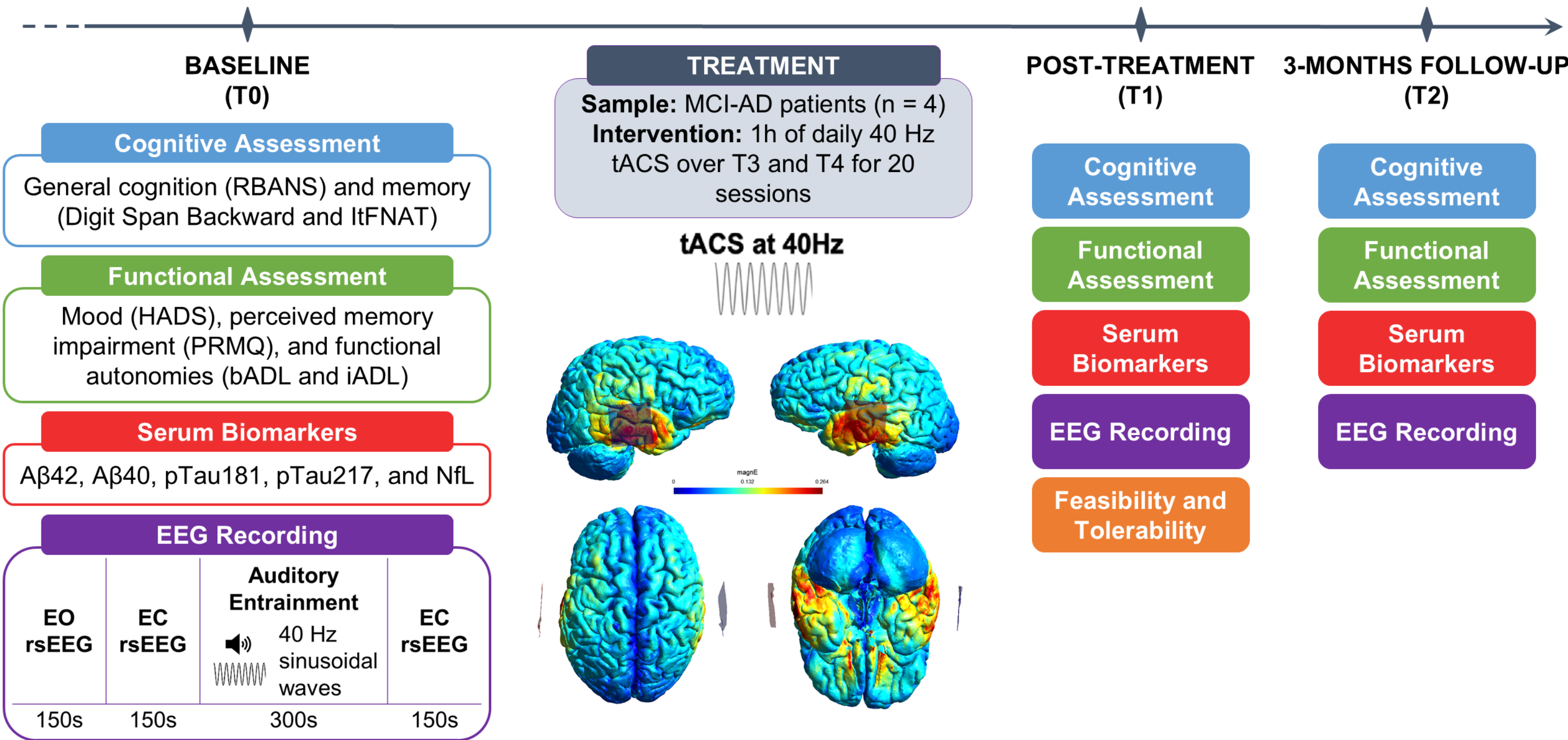
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INTRODUCTION

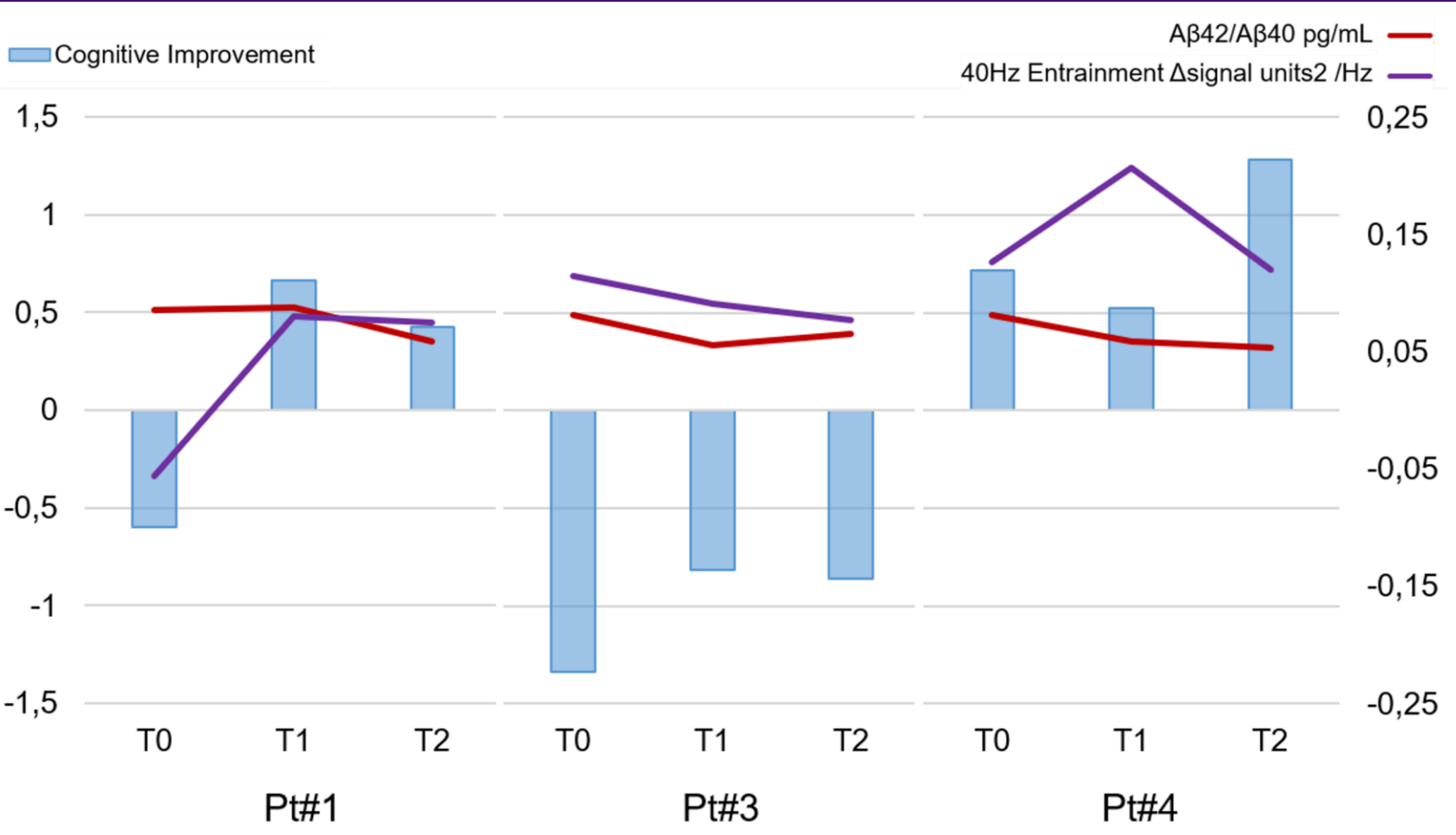
Gamma-frequency transcranial alternating current stimulation (tACS) has emerged as a promising non-invasive neuromodulatory approach for Alzheimer's Disease (AD), leveraging on the role of 40Hz oscillatory dysfunction in amyloid- and tau-related pathology (Iaccarino et al., 2016; Jafari et al., 2020).

Evaluate feasibility, safety, and multimodal response patterns of multi-session 40 Hz gamma-tACS in MCI-AD, distinguishing the role of gamma entrainment and blood biomarkers in shaping individual cognitive trajectories.

STUDY DESIGN & INTERVENTION PROTOCOL



NEURAL VS BLOOD BIOMARKERS



Cognitive trajectories tracked tightly with improvements in gamma entrainment, rather than with blood biomarker fluctuations, at both post-treatment and 3-month follow-up.

CLINICAL IMPLICATIONS

Multi-session gamma-tACS is safe, feasible, and effective in MCI-AD, with sustained cognitive and electrophysiological effects.

- Objective cognitive performance improved substantially post-treatment and was maintained at 3-month follow-up, confirming a genuine and durable treatment effect.
- Cognitive gains closely parallel neural entrainment improvements, identifying gamma entrainment as the most sensitive marker of treatment response.
- Consistent 40Hz entrainment, with evidence of individual neuroplastic reorganization, supports gamma-tACS as a genuine neuromodulatory tool.

Gamma neuromodulation provides a direct, non-invasive, and cost-effective candidate for personalized treatments in prodromal AD.

COGNITIVE, FUNCTIONAL, BLOOD & EEG OUTCOMES

98% adherence (59/60 sessions). Side effects minimal and transient; no seizures, epileptiform activity, or clinically significant adverse events.

RBANS: $g = 1.82$ (T1), $g = 0.65$ (T2). Associative memory (**ItFNAT-DTR**): $g = 1.32$ (T2). **Autonomy** preserved. Increased memory complaints (**PRMQ**) likely reflect enhanced metacognitive awareness rather than true functional decline.

Plasma biomarkers largely stable. Progressive **Aβ42/Aβ40 ratio** reduction at T1 ($g = -0.58$) and T2 ($g = -2.10$), driven by rising Aβ40.

Auditory 40 Hz entrainment: temporal $g = 3.48$, central $g = 1.82$ (both T2), robust and consistent across all completers.

