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Transcranial Electrical Stimulation in Alzheimer's Disease: A Summary of Clinical Applications and Outcomes

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Alzheimer's Disease (AD) pathology

AD is characterized by cognitive decline resulting from intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein bound to microtubules, and extracellular accumulation of amyloid-β (Aβ) forming dense plaques (Selkoe and Hardy, 2016). These pathological hallmarks lead to the proliferation and activation of microglia and reactive gliosis, culminating in neurotoxicity and neuronal loss (Selkoe, 2011). Such alterations cause neuronal synaptic dysfunction and death, which disrupt brain circuits and oscillations, shifting neural activity from higher frequencies (e.g., gamma) to slower oscillations (e.g., theta). This ultimately leads to dementia, marked by a gradual decline in memory, thinking, behavior, and social skills.

Transcranial direct current stimulation (tDCS) targeting early cognitive symptoms

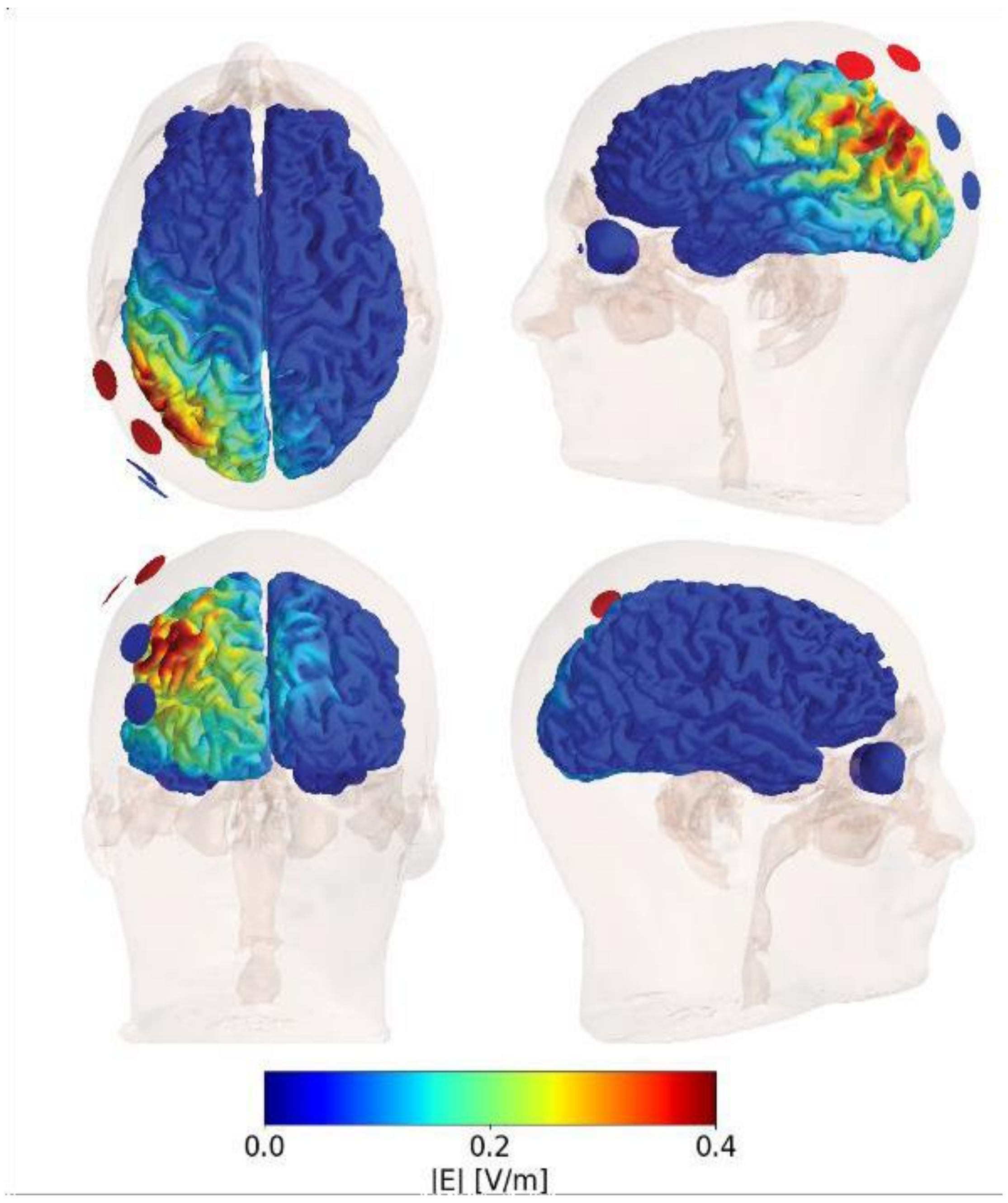
The majority of studies utilizing transcranial electrical stimulation (tES) in mild cognitive impairment (MCI) and AD have explored the use of tDCS to ameliorate early cognitive symptoms that draw clinical attention, such as deficits in memory, language, and orientation. The most commonly targeted regions include the dorsolateral prefrontal cortex (DLPFC) to enhance language, attention (Im et al., 2019), and working memory functions (Rezakhani et al., 2024); and the temporal cortex to improve overall cognition (Khedr et al., 2019), verbal and visual recognition memory (Boggio et al., 2012), as well as spatial orientation (Gangemi et al., 2020).

Transcranial alternate current stimulation (tACS) targeting pathological progression

Recent clinical trials exploring transcranial alternating current stimulation (tACS) at gamma frequencies have demonstrated its potential to influence the pathological progression of Alzheimer's disease. These studies have shown promising results, including the reduction of amyloid and phosphorylated tau (pTau) burden (Dhaynaut et al., 2022), enhancement of cerebral blood flow (Sprugnoli et al., 2021), and improvement in memory functions (Bréchet et al., 2021; Benussi et al., 2021). Given that the patterns of proteinopathy and atrophy in AD align with known neural networks, such as the Default Mode Network, targeting cortical nodes within these networks presents a promising approach for stimulation. Notable targets include the temporal lobe (Sprugnoli et al., 2021; Dhaynaut et al., 2022), angular gyrus (Bréchet et al., 2021), and precuneus (Benussi et al., 2021).

Optimizing tES outcomes through early intervention and personalized home-based protocols

Early intervention before significant disease progression, coupled with a personalized approach to optimize the electric field targeting, is expected to enhance the beneficial outcomes of tACS (Menardi et al., 2022), cp. Figure below. The logistical challenges and burdens of in-clinic interventions often limit treatment duration to a few weeks or months, impacting both patients and caregivers. However, a breakthrough has been achieved with a recent study demonstrating safety, high compliance, and adherence to a home-based, remotely supervised tACS protocol. This study targeted the angular gyrus and reported improved memory functions after 97 sessions over 9 months (Cappon et al., 2023), showcasing the feasibility and effectiveness of long-term, home- based treatment.



Electric field distribution. *Biophysical modeling by SimNIBS estimates the subject-specific impact of multi-electrode tES.*

Recommended reviews

Applications of transcranial electrical stimulation (tES) were thoroughly reviewed by Menardi et al., in 2023 (Toward noninvasive brain stimulation 2.0 in Alzheimer's disease). Safety of stimulation parameters and tES applications is reviewed by Antal et al., 2017 (Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines).