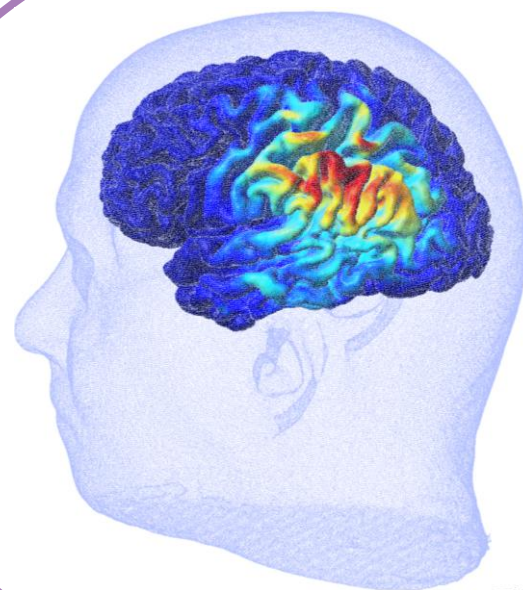


CLINICAL TRIALS BOOKLET

Transcranial electrical stimulation for treatment of Alzheimer's disease:

Selected CLINICAL TRIALS

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The following summary of clinical trials using various modes of transcranial electrical stimulation (tES) for the treatment of Alzheimer's disease were selected due to their clinical and scientific impact underpinning the **high potential of tES to improve cognitive functions, slow disease progression and modulate the underlying disease pathophysiology**. Whereas the studies vary in treatment duration, patient population, tES stimulation modality and analysed clinical outcomes they all show the high safety profile of repeated tES therapies and the importance of careful selection of stimulation parameters and brain targets to induce the desired clinical outcome.

Intervention	Up to 140 tES sessions per patient Up to 8 months of daily tES sessions (1-5x / week) In total more than 7'000 tES sessions, each between 20-60 min
Design	10 sham-controlled, 4 open-label/single-arm trials
Patients treated	300 patients with MCI-AD, mild or moderate Alzheimer's disease
Neuropsychological Improvements	Memory (MIS, RAVLT, BVRT, FNAT) Executive functions (Stroop, TMT-B) Language (BNT) Global cognition (MoCA, MMSE, ADAS-Cog) Quality of Life (QoLAD) Mood (Cornell)
Biological Improvements	Increased cerebral blood perfusion, cholinergic transmission (SLI), serum A β_{42} , increased neural activity Reduced pTau, microglia activity, peripheral A $\beta_{42/40}$ ratio Preserved neurophysiological slowing, metabolic activity
Safety	No serious adverse events Transient mild tingling, itching under the electrodes

SUMMARY OF CLINICAL TRIALS

Alzheimer's Disease pathology

AD is characterized by a cognitive decline as a result of intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein bound to microtubuli and extracellular accumulation of amyloid- β ($A\beta$) forming dense plaques (Selkoe and Hardy, 2016). These pathological hallmarks result in proliferation and activation of microglia and reactive gliosis, which leads to neurotoxicity and neuronal loss (Selkoe 2011). These alterations lead to neuronal synaptic dysfunction, neuronal death, and subsequently to brain circuit and brain oscillation disruption and a shift of neural activity from higher frequencies (e.g. gamma) to slower oscillations (e.g. theta). Finally leading to dementia – a gradual decline in memory, thinking, behavior and social skills.

Transcranial direct current stimulation targeting cognitive symptoms

Majority of studies using tES in MCI and AD have investigated the use of tDCS to **improve early cognitive symptoms** which brings the individual under clinical attention such as **memory, language, and orientation** deficits. Most common target regions are dorsolateral prefrontal cortex (DLPFC) to improve language, attention (Im et al., 2019), working memory functions (Rezakhani et al., 2024; temporal cortex: for improving overall cognition (Khedr et al., 2019) verbal and visual recognition memory (Boggio et al., 2012), as well as for spatial orientation improvement (Gangemi et al., 2020).

Transcranial alternate current stimulation targeting pathological progression

Recent clinical trials investigating transcranial alternate current stimulation (tACS) in the gamma frequency has proven their potential to **restore pathological progression** of the disease by **reducing amyloid and pTau** burden (Dhaynaut et al., 2022), **increase cerebral blood flow** (Sprugnoli et al., 2021), and **improving cognition** (Br chet et al., 2021) and **episodic memory** functions (Benussi et al., 2022). As the proteinopathy and atrophy patterns in AD occur along known neural networks (e.g. Default Mode Network), cortical nodes of these networks are promising stimulation targets. (Sprugnoli et al., 2021 & Dhaynaut et al., 2022: temporal lobe, Br chet et al., 2021: angular gyrus, Benussi et al., 2021: precuneus).

Next steps of tES in MCI & AD

It is expected that early intervention before severe disease progression and a personalized approach to optimize the electric field on the target can elevate the beneficial findings (Menardi et al., 2022). Due to the large burden of repeated in-clinic interventions on the patients and caregiver, tES therapies are commonly limited to a few weeks or months. A few studies have shown the safety, the high compliance and protocol adherence and improved cognitive performance of home-based tACS (Cappon et al., 2023, Br chet et al., 2021) and home-based tDCS protocols (Im et al., 2019). However, long-term tES therapies at home remain sparse as all studies were conducted with research devices only, developed for medical and scientific professionals rather than patients.

Recommended reviews

Applications of transcranial electrical stimulation (tES) was thoroughly reviewed by Menardi et al., in 2023 (*Toward noninvasive brain stimulation 2.0 in Alzheimer's disease*). The potential of tACS to alter the underlying disease biology and slow down AD disease progression was recently reviewed thoroughly by De Paolis (*Transcranial alternating current stimulation (tACS) at gamma frequency: an up-and-coming tool to modify the progression of Alzheimer's Disease*).

The 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).

SUMMARY OF CLINICAL TRIALS

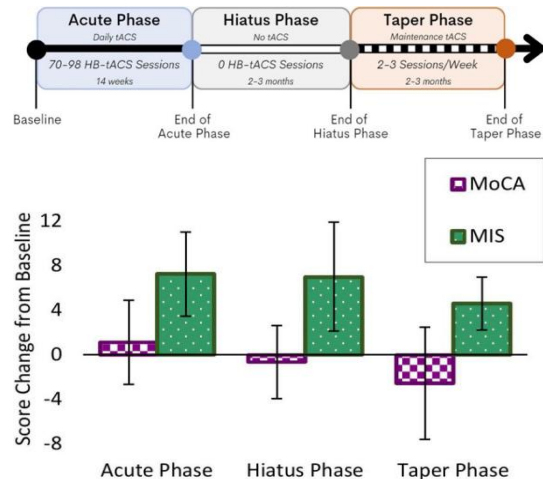
STUDY

Tele-supervised home-based transcranial alternating current stimulation (tACS) for Alzheimer's disease: a pilot study

Cappon et al. 2023

Harvard Medical School, Boston, USA

- **40 Hz tACS** left Angular Gyrus at home over 9 months (0-5x/week)
- Single-arm 8 subjects
- Selective **improvement of episodic memory** associated to stimulated brain region

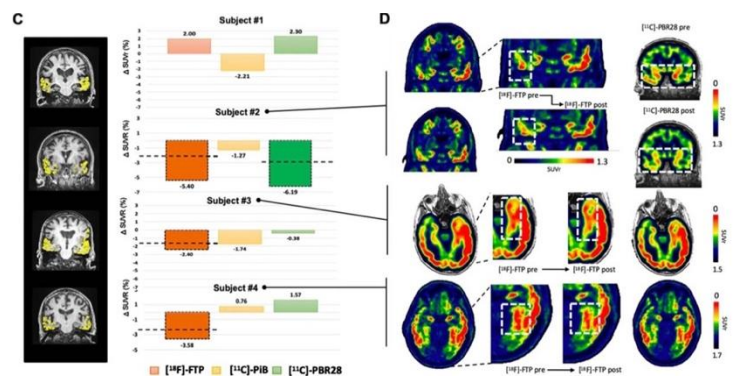


Impact of 40 Hz Transcranial Alternating Current Stimulation on Cerebral Tau Burden in Patients with Alzheimer's Disease: A Case Series (2022)

Dhayanaut et al., 2022

Harvard Medical School, Boston, USA

- Daily **40 Hz tACS** bilateral temporal lobe over 4 weeks
- 4 subjects case series
- **Induced protein clearance** and **neuroinflammatory modulation** (pTau & microglia activity)

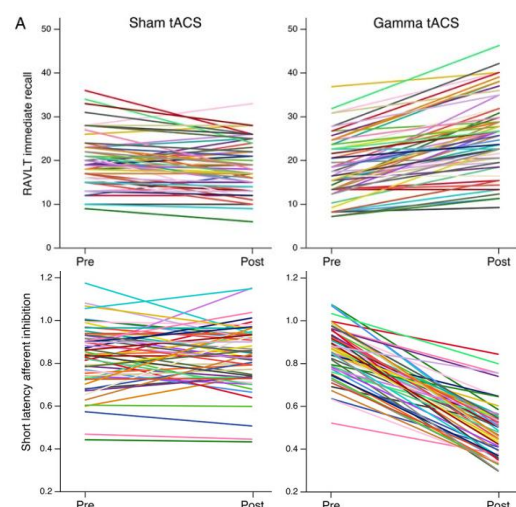


Increasing Brain Gamma Activity Improves Episodic Memory and Restores Cholinergic Dysfunction in Alzheimer's Disease

Benussi et al., 2022

University of Brescia, Brescia, Italy

- Single session of **40 Hz tACS** precuneus
- 60 subjects sham-controlled cross over
- Induced neural activity
- **Improved episodic memory** (RAVLT)
- Increase in cholinergic transmission indicates a **restoration of intracortical excitability**.



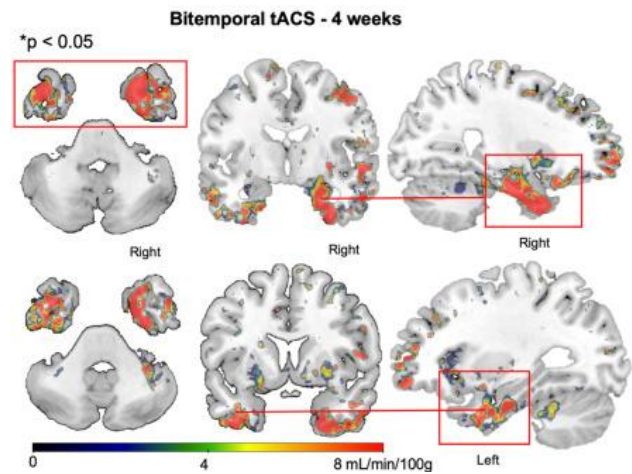
SUMMARY OF CLINICAL TRIALS

Impact of multisession 40Hz tACS on hippocampal perfusion in patients with Alzheimer's disease

Sprugnoli et al. 2021

Harvard Medical School, Boston, USA

- Daily **40 Hz tACS** bilateral temporal lobe over 4 weeks
- 15 subjects open label
- **Increased fast brain oscillations**
- **Increase in cerebral blood perfusion**

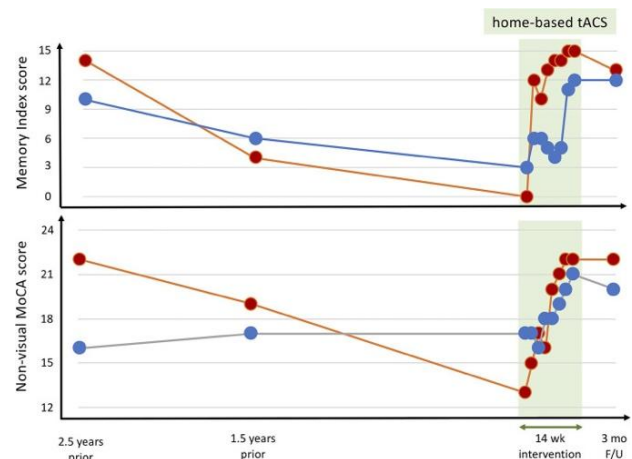


Patient-Tailored, Home-Based Non-invasive Brain Stimulation for Memory Deficits in Dementia Due to Alzheimer's Disease

Bréchet et al., 2021

Harvard Medical School, Boston, USA

- Daily **40 Hz tACS** left Angular Gyrus at home over 14 weeks
- 2 subjects case series
- **Safety and feasibility of home-based tES**
- **Improvement in episodic memory (MIS) & general cognition (MoCA)**

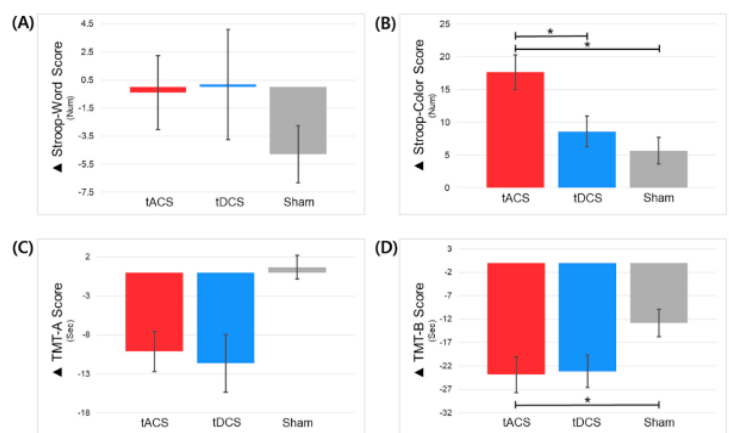


tACS as a promising therapeutic option for improving cognitive function in mild cognitive impairment: A direct comparison between tACS and tDCS

Kim et al., 2021

Hallym University, Chuncheon, Republic of Korea

- Single session **tDCS** or **tACS** bilateral DLPFC
- 20 subjects sham-controlled cross over
- **Improved executive functions** (tACS > tDCS)
- Restored neural activity



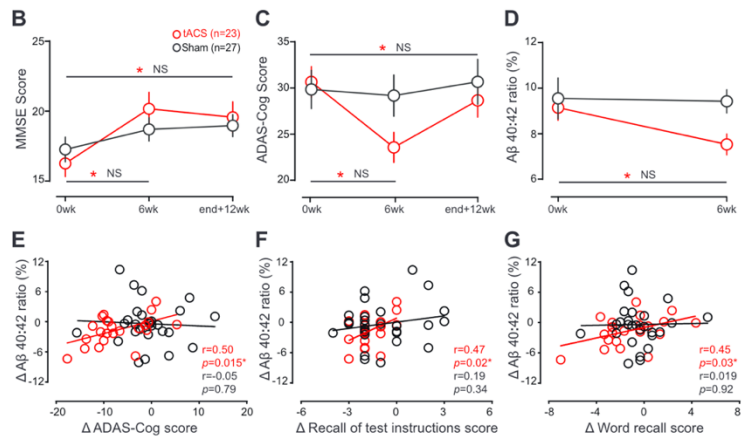
SUMMARY OF CLINICAL TRIALS

Effects of 40 Hz transcranial alternating current stimulation (tACS) on cognitive functions of patients with Alzheimer's disease: a randomised, double-blind, sham-controlled clinical trial

Zhou et al., 2021

Nantong University, Nantong, People's Republic of China

- Daily **40 Hz tACS** bilateral temporal lobe over 6 weeks
- 50 subjects RCT (23/27)
- **Reduction of plasma $A\beta_{40:42}$ ratio**
- Cognitive performance correlates with $A\beta_{40:42}$ ratio reduction

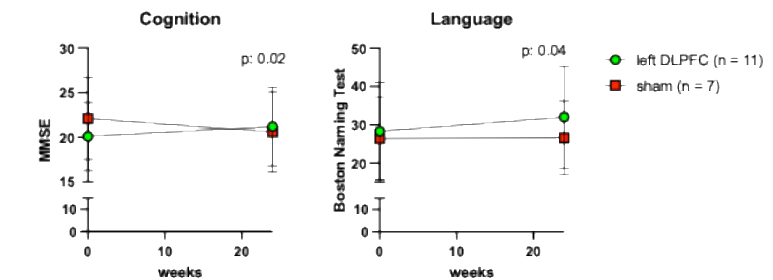


Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease

Im et al., 2019

The Catholic University of Korea, Seoul, South Korea

- Daily **tDCS** left DLPFC over 6 months
- 18 subjects RCT
- **Improved overall cognition and language functions**
- Preserved cerebral glucose metabolism



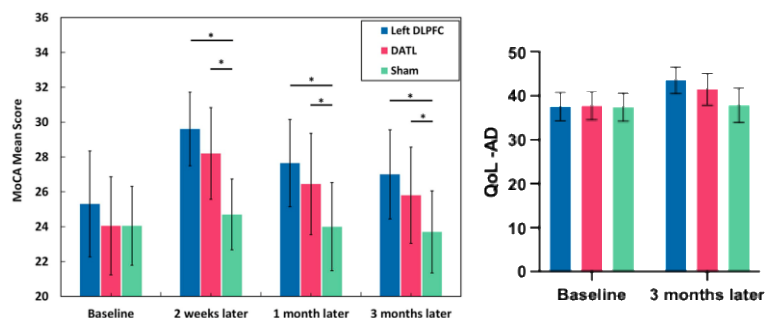
*adapted by Hopf

Anodal HD-tDCS on the dominant anterior temporal lobe and dorsolateral prefrontal cortex: clinical results in patients with mild cognitive impairment

Rezakhani et al., 2024

Kerman University of Medical Sciences, Kerman, Iran

- Daily **tDCS** left DLPFC or temporal lobe over 2 weeks
- 60 subjects RCT
- **Improved cognitive functions & QoL**
- **Long-term effects** for at least 3 months



*adapted by Hopf

SUMMARY OF CLINICAL TRIALS

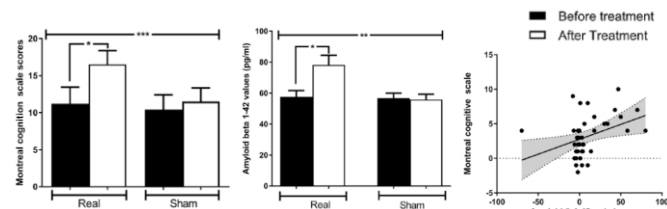
Therapeutic Role of Transcranial Direct Current Stimulation in Alzheimer Disease Patients: Double-Blind, Placebo-Controlled Clinical Trial

Khedr et al., 2019

Assiut University Hospital, Egypt

- Daily **tDCS** left/right temporo-parietal lobe over 2 weeks
- 44 subjects RCT
- **Improved cognitive functions**
- **Induced A β 42 clearance** (increased A β 42 in serum)

*adapted by Hopf

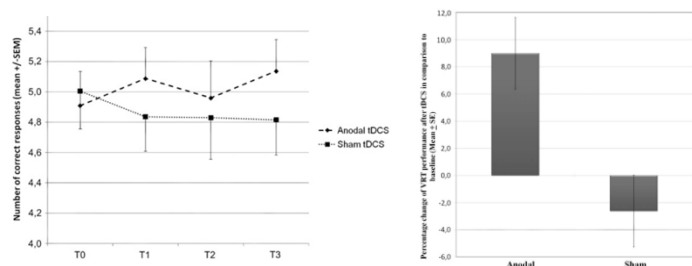


Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease

Boggio et al., 2012

Università degli Studi di Milano, Milano, Italy

- Daily **tDCS** temporal lobe over 5 days
- 15 subjects sham controlled cross-over
- **Improved visual memory**
- **Persistent improvements** for at least 3 weeks (T3)



Effects of short- and long-term neurostimulation (tDCS) on Alzheimer's disease patients: two randomized studies

Gangemi et al., 2021

University of Messina, Messina, Italy

Study 1 short term:

- Daily **tDCS** left frontotemporal lobe over 2 weeks
- 26 subjects RCT

Study 2 long term:

- 10x/months **tDCS** left fronto-temporal lobe over 8 months
- 18 subjects RCT
- Short term: **Improved cognition**
- Long-term: **Halted cognitive decline**
- **Preservation of neurophysiological activity**

*adapted by Hopf

