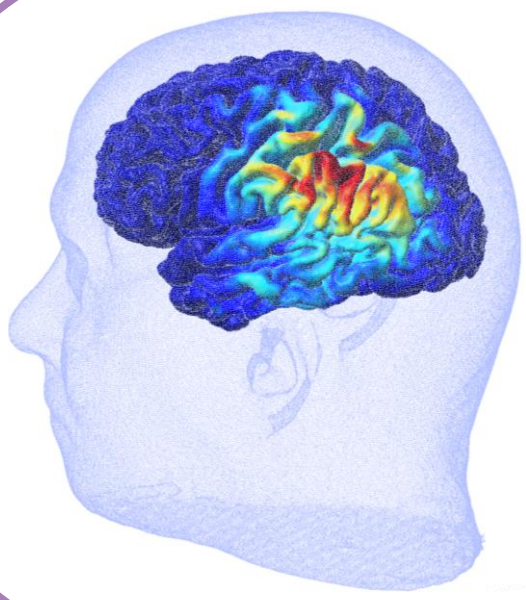
CLINICAL TRIALS BOOKLET



transcranial Alternating Current Stimulation (tACS) and transcranial Direct Current (tDCS) for the treatment of Depression

Selected CLINICAL TRIALS

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The following summary of clinical trials using various modalities of tES for the treatment of Major Depressive Disease were selected due to their clinical and scientific impact underpinning the **high potential of tES to improve depressive symptoms such as apathy or anhedonia and modulate the underlying disease pathophysiology**. Whereas the studies vary in treatment duration, 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 37 sessions per patient Up to 10 weeks of tES sessions (1-5x/week) In total more than 14'000 tES sessions, each between 20-40min
Design	7 sham-controlled, 2 open-label/single-arm trials
Patients treated	700+ patients with MDD
Neuropsychological Improvements	Depression (Montgomerry-ADRS, Hamilton DRS, IDS, QIDS, PHQ-9, Beck DI) Anxiety (HAM-A, STAI) Mania & Suicidality (Young MRS, Columbia-SSRS) Quality of Life (SDS, CGI-S, Q-LES) Attention (SDMT, WAIS) Learning & Executive function (RAVLT, Stroop)
Safety	No serious adverse events Transient mild tingling, itching under the electrodes

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transcranial Electrical Stimulation (tES) for the treatment of Depression CLINICAL TRIALS

Major Depressive Disorder (MDD) pathology

The prevalence of depressive disorders is estimated to be 6% in Europe, with women being twice as much affected than men[1]. MDD is usally accompanied by alterations of cortical activity and excitability, especially in prefrontal areas. Studies investigating these neural alterations indicate that MDD affects the brain's hemispheres assymetrically[2], resulting in defined patterns detectable by EEG and potentially treatable by tES[3]. One of the best examined alterations in brain activity, is the frontal assymetry shown by a hyperactive right and a hypoactive left dorsolateral prefrontal cortex (DLPFC) in particular within the alpha frequency band[4,5]. Pharmacological treatments exist for Major Depressive Disorder (MDD), the most common being Selective Serotonin Reuptake Inhibitors, but the therapeutical benefits are often delayed and bring unwanted side effects. Moreover more than half of MDD patients receiving psychotherapy do not respond, and only one-third achieve remission[6]. There is therefore a need for novel complementary approaches to treat depression.

Transcranial Direct Current Stimulation (tDCS) targeting MDD

Common non-invasive neuromodulation techniques for MDD treatment include repetitive Transcranial Magnetic Stimulation (rTMS), Electroconvulsive therapy (ECT) and Transcranial Electrical Stimulation (tES). While the first two have shown good results, they require trained personnel to operate costly devices at clinics. tES on the other hand is safe to be applied independently with proper guidance and training. The effects of tES in MDD are mainly associated to the restoration of neural activity and induced cerebral blood flow in the left DLPFC[7]. Most commonly, anodal (excitatory) tDCS of the left and cathodal (inhibitory) tDCS of the right DLPFC is used to ameliorate depressive symptoms. Based on this approach, the first tDCS system received CE Mark approval for the treatment of MDD in 2015[8].

Transcranial Alternating Current Stimulation (tACS) and MDD

Recent studies suggest that the manipulation of oscillations in neuronal networks through tACS is possibly a more efficient treatment modality for MDD[9]. By entraining the bilateral DLPFC at alpha frequency, tACS could restore frontal alpha assymetry (FAA) achieving this way sustained clinical benefits. This entrainment could also restore neural network functions to alleviate clinical symptoms and improve cognition[10].

Personalization in transcranial Electrical Stimulation (tES)

Current solutions for at home tES are rudimentary one-size-fits-all electrode montage. The effective electric field in the target area can thus vary greatly from one patient to another. To achieve the best treatment possible, the literature seems to emphasize the need for personalized therapies[6]. A further extension of personalization is to target different hubs in affected brain networks.

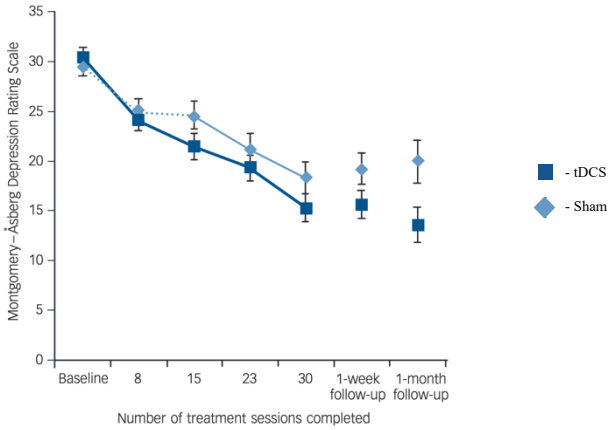
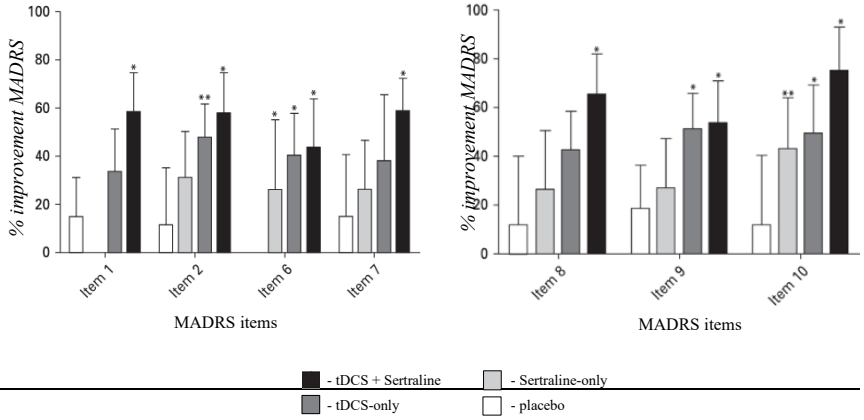
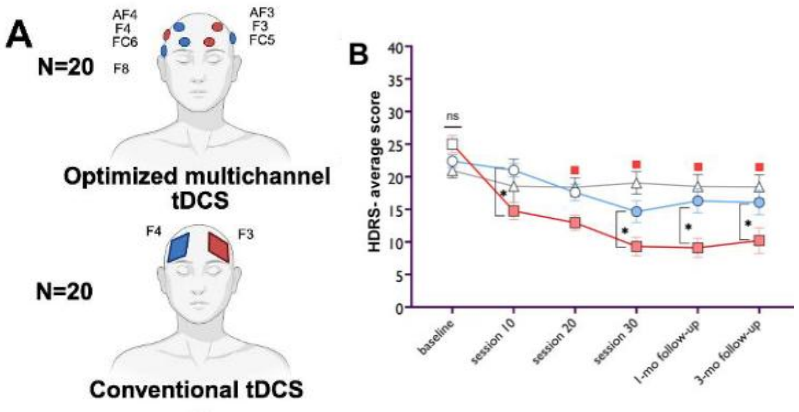
Home-based tES for the treatment of MDD

Longer courses of treatment seem particularly important to ensure sustained, lasting benefits in MDD patients. A recent meta analysis has shown that the effects of tDCS continue to increase for up to 10 weeks[11,12], with shorter duration trials struggling more to show effects. Longer duration of individual sessions has also been shown to have improved results[13]. For wide clinical implementation and long term application, self-adminsitered home based approaches are required.

Recommended reviews

For an evidence-based domain-expert review of tDCS applications see Fregni et al. 2020 (*Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders*). For a review specific to MDD see Moffa et al. 2020 *Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: An individual patient data meta-analysis*. 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*).

transcranial Electrical Stimulation (tES) for the treatment of Depression CLINICAL TRIALS

STUDY	CONCLUSION
Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial *Loo et al. 2012* University of New South Wales, Sydney, Australia • tDCS with anode left DLPFC, cathode lateral aspect of the contralateral orbit • RCT 64 subjects over 3 weeks (5x/week) then 3 weeks open-label possible • **Significant improvement in mood** • Treatment should be **given for longer than 3w** for an adequate response	
The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study: Results From a Factorial, Randomized, Controlled Trial *Brunoni et al., 2013* University of São Paulo, São Paulo, Brasil • tDCS with anode left DLPFC, cathode rDLPFC • RCT 120 participants, factorial design (Drug/No-Drug x tDCS/Sham) over 3 weeks (5x/week) • The combination of **active tDCS and sertraline was superior to tDCS alone or Sertraline alone** • tDCS (alone and combined with Sertraline) improved concentration difficulties and pessimistic and suicidal thoughts.	
Optimized multichannel tDCS protocol for clinical use in patients with major depressive disorder *Salehinejad et al., preprint* Leibniz Research Centre, Dortmund, Germany • Optimized tDCS targetting left DLPFC (anodes: AF3, F3 & FC6, cathodes: AF4, F4 & FC5) • 60 subjects RCT over 5 weeks • Compared conventional with optimized tDCS electrode positions • **Optimized tDCS** shows **significantly larger improvements** in two depression scores at multiple timepoints **than conventional tDCS**	

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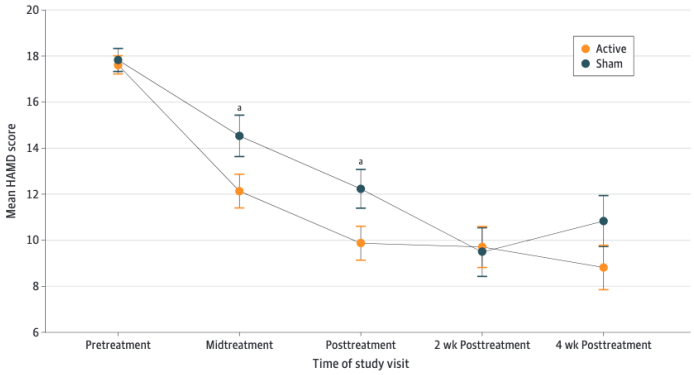
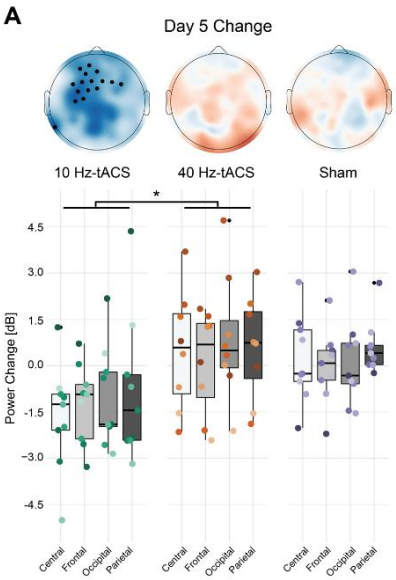
Personalized High-Definition Transcranial Direct Current Stimulation for the Treatment of Depression
Jog et al., 2025
UCLA, Los Angeles, USA

- Optimized **HD-tDCS** with anode left DLPFC, 4 surrounding cathodes in circular configuration
- 71 subjects RCT over 12 consecutive workdays
- Significant changes in HAMD score at the end with respect to baseline
- Even with reduced number of short sessions, this study achieved **comparable results to longer protocols thanks to the optimization of tDCS electrodes**



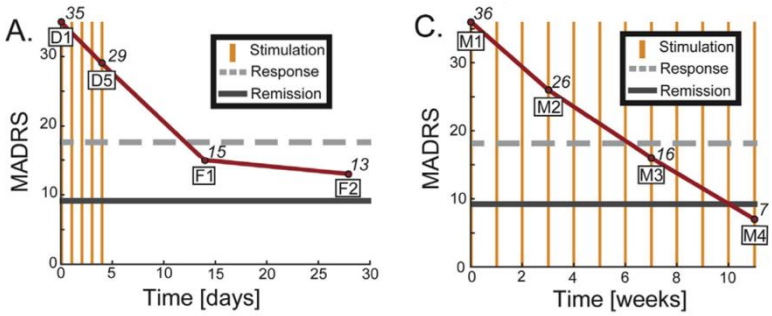
Double-blind, randomized pilot clinical trial targeting alpha oscillations with transcranial alternating current stimulation (tACS) for the treatment of major depressive disorder (MDD)
Alexander et al. 2019
University of North Carolina, Chapel Hill, USA

- Daily 10Hz tACS over left and right DLPFC
- Pilot RCT 32 participants for 5 consecutive days
- 10 Hz-tACS showed a **significant decrease in alpha power over the left frontal regions of the brain the last day of stimulation** but the effect did not last (4-week followup)
- MADRS scores for all groups decreased significantly with respect to baseline, including in Sham



A case study of weekly tACS for the treatment of major depressive disorder
Riddle et al. 2020
University of North Carolina, Chapel Hill, USA

- Weekly 10Hz tACS over left and right DLPFC
- Case study-extension of Alexander et al. 2019
- Single subject
- Achieved remission after 12 weeks of stimulation



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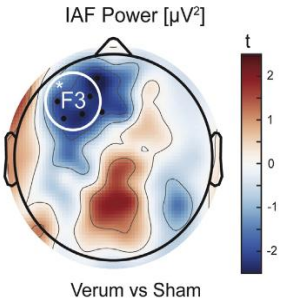
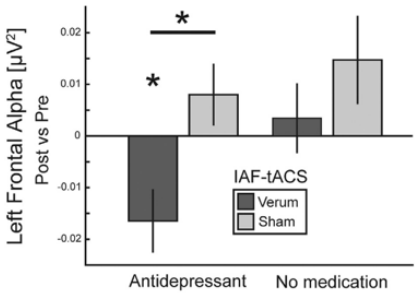
Reduction in Left Frontal Alpha Oscillations by Transcranial Alternating Current Stimulation in Major Depressive Disorder Is Context Dependent in a Randomized Clinical Trial
Riddle et al. 2022
University of North Carolina, Chapel Hill, USA

- Single session **tACS** left DLPFC at individually personalised frequency
- RCT 84 partcipants
- Single session of bifrontal tACS **reduced pathological left** frontal resting-state **alpha power** when compared with placebo





Adjunctive home-based transcranial direct current stimulation treatment for major depression with real-time remote supervision: An open-label, single-arm feasibility study with long term outcomes
Woodham et al., 2022
University of East London, United Kingdom

- tDCS with anode left DLPFC, cathode right DLPFC
- 26 participants open-label study over 6 weeks (weekdays for 3weeks then 2x/week)
- High feasibility of **home-based tele-supervised** study with **high participant retention**
- **Significant improvement** in depressive symptoms, which was **maintained at 6 months**

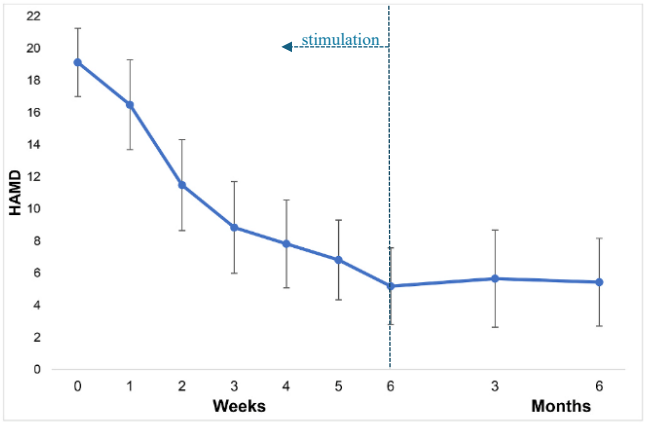
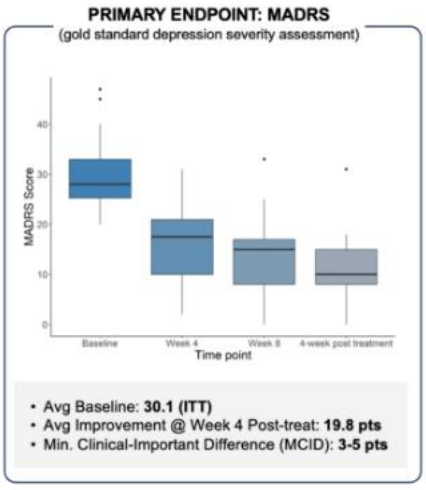


Fig. 2. Mean Hamilton Depression Rating Scale (HAMD) total scores in patients at every assessment time point from baseline to 6-month follow up

Multichannel tDCS with advanced targeting for major depressive disorder: a telesupervised at-home pilot study
Ruffini et al., 2024
Harvard Medical School, Boston, USA

- Optimized **tDCS** targetting left DLPFC (anodes: AF3 & F3, cathodes: T7 & AF4)
- 35 subjects open-label home-based over 8 weeks (4w daily then 4w taper phase)
- **Group optimization** of the electrode montage
- Demonstrated **feasibility of home-based approach** with high treatment adherence
- **64.5% median MADRS decrease** 4 weeks post treatment



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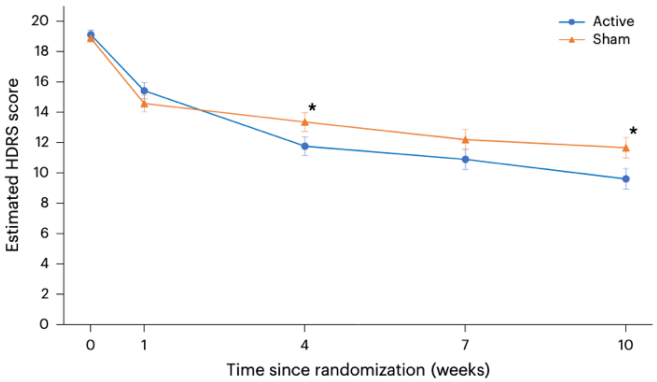
Home-based transcranial direct current stimulation treatment for major depressive disorder: a fully remote phase 2 randomized sham-controlled trial
Woodham et al., 2025
University of East London, London, UK

- tDCS with anode left DPFC, cathode right DLPFC
- RCT **174 participants** over 3 weeks (5x/week) then another 7 weeks (3x/week)
- **Significant improvement in depressive symptoms** (HDRS decrease of 9.41 vs 7.14 in sham, equivalently in MADRS)
- Significantly **greater treatment response** and remission rate in tDCS group (by a factor of 2)
-



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