Transcranial alternating current stimulation and its effects on cognition and the treatment of psychiatric disorders: a systematic review and meta-analysis

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Abstract

Background: Transcranial alternating current stimulation (TACS) is a non-invasive method of brain stimulation that is hypothesised to alter cortical excitability and brain electrical activity, modulating functional connectivity within the brain. Several trials have demonstrated its potential in treating psychiatric disorders such as depression and schizophrenia.

Objectives: To study the efficacy of TACS in ameliorating symptoms of depression and schizophrenia in patients and its effects on cognition in patients and healthy subjects compared to sham stimulation.

Design: Systematic review with meta-analysis.

Data Sources and Methods: This PROSPERO-registered systematic review (CRD42022331149) is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, EMBASE, CENTRAL and PsycINFO were searched from inception to March 2022. Only randomised-controlled trials were included.

Results: A total of 12 randomised-controlled trials are reviewed for meta-analysis, with three randomised-controlled trials reporting only effects on cognition in psychiatric and cognitively impaired patients, three trials on cognition in healthy subjects, one trial on cognition in both patients and healthy subjects, one trial on only depression, two on both cognition and depression in patients and two on schizophrenia symptoms. No studies were at significant risk of bias. For cognition, TACS showed significant improvement [positive standardised mean differences (SMD) denoting improvement] over sham stimulation in those with psychiatric disorders with an SMD of 0.60 [95% confidence interval (CI): 0.14, 1.06]. Similarly, among patients with depression, an SMD of 1.14 [95% CI: 0.10, 2.18] was found significantly favouring TACS over sham stimulation. Two studies assessed the effect of TACS on schizophrenia symptoms with mixed results.

Conclusion: TACS has shown promise in ameliorating symptoms of both schizophrenia and depression in patients. TACS also improves cognition in both patients and healthy subjects. However, these findings are limited by the sample size of included studies, and future studies may be required to better our understanding of the potential of TACS.

Registration: PROSPERO (CRD42022331149)

Keywords: cognition, cognitive impairment, depression, non-invasive brain stimulation, schizophrenia
Introduction

Transcranial alternating current stimulation (TACS) has been used for many years in fields such as cognitive neuroscience. Compared to the more well-established transcranial direct current stimulation (TDCS), TACS delivers an electrical current at a specified frequency in a bidirectional manner. In contrast, TDCS delivers current in a unidirectional manner. TACS alters the transmembrane potential of single neurons. This has been hypothesised to modify cortical excitability and brain electrical activity by adjusting the probability of action potentials being generated, entraining brain oscillations to the stimulation frequency and modulating functional connectivity within the brain.

In recent years, the potential of TACS has been explored and increasingly utilised as a non-pharmacological treatment for psychiatric conditions, such as depression, anxiety, schizophrenia and neuropsychiatric conditions such as Alzheimer’s disease. Depression is a common psychiatric disorder, with a lifetime prevalence of about 16.6% in adults, and results in the highest burden of disability among all mental and behavioural disorders. In schizophrenia, poorly controlled cognitive deficits have been noted, which vastly reduce the quality of life. Currently recommended drug therapies are associated with suboptimal remission rates and, often, undesirable side effects. Pharmacological interventions remain insufficient, with an estimated 60% of patients responding to treatments significantly.

Abnormalities in brain oscillatory activity have been linked with various psychiatric disorders, such as depression, for which increased alpha activity in the left central cortex is a good predictor. In a recent randomised-controlled trial, it was shown that alpha TACS stimulation at the prefrontal cortex could improve depressive outcomes. Similarly, another randomised-controlled trial demonstrated that exposure to gamma-TACS caused a significant improvement in memory in Alzheimer’s patients. Recent literature has shown that TACS is superior to TDCS in improving cognition in patients with mild cognitive impairment. TACS has increasingly been investigated for its effects on cognition in patients and healthy subjects. This is of interest as TACS and potentially be used to enhance cognitive processes or delay the onset of cognitive defects in healthy individuals.

This systematic review and meta-analysis will be the first to consolidate the effects of TACS on psychiatric disorders. We examine the impact of TACS on cognition, depression and schizophrenia.

Methodology

This systematic review is reported according to the PRISMA guidelines. This study is registered with PROSPERO at CRD42022331149.

Search strategy

We searched several databases—Medline via PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and PsycINFO—for articles from inception to March 2022 (Supplementary table 1). No restrictions on the language of publication were applied. To improve data validity, we excluded non-peer-reviewed articles in preprint databases.

Study selection

We used a two-stage approach for screening: first by title and abstract and then by full-text article. Two researchers (ARYBL and WAT) independently screened each title, abstract and full text, with discrepancies resolved by consensus with a third researcher (CSHH). Studies were limited to human participants.

We performed a meta-analysis of randomised-controlled trials that met several criteria included human participants who received TACS, studies that included and reported data on a control group receiving sham or placebo therapy, studies that reported quantitative outcomes related to cognition or the symptoms and clinical severity of psychiatric disorders including depression and schizophrenia.

Data extraction

Four researchers (ARYBL, CEY, NEY and BSYO) extracted data using a predetermined proforma in Microsoft Excel Version 16.45. All key extracted data were independently reviewed,
and quality checked at the end of the data extraction phase. Data on study characteristics comprised setting, primary and secondary outcomes, study design, sample size, dropout and non-response rates and inclusion and exclusion criteria. Participant data contained age, sex, disease and treatment history. Intervention-related data included the type of TACS, frequency and duration of administration. Outcome-related data comprised a questionnaire or scale used to determine outcomes and timepoints of data collection. Where studies utilise more than one instrument to measure a single outcome, such as cognition, results for all instruments will be extracted. Sensitivity analysis will be performed by repeating meta-analysis using the different instruments to investigate for significant differences.

Quality assessment
The studies’ methodological quality and risk of bias were assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for randomised-controlled studies. The risk of bias for each study was evaluated independently by two researchers, with any differing opinions resolved by consensus.

Data analysis
The extracted data were quantitatively pooled and analysed in R Version 4.1.0 using the meta and metafor packages. In studies without standard deviations (SDs), confidence intervals (CIs) were converted to SDs. In studies without relevant baseline data, the simple analysis of the final values method was used. Studies were pooled for meta-analysis using standardised mean differences (SMD) and the common-effects model. Between-study heterogeneity was represented by $I^2$ and $t^2$ statistics. $I^2$ of <30% indicated low heterogeneity between studies, 30% to 60% showed moderate heterogeneity, and >60% indicated substantial heterogeneity. Two-sided $p$ values of <0.05 were considered to indicate nominal statistical significance. Unless specified otherwise, we considered a two-sided $p$ value of <0.05 statistically significant.

Results
From 6353 records, 12 research papers were included in this review.\cite{3,10,13,22-30} All studies were randomised-controlled trials. This process is detailed in the PRISMA flowchart in Figure 1. Characteristics of included studies are presented in Table 1.

Cognition
Regarding cognition, analysis was performed for participants recruited in the studies who had psychiatric conditions (Figure 2). One study\cite{13} studied the cognitive outcomes of these subjects using the Rey Auditory Verbal Learning Test, one\cite{10} using the Montreal Cognitive Assessment, two\cite{26,28} using the d prime 2-back test and two\cite{3,25} using the Trail Making Test.

Among psychiatric patients, 172 participants were included in the meta-analysis (Figure 2), with 86 in the intervention group and 86 in comparators from six studies.\cite{3,10,13,25-28} As the Trail Making Test consists of results for Trail Making Tests-A and -B, a sensitivity analysis was performed using both test results. Similarly, as pre- and post-intervention results for the Rey Auditory Verbal Learning Test total recall and delayed recall were reported by Alexander et al., sensitivity analysis was performed using both results. In Figure 2, Trail Making Test-A and Rey Auditory Verbal Learning Test total recall results are presented. Overall, an SMD of 0.60 (95% CI: 0.14, 1.06) (random effects) with low heterogeneity ($I^2 = 46\%$) was noted in the TACS compared to the control group. Sensitivity analysis utilising Trail Making Test-B scores instead (Supplementary Figure 1) did not significantly affect results, with TACS still being favoured with an SMD of 0.67 (95% CI: 0.21, 1.14) with random effects. Using Rey Auditory Verbal Learning Test delayed recall instead (Supplementary Figure 2) similarly did not demonstrate significant differences with an SMD of 0.53 (95% CI: 0.15, 0.90). Among psychiatric patients, two\cite{3,13} included patients with mild cognitive impairment, three\cite{10,25,26} included patients with depression, and one\cite{28} included patients with schizophrenia. Alexander et al. administered TACS of two different frequencies, 10 Hz and 40 Hz, with 40 Hz demonstrating better results than placebo (SMD: 0.05; 95% CI: -0.79, 0.88) and 10 Hz performing more poorly than placebo (SMD: -0.61; 95% CI: -1.50, 0.27), both of which were statistically insignificant.

Among healthy individuals, we conducted a systematic review without meta-analysis as heterogeneity in outcome assessment and reporting made
it unamenable to statistical pooling. For studies including healthy individuals, two\textsuperscript{22,27} used the 2- and 3-back test while one\textsuperscript{29} used a cognitive composite score calculated from principal component analysis of a broad neuropsychological test battery and computer-based cognitive training. TACS appeared to have diverse results in the study by Pahor and Jaušovec,\textsuperscript{22} reporting that most placements of electrodes did not yield significant benefit with bilateral frontal stimulation with theta TACS being an outlier. Hoy \textit{et al.}\textsuperscript{27} demonstrated a statistically significant improvement in d prime difference scores for TACS of 0.4383 (standard error: 0.141) with the 3-back while no difference with the 2-back test. This was a significant overall improvement compared to sham stimulation which showed a difference of 0.144 (standard error: 0.077) and 0.028 (standard error: 0.051) on the 3-back and 2-back tests, respectively. Krebs \textit{et al.}\textsuperscript{29} however, while there was a significant improvement in cognitive score across the 12 months of study period, there was no significant effect attributable to TACS. This signified a trend in studies that TACS could improve cognition even in healthy individuals, but further studies may be required to determine if TACS delivers considerable benefit in these healthy individuals. In contrast, a significant benefit was generally demonstrated in psychiatric patients.

**Depression**

Among individuals with depression, a total of 122 participants were included in the meta-analysis (Figure 3), with 62 in the intervention group and 60 in comparators from three studies.\textsuperscript{10,25,30} An SMD of 1.14 (95% CI: 0.10, 2.18) (random effects) with notable heterogeneity (I\textsuperscript{2} = 72\%) were found in the TACS compared to the control.
### Table 1. Characteristics of TACS in included studies.

| Study                  | Year of publication | N (intervention) | N (control) | Background                                                                 | Mean age ± standard deviation | Study arms | Location of electrodes                                                                 | Duration (min) | Outcomes                                      |
|------------------------|---------------------|------------------|-------------|-----------------------------------------------------------------------------|------------------------------|------------|------------------------------------------------------------------------------------------|----------------|-----------------------------------------------|
| Benussi et al.         | 2021                | 20               | 20          | Patients with mild cognitive impairment due to Alzheimer’s disease          | 71.9 ± 7.0                   | 40 Hz gamma-TACS Sham                                                                | Overlying the medial parietal cortex and the precuneus, and right deltoid | 60              | Cognition in psychiatric patients            |
| Kim et al.             | 2021                | 20               | 20          | Mild cognitive impairment                                                  | 76.8 ± 3.2                   | 40 Hz TDCS gamma-TACS Sham                                                           | F3 and F4                                                              | 30              | Cognition in psychiatric patients            |
| Haller et al.          | 2020                | 6 in total       |             | Depression                                                                  | 35.7 ± 16.5                  | 40 Hz gamma-TACS                                                                    | Left and right prefrontal cortex (F3 and F4)                            | 2*10 or 20      | Cognition in psychiatric patients Depression |
| Alexander et al.       | 2019                | 10 undergoing 10 Hz, 11 undergoing 40 Hz | 11          | Depression                                                                  | 36.69 ± 13.08                | 10 Hz TACS 40 Hz TACS Sham                                                           | Left and right frontal regions                                        | 40              | Cognition in psychiatric patients Depression |
| Palm et al.            | 2022                | 22 depressed     | 21 healthy  | Depression                                                                  | 40.8 ± 13.71                 | 40 Hz gamma-TACS                                                                    | Bilateral dorsolateral prefrontal cortex                               | 20              | Cognition in psychiatric patients           |
| Hoy et al.             | 2016                | 11 in total      |             | Schizophrenia                                                              | 43.27 ± 10.02                | 40 Hz c-TACS Sham                                                                  | F3 and right supraorbital region                                      | 20              | Cognition in psychiatric patients           |
| Mellin et al.          | 2018                | 8 TACS           | 7           | Schizophrenia                                                              | 47 ± 9.72 38.86 ± 10.01      | received twice daily, 20 min sessions of sham, 10 Hz 2 mA peak-to-peak TACS        | Dorso-lateral prefrontal cortex to target hypoactivity And temporo-parietal junction to target hyperactivity | 20              | Schizophrenia                                |

(Continued)
| Study        | Year of publication | N (intervention) | N (control) | Background       | Mean age ± standard deviation | Study arms | Location of electrodes | Duration (min) | Outcomes          |
|--------------|---------------------|------------------|-------------|------------------|-------------------------------|------------|------------------------|----------------|-------------------|
| Chang et al. | 2021                | 18               | 18          | Schizophrenia    | TACS: 41.78 ± 8.84            | Either twice daily, 6 Hz 2 mA, 20 min sessions of in-phase frontoparietal TACS or sham for five consecutive weekdays. | 1st stimulator: International 10–10 electrode position F1, F5, AF3, and FC3, CPz 2nd stimulator: P1, P5, CP3, P03 and FCz | 20             | Schizophrenia      |
| Pahor et al. | 2018                | 72 in total      |             | Healthy          | -                             | active theta TACS, active gamma-TACS Sham | F3 and P4 |                        | 15             | Cognition in healthy individuals |
| Hoy et al.   | 2015                | 18 in total      |             | Healthy          | 29.3 ± 7.65                   | 40 Hz c-TACS Sham | F3 and right supraorbital region | 20             | Cognition in healthy individuals |
| Krebs et al. | 2021                | 20               | 22          | Healthy          | 71.7 ± 6.1                    | 10 sessions, 50 min, twice weekly using TDCS [2 mA], 5 Hz TACS, or sham | Over the left dorsolateral prefrontal cortex | 20             | Cognition in healthy individuals |
| Wang et al.  | 2022                | 50               | 50          | Unipolar, non-psychotic MDD | 40.0 ± 12.6                  | 77.5 Hz tACS sham | Forehead and mastoid | 40             | Depression         |

MDD, major depressive disorder; TACS, transcranial alternating current stimulation; TDCS, transcranial direct current stimulation.
group. Of note, Alexander et al.,10 randomised 32 patients with depression to receive 40-min sessions of either TACS at 10 Hz or 40 Hz or sham stimulation for five consecutive days. For consistency during meta-analysis, we used the 40 Hz frequency TACS. Symptoms of depression were assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS),31 Hamilton Depression Rating Scale (HDRS) 32 and Beck’s Depression Inventory (BDI). 33 No significant improvements in scores overall were reported at baseline up to 4 weeks after completion of the intervention, and no significant differences were noted between treatment arms. However, the numbers of participants who reported improvements in scores measured by MADRS, HDRS and BDI were highest in those receiving TACS at 40 Hz. Thus, future studies with a larger sample size may be conducted to elucidate if there is any significant difference in the incidence of remission of depression following TACS.

Schizophrenia
Two studies evaluated the use of TACS in schizophrenia patients (Figure 4).23,24 As only two studies met the inclusion criteria, statistical pooling was limited. Mellin et al. randomised 22 participants into three arms, receiving sham, TACS or TDCS over five consecutive days, and assessed the presence and severity of hallucinations, positive and negative symptoms using the Auditory Hallucination Rating Scale, Positive and Negative Syndrome Scale (PANSS) and the Brief Assessment of Cognition in Schizophrenia. The analysis yielded significant benefits after TACS, with effect sizes for the arms being 1.31 for TACS, followed by 1.06 for sham and 0.17 for TDCS. Heterogenous results with no significant differences in positive and negative symptoms were noted.

Chang et al. randomised 36 patients with schizophrenia to receive either twice-daily 20-min sessions of frontoparietal TACS or sham stimulation for five consecutive days. During the stimulation administration, the participants performed tasks involving active use of working memory. Positive and negative symptoms were assessed using PANSS, and neurocognitive performance data were collected. Overall, the intention-to-treat analysis demonstrated significant reductions in the PANSS negative subscale scores at the end of stimulation in those receiving TACS (-13.84%)
compared to those receiving sham stimulation (-3.78%). A large effect size was yielded (Cohen’s d = 0.96, p = 0.006).

However, neither Mellin et al. nor Chang et al. assessed outcomes in the longer term after the trial’s cessation. Thus, the duration of the effects on schizophrenia could not be determined. Future studies may seek to follow-up with patients after administration to assess how enduring the improvements in symptoms are.

**Risk of bias**

There were no significant concerns regarding the risk of bias among the included randomised-controlled trials (Supplementary Table 2) using the JBI Critical Appraisal Tools Checklist for Randomised-Controlled Trials.

**Discussion**

This systematic review and meta-analysis is the first to critically evaluate the effect of TACS on cognition and the treatment of psychiatric disorders. TACS has been employed in various settings to treat psychiatric disorders, including mild cognitive impairment, depression and schizophrenia. Studies have also sought to explore whether TACS benefits cognition in those without evidence of cognitive impairment. While its mechanism of action is not fully elucidated, the principal concept of TACS is to simulate brain oscillations, which are naturally occurring rhythmic patterns of brain electrophysiological activity. This temporally aligns neural firing and entrains endogenous oscillations in the brain. TACS may induce longer-lasting synaptic changes through spike-time-dependent plasticity. While TACS did not show convincing improvements in cognition in healthy subjects, it may benefit those with psychiatric conditions, particularly mild cognitive impairment. The systematic review also demonstrated that TACS might have considerable clinical benefit in improving the symptoms of depression and schizophrenia. Overall, the management of cognitive impairment and psychiatric disorders often involve a complex host of behavioural and psychosocial treatments, non-pharmacological adjuncts such as neural stimulation and pharmacological therapy. With long-term pharmacological treatment often associated with stigma and fear of side effects, greater attention is now being given to alternative treatments, including nutrition and electrical stimulation. Thus, TACS may be a promising addition to the repertoire of non-pharmacological therapeutics.

The optimal current, frequency, duration and location of the cathodes for treating psychiatric disorders are unknown. A case series by Haller et al. involved six patients with depression treated with gamma-TACS at a frequency of 40 Hz, randomised to either receive two 10-min stimulations or a single 20-min stimulation per day for 10 days. The HDRS and Beck Depression Inventory were used to assess symptoms of depression. After 10 days, symptoms of depression improved in both groups, with HDRS and BDI scores decreasing by 85% and 78% in the group receiving two 10-min stimulations and by 62% and 24% in the group receiving a single 20-min stimulation per day. As assessed by verbal fluency and n-back test, cognition also improved after TACS. Thus, the more significant improvement in symptoms of depression with two 10-min stimulations shows that the method of administering TACS may have differential effects on its efficacy, highlighting a point of future research interest.

The long-term side effects of TACS are not well established and demonstrated in large-scale trials. Current reviews indicate that, similar to TDCS, there are no persistent adverse effects for TACS. Most side effects of TACS are non-serious...
adverse natures, such as tingling, skin lesions or phosphenes. Further safety investigations are warranted.

Limitations of review

Our review is primarily limited by the paucity of randomised-controlled trials evaluating the efficacy of TACS in psychiatric disorders, including depression and schizophrenia. With TACS being a newer addition to the range of non-invasive transcranial stimulation technology, less published data are available from randomised controlled trials.

The small sample sizes in the randomised-controlled trials further limited statistical significance, with four studies including 20 or fewer participants receiving TACS. However, no study suffered from a significant attrition rate or missing outcome data that would pose a concern for risk of bias.

There is also a lack of homogeneity in electrode placement locations in TACS. This variance may have contributed to heterogeneity among studies as different electrode placements may have a differential effect on the brain’s oscillatory waves.

Conclusion

In conclusion, while there is a paucity of high-powered randomised-controlled studies evaluating the efficacy of TACS, it has shown promise in ameliorating symptoms of both schizophrenia and depression. It may also improve cognition in those with cognitive impairment, though further evidence of benefits in healthy subjects may still be required. Given the potential issues with stigma and medication adherence associated with long-term pharmacotherapy, TACS, which involves short sessions of non-invasive stimulation, may have potential as a treatment modality in managing psychiatric disorders.

Declarations

Ethics approval and consent to participate

Not applicable, as no human and animal subjects or data were used.

Consent for publication

Not applicable.

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