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Transcranial Alternating Current Stimulation (tACS) and Its Role in Schizophrenia: A Scoping Review

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Transcranial alternating current stimulation (tACS) may modulate neuronal oscillations by applying sinusoidal alternating current, thereby alleviating associated symptoms in schizophrenia. Considering its possible utility in schizophrenia, we reviewed the literature for tACS protocols administered in schizophrenia and their findings. A scoping review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline in databases and clinical trial registers. The search resulted in 59 publications. After excluding review articles unrelated to tACS, trials without published results or not involving patients with schizophrenia, 14 studies were included. Among the included studies/case reports only 5 were randomized controlled therapeutic trials. The studies investigated the utility of tACS for clinical and neurobiological outcomes. All studies reported good tolerability with only transient mild side effects. It was administered mostly during the working memory task (such as computerized n-back task, dual back task, and computerized digit symbol substitution task) for schizophrenia patients with cognitive deficits and during resting state while targeting positive symptoms. A possible reduction in hallucinations and delusions using alpha tACS, and improvement in negative and cognitive deficits with theta and gamma tACS were reported. Nevertheless, one of the randomized controlled trials targeting hallucinations was negative and rigorous large-sample studies are lacking for other domains. The current evidence for tACS in schizophrenia is preliminary though promising. In future, more sham controlled randomized trials assessing the effect of tACS on various domains are needed to substantiate these early findings.

KEY WORDS: Electric stimulation therapy; Psychiatric somatic therapy; Neural oscillation; Hallucination; Delusion; Cognitive impairments.

INTRODUCTION

Schizophrenia is a severe mental disorder characterised by delusions, hallucinations, disorganisation, negative symptoms, cognitive symptoms, and significant impairment in multiple domains of one's life. Schizophrenia affects around one in every hundred in the general population [1] and ranks among the leading causes of disability between the age group of 25−49 years [2]. Since the fortuitous discovery of chlorpromazine, antipsychotic medications continue to remain the primary treatment modality for schizophrenia. The current guidelines recommend the long-term use of antipsychotic medications in treating schizophrenia in conjugation with psychosocial interventions [3]. However, the current antipsychotic medications possess significant limitations. Firstly, despite treatment, around 10−30% of the patients show no response, and another 30% show residual positive symptoms [4,5]. Secondly, antipsychotic medications do not optimally ameliorate the negative and cognitive symptoms; the persistence of these symptoms leads to significant dysfunction and poor quality of life [6,7]. Thirdly, antipsychotic medications are associated with the risk of various adverse effects such as extrapyramidal side effects, hyperprolactinemia, weight gain, and metabolic abnormalities [8,9].

The limitations of antipsychotic medications kindled

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investigation into other treatment modalities for treating patients with schizophrenia. Neuromodulation is one of them. Among the various methods of neuromodulation, transcranial alternating current stimulation (tACS) has been recently explored in the treatment of psychiatric disorders, especially in the treatment of schizophrenia.

tACS is a non-invasive brain stimulation technique involving the application of alternating electric currents, sinusoidal in nature, through the scalp using electrodes to the specific brain regions to modulate their activity. The current amplitude, frequency, phase difference and duration of stimulation, along with the site of stimulation, are the major parameters involved in the application of tACS [10,11]. The intensity of the alternating current is generally administered within the range of 0.5−2 mA using metal or rubber electrodes with a skin-electrolyte contact area of 25−35 cm^2. Unlike transcranial direct current stimulation (tDCS), the amplitude here is measured from peak-to-peak of the positive and negative phases of the cycle. The alternating current mimics the rhythmic electrophysiological brain activity and helps to modulate the brain functions associated with them [12]. Hence, the stimulation involves sinusoidal waves of a frequency that matches the frequency of the intrinsic neural oscillations, ranging from 0.5−80 Hz. The electric current has to have one or more entry points as well as one or more exit points on the scalp through electrodes. Conventional montage involves 2-electrode, and the fluctuations in the polarity of the current maintain the electrodes in fluctuating states of anode/cathode. Adding a DC offset can keep these fluctuations within a single polarity. The offsets are generally kept zero in tACS. But when non-zero offsets with/without overlapping to other polarity are used, the stimulation will be termed "oscillatory transcranial direct current stimulation" (otDCS) [10].

The difference in the phase of the oscillating current is usually kept similar when the current is told to be "in-phase". Whereas the electrodes can be kept "out-of-phase" where the phase difference will be at 180°. The studies may use the whole range of phase differences between 0−360°; the physiological/clinical implications of these are yet to be ascertained. Novel high-definition tACS applications with single-entry and multiple-exit or vice-versa are also being utilised in clinical studies [13] aiming to achieve focused stimulation.

The exact mechanism of action of tACS is an area of immense research interest. The current evidence points toward the possible effect of tACS on neural oscillations. The neural oscillations are synchronized rhythmic patterns of electrophysiological activity produced by neurons in the brain. These neural oscillations are associated with multiple perceptual, behavioural and cognitive functions as well as different brain states [14]. Also, the connectivity between various cortical brain regions is mediated by synchronizing brain oscillations across these regions [15]. Various psychiatric disorders, such as schizophrenia, have been implicated to have abnormalities in these neural oscillations [16].

tACS is thought to have online effects, i.e., effects noticed during the stimulation period, as well as after-effects that outlast the stimulation period [17,18]. The online effects and after-effects are attributed to entrainment and neuroplasticity, respectively [18,19]. Entrainment is a phenomenon wherein the rhythmicity of 2 systems synchronizes with each other [19,20]. In tACS, it is hypothesised that an externally applied sinusoidal current of a specific frequency can modulate the endogenous neural oscillations in the brain either by synchronizing or desynchronising the oscillatory activities in the specific region of the brain leading to ameliorating the abnormalities in neural oscillations, which translates into an improvement in clinical symptoms [18,19,21]. For entrainment to be possible, an endogenous oscillation should be present in the range of the frequency of the applied alternating current [18,19,21]. This entrainment can also happen at harmonic frequencies, which are integral multiple of the stimulating frequency (resonant frequency), such as twice or half of the stimulation frequency [19,21,22]. There will be an enhancement of the power of these frequency-specific oscillations contributing to the psychophysiological effects. Entrainment also depends on the amplitude of the stimulation, as described by the Arnold's Tongue [18,19]. This property of tACS describes the ability of higher amplitude current to entrain wider frequencies of endogenous oscillations with peak entrainment at the stimulation frequency. In contrast, lower amplitude stimulation will be able to entrain among the narrower frequency range [19]. Also, it is known that during cognitive processes, it is not the oscillation of a single frequency (frequency range) that is involved, but the waves of different frequency ranges interact with each other, i.e., cross-frequency coupling [22,23]. The coupling could be at the inter-frequency domains, in-

ter amplitudes or, more commonly, amplitude-frequency coupling [24]. Hence, the application of tACS at one specific frequency may also affect the properties of other endogenous frequencies leading to improvement in symptoms [18,19]. The effects of entrainment last for the stimulation period. However, tACS may have a long-lasting effect due to neuroplastic changes. The synapses are strengthened or weakened based on the timing of input and output activity, a mechanism referred to as spike-timing-dependent plasticity (STDP) [21,22]. Thus, synapses with a resonance frequency similar to repetitive input are strengthened, leading to long-lasting effects [25].

In patients with schizophrenia, specific abnormalities in brain oscillations have been noted. These abnormalities are frequency, brain region and state specific. A consistent finding in patients with schizophrenia is a decrease in alpha rhythm in the prefrontal and parietal regions of the brain [26-30]. The alpha is an inhibitory waveform, and its deficits suggest dysregulation in top-down processing [28,31]. Alpha tACS has been used in studies targeting positive symptoms (hallucinations and delusions) of schizophrenia. The idea behind this is to regulate top-down processing by inhibiting the activity of targeted areas. Aberrant activity in the temporoparietal junction (TPJ) (the site of auditory processing) and medial prefrontal cortex (the site of self-referential processing) [28] were targeted to be regulated using alpha tACS.

Theta waves and the amplitude-modulated gamma within the phase of theta waves are found to be crucial in the flow of information packages across short- and long-range brain networks, respectively. Deficit theta oscillations in the frontal lobe are associated with working memory impairment in patients with schizophrenia [32, 33]. Aberrant gamma oscillations have been linked to an imbalance between excitatory and inhibitory networks due to impaired GABAergic inter-neuronal activity [34]. In patients with schizophrenia, there is a reduction of task-related gamma oscillation and associated synchronization [33-38] that correlated with deficit symptoms, including negative symptoms [39]. tACS attempting to enhance the theta and gamma oscillations in the frontoparietal network is thus shown to improve the cognitive and negative symptoms of schizophrenia. A novel tACS approach by combining these 2 frequencies termed theta-gamma tACS is attempted in healthy controls showing its superiority over theta tACS [40]. It would be interesting to see its translational application in schizophrenia patients.

Given the advancing conceptualization of schizophrenia as a disorder of abnormal oscillatory activity, the application of tACS exploring its utility and safety in this population is imperative. This article provides an up-to-date review of the clinical utility, including the clinical effect and safety, as well as any research application of tACS in schizophrenia.

METHODS

This is a scoping review of the literature on the utility of tACS in Schizophrenia. A systematic literature search on the MEDLINE and Scopus databases as well as in the WHO International Clinical Trials Registry Platform (ICTRP) was conducted based on combination of keywords: ((tACS [Title/Abstract]) OR (transcranial alternating current stimulation [Title/Abstract])) AND (schizophrenia [Title/Abstract]). The search process was last performed on 15th October 2022. All the original studies investigating the effect of the administration of tACS in patients with schizophrenia with published results in the English language till date were included.

The search resulted in 59 publications after the removal of duplicates. Screening of the study was done by 2 authors (HP and VSS), and a final consensus was taken for the inclusion/exclusion of a study. Overall, 45 studies were excluded as they were review articles/they did not involve studying patients with schizophrenia/they were unrelated to tACS/trials in the registries without published results. The remaining studies were reviewed in full text to assess for eligibility and were included. One trial result was found unpublished in a peer-reviewed journal and has been included in the review. The studies included 2 conference abstract papers investigating the effect of tACS in schizophrenia, one of them being an unpublished Master's thesis work where we could find the full thesis [41]. We reviewed the protocols used in these studies, their clinical/neurobiological outcomes and their safety profile. See Figure 1.

RESULTS

In total, 14 articles studied the role of tACS in patients with schizophrenia [41-54]. Out of 14 publications, 8 ar-

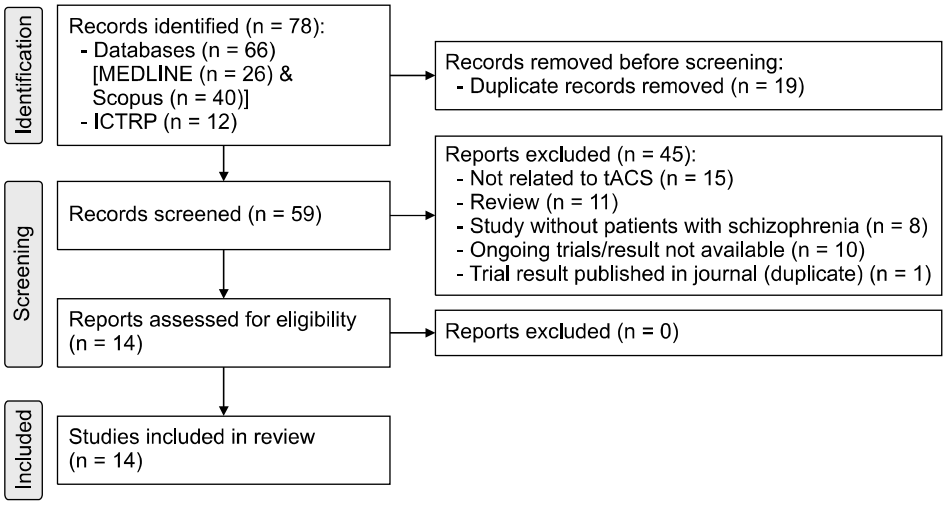

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Flow-chart. ICTRP, International Clinical Trials Registry Platform; tACS, transcranial alternating current stimulation.

ticles were clinical trials, including 4 double-blind, randomized controlled trials (RCT). Four case reports and 2 case series were also reported. The 2 RCTs [45,46] among these were of the same set of subjects evaluating the clinical and biological outcomes in separate articles. The findings are summarized in Table 1.

Sample profile: The number and the clinical profile of participants differed across the studies based on the design and objectives of the studies. The number of participants in the studies ranged from 1 [44,47,52] to 36 [53]. The participants included were diagnosed with schizophrenia. However, 4 studies also included participants diagnosed with schizoaffective disorder [43,45,46,53,54]. Most studies included a specific subgroup of schizophrenia targeting specific symptom domains, such as those having treatment-resistant negative symptoms [42,50], treatment-resistant delusions [48], treatment-resistant auditory hallucinations [45,46,52,54], or those with cognitive deficits [41,44,47]. But few studies seemed to have heterogeneous samples without specific symptom profiles.

Stimulation parameters: In studies investigating the effect of tACS on positive symptoms, 4 studies [45,46,52,54] examined the effect on auditory hallucinations. In these studies, an alternating current of 2 mA intensity and 10 Hz frequency (alpha frequency) was applied using electrodes (5 × 5 cm) at the left dorsolateral prefrontal cortex (DLPFC) and left TPJ with a reference electrode (5 × 7 cm) at the central region. While another study in patients with persistent delusions [48] applied electrodes (5 × 7 cm) at the medial prefrontal cortex and vertex region with alternating currents of similar intensity and frequency. All these studies administered alpha tACS for 20 minutes twice daily sessions for 5 days [45,46,48,52,54]. Few patients in one study were continued for 10 days [27], and 2 other studies evaluated the continuation therapy by administering a 40 minutes weekly session for up to 20 sessions [52, 54].

One RCT [53], 2 case series [42,49] and one case report [50] investigated the tACS effect on negative symptoms. All studies applied 2 mA alternating current over bilateral DLPFC except the RCT, wherein the frontoparietal area was stimulated. However, other parameters varied among the studies. The electrode size ranged from 25 cm^2 [42] to 35 cm^2 [49,50]. However, for the RCT, 2 sets of 4 electrodes of 1 cm^2 size in the left frontal and left parietal regions referenced to the frontoparietal midline electrodes were used. Theta frequency (4.5 Hz and 6 Hz respectively) alternating current was applied in one case series and RCT [42,53], while the other 2 studies [49,50] applied gamma frequency alternating current (40 Hz). The number and frequency of sessions varied from 10 sessions (once daily for 10 days) to 20 sessions (once daily for 20 days or twice daily for 10 days), with the duration of sessions ranging between 10−20 minutes.

The studies [41,43,44,47,51] investigating the effect of tACS on working memory applied the stimulation, using electrodes of 35 cm^2, mainly on the left DLPFC with the other electrode either on the left posterior parietal region or right supraorbital region. Theta frequency stimulation was applied in 2 studies, while gamma frequency stimulation was used in 3 studies [43,44,51]. Three studies piloted with single session tACS administration crossing-

Table 1. Studies using tACS in patients with schizophrenia

Study	Study design	Participants	tACS protocol						Outcome measures	Key findings
			No. of sessions	Duration of sessions	Current amplitude	Frequency	Electrode placement	State (during stimulation)		
Kallel *et al.* [42] (2016)	Case series	3 (clozapine-resistant negative symptoms of schizophrenia)	20 sessions (once daily for 4 consecutive weeks on weekdays)	20 min	2 mA	4.5 Hz (theta)	Left (F3) and right (F4) DLPFC	NA	SANS, PANSS, SUMD, HAMA	Reduction in negative symptoms (10%) on SANS, and general psychopathology symptoms (18%) on PANSS subscale. Improvement in insight (25%) on SUMD. Reduction in anxiety (29%) on HAMA.
Hoy *et al.* [43] (2016)	Single blinded randomized controlled trial	10 (schizophrenia or schizoaffective)	3 separate sessions (at least 72 hours apart)	20 min	2 mA	40 Hz tACS (gamma), tDCS or sham stimulation	Active/anode: Left (F3) DLPFC; reference/cathode-right supraorbital region. No offset configuration.	Working memory task (online) done in 2 blocks of 5 minutes	D-prime and accurate reaction time on working memory task (2-back test) done both pre-and post-stimulation as well as intrastimulation.	No significant change with tACS noted in either d-prime or accurate reaction time in both the conditions.
Sreeraj *et al.* [44] (2017)	Case report	1 (schizophrenia with cognitive deficits)	2 sessions (48 hours apart)	20 min	2 mA (1st session) 1 mA (2nd session)	6 Hz–theta tACS (1st session) & 40 Hz–gamma tACS (2nd session)	Left DLPFC (F3) and the left posterior parietal region (P3). Zero phase difference and no offset configuration.	Computerized Sternberg's task (online)	Accuracy on n-back test (0-,1-,2-) and dual 2-back test.	Improved performance (accuracy of responses) in task (1-, 2- & dual 2-back) with 6 Hz (theta) tACS, not with 40 Hz (gamma) tACS.
Mellin *et al.* [45] (2018)	Double-blind randomized controlled trial	22 (schizophrenia or schizoaffective with persistent auditory hallucination)	10 sessions (twice daily for 5 consecutive days)	20 min	2 mA	10 Hz (alpha), tDCS, or sham 10 Hz	Active/anode: Left DLPFC (between F3 & Fp1). Active/cathode: Left (TPJ) (between T3 & P3). Reference electrode over central region (Cz). Zero phase difference and no offset configuration.	Relaxed state, focussing on "ReefScapes" video during stimulation.	Primary: AHRS. Secondary: PANSS, BACS.	No significant improvement in AHRS noted. However, effect size was largest for tACS (1.31) compared to tDCS (1.06) and sham (0.17). For secondary outcomes, tDCS had larger effect size for improvement in PANSS & BACS score compared to tACS.

Table 1. Continued 1

Study	Study design	Participants	tACS protocol						Outcome measures	Key findings
			No. of sessions	Duration of sessions	Current amplitude	Frequency	Electrode placement	State (during stimulation)		
Ahn *et al.* [46] (2019)	Double-blind randomized controlled trial	Same set of subjects as mentioned above [45]	Same as the above mentioned protocol						Network oscillations during EEG (resting state & auditory task).	Enhancement of alpha power in left temporal region (not statistically significant). Also, 10 Hz tACS leads to enhancement in functional connectivity and 40 Hz ASSR. This enhancement correlated improvement in auditory hallucination.
Sreeraj *et al.* [47] (2019)	Case report	1 (schizophrenia with cognitive deficits)	5 sessions (1 session per day)	20 min	2 mA	Individualised theta frequency-6 Hz (IAF-5)	Left DLPFC (F3) and the left posterior parietal region (P3). Zero phase difference and no offset configuration.	Computerized Sternberg's task (online)	Computerized n-back (0-, 1-, & 2-back) test. cDSST and computerized emotion matching and labeling task.	Improvement in the accuracy of all task except emotional matching test. Reduction in the average reaction time in all task. Improvement in working memory and other cognitive domains with persistence of improvement for 50 days.
Shanbhag *et al.* [41] (2019)	Open-label study	11 (schizophrenia with cognitive deficits)	10 sessions (twice daily for 5 days)	20 min	2 mA	Individualised theta frequency (IAF-5)	Left DLPFC (F3) and the left posterior parietal region (P3).	Resting state	Computerized n-back test (0-, 1-, & 2-back) & cDSST	Significant improvement in working memory and processing speed as noted with improvement in accuracy of performance in n-back test and cDSST.
Sreeraj *et al.* [48] (2020)	Open-label non controlled clinical trial	12 (schizophrenia with persistent delusions)	Twice daily (3 hours apart) for 5 days. 8 patients continued for 5 more days, and another patient continued for 4 more days)	20 min	2 mA	10 Hz (alpha)	Electrodes on AFz (medial prefrontal cortex) and Cz. Zero phase difference and no offset configuration.	Wakeful resting state	PSYRATS: Delusions, SAPS, SANS	Significant improvement in delusion severity, positive and negative symptoms after 5th and 10th day of stimulation. Improvement persisted for 1 month in responder.

Table 1. Continued 2

Study	Study design	Participants	tACS protocol						Outcome measures	Key findings
			No. of sessions	Duration of sessions	Current amplitude	Frequency	Electrode placement	State (during stimulation)		
Haller *et al.* [49] (2020)	Case series	3 (persisting negative symptoms in schizophrenia)	Twice daily for 10 days (with 3 hours interval)	10 min	2 mA	40 Hz (gamma)	Bilateral DLPFC (F3 & F4). Zero phase difference and no offset configuration.	NA	PANSS, SANS, CDSS, RWT, TMT-A/B, PANAS, CGI	Improvement noted in negative symptoms, depression and cognitive symptoms with improvement in severity of illness.
Haller *et al.* [50] (2020)	Case report	2 (treatment-resistant schizophrenia with predominant negative and cognitive symptoms)	Once per day for 10 days (excluding weekends)	20 min	2 mA	40 Hz (gamma)	Bilateral DLPFC (F3 & F4). Zero phase difference and no offset configuration.	NA	PANSS, SANS, CDSS, RWT, TMT-A/B, CGI	Improvement noted in negative symptoms, and cognitive symptoms with improvement in severity of illness.
Papazova *et al.* [51] (2020)	Double-blind cross over study	15 (schizophrenia)	Single session of tACS and single session of sham tACS	20 min	2 mA	40 Hz (gamma)	Bilateral DLPFC (F3 & F4).	Working memory task (online)	Working memory during stimulation using n-back task (1- to 3-back). Primary outcome: Reaction time and d-prime	No significant improvement in working memory with tACS compared to sham tACS.
Force *et al.* [52] (2021)	Case report	1 (schizophrenia with persistent auditory hallucinations)	Once weekly for 20 weeks	40 min	2 mA	10 Hz	Left DLPFC (between F3 & Fp1) and the temporal parietal junction (between T3 & P3). Reference electrode over central region (Cz). Zero phase difference.	Wakeful resting state	AHRS, HPSVQ	Improvement with respect to duration and controllability of auditory hallucinations.

Table 1. Continued 3

Study	Study design	Participants	tACS protocol						Outcome measures	Key findings
			No. of sessions	Duration of sessions	Current amplitude	Frequency	Electrode placement	State (during stimulation)		
Chang *et al.* [53] (2021)	Double-blind, randomized, sham controlled trial	36 (schizophrenia or schizoaffective disorder)	Twice daily for 5 consecutive days	20 min	2 mA	6 Hz	Left frontoparietal area using two 4 × 1 electrodes (1 cm^2 area). Zero phase difference and no offset configuration.	During dual n-back task (online)	The primary outcome measure: Negative symptom subscale score of the PANSS Secondary outcome measures: PANSS total score, PANSS five-factor subscale score, PANSS 2-subdomain score of negative symptoms, SANS score, PSP score, abbreviated version SUMD score, the accuracy of the dual 2-back task, BCIS, SAIQ, SRG-PSP, SQLS-R4, & HRV (2 resting state indices [RR interval rest and HF-HRV rest] and 2 indices of reactivity to dual 2-back tasks [RR interval task-minus-rest and HF-HRV task-minus-rest])	Significant improvement in negative symptoms severity following tACS compared to sham. Significant reduction in PANSS total score, along with improvement in factor score for negative symptoms as well as cognitive symptoms. Improvement in PANSS social amotivation score & SANS score. Improvement in the accuracy of dual 2-back task was noted. PSP social useful activities & global scores, SRG-PSP social useful activities score, and self-certainty subscale score of BCIS showed improvement with tACS. All the HRV indices showed no significant between- group difference at baseline and postbaseline assessments.

Table 1. Continued 4

Study	Study design	Participants	tACS protocol						Outcome measures	Key findings
			No. of sessions	Duration of sessions	Current amplitude	Frequency	Electrode placement	State (during stimulation)		
Clinical-Trials.gov. [54] (2022)	Double-blind, randomized, sham controlled trial	25 (schizophrenia or schizoaffective disorder with persistent auditory hallucinations)	Twice daily sessions for 5 consecutive days followed by once weekly for 8 weeks (maintenance stimulation)	20 min/ 40 min double-blind, randomized, sham controlled trial	2 mA	10 Hz	Left DLPFC (between F3 & Fp1) and the temporal parietal junction (between T3 & P3). Reference electrode over central region (Cz).	Relaxed state, focussing on "ReefScapes" video during stimulation.	Primary: AHRS	No significant change in AHRS in acute or maintenance phase.

SANS, scale for the assessment of negative symptoms; PANSS, Positive and Negative Syndrome Scale; SUMD, Scale to Assess Unawareness of Mental Disorder; HAMA, Hamilton anxiety rating scale; DLPFC, dorsolateral prefrontal cortex; TPJ, temporoparietal junction; AHRS, Auditory Hallucination Rating Scale; BACS, Brief Assessment of Cognition in Schizophrenia; ASSR, auditory steady-state response; EEG, electroencephalography; cDSST, computerized digit symbol substitution test; PSYRATS, The Psychotic Symptom Rating Scales; SAPS, Scale for Assessment of Positive Symptoms; CDSS, Calgary Depression Rating Scale for Schizophrenia; RWT, Regensburg Word Fluency Test; TMT-A/B, Trail Making Test A and B; PANAS, Positive and Negative Affect Schedule; CGI, Clinical Global Impression; HPSVQ, Hamilton Program for Schizophrenia Voices Questionnaire; PSP, Personal and Social Performance scale; BCIS, Beck Cognitive Insight Scale; SAIQ, Self-Appraisal of Illness Questionnaire; SRG-PSP, self-reported version of the graphic personal and social performance scale; SQLS-R4, Schizophrenia Quality of Revision Four; HRV, heart-rate variability; HF, high frequency; NA, not available; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; IAF, individual alpha frequency.

over from theta-tACS to gamma-tACS, sham-tACS or tDCS stimulation on different days [43,44,51]. The 2 reports [41,47] of therapeutic applications involved the administration of 20 minutes sessions for 5 days (once/twice daily sessions).

All studies that reported phase differences between the electrodes had administered tACS in-phase (zero phase difference). At the same time, most studies had no mention of phase difference [42,43,51,54]. None of the studies on schizophrenia had used any DC offset (otDCS).

Five of the studies [43,44,47,51,53] involved the application of tACS while participants engaged in certain working memory tasks, including online n-back task, dual back task, and computerized digit symbol substitution task. These studies mostly looked at cognitive symptoms or negative symptoms as the primary outcome measure. In 2 of the studies [48,52] involving positive symptoms and 1 study [41] involving cognitive symptoms, participants were in a resting wakeful state. However, in 2 studies [45,54] with persistent auditory hallucinations, participants were in a relaxed state watching "reefscapes" videos.

Outcome and findings: tACS have shown promising results in patients with schizophrenia. In studies assessing effects on auditory hallucinations, a study [23] reported improvement in auditory hallucinations, which was later shown to be associated with enhancement of alpha oscillations, connectivity and auditory steady-state response (ASSR) in another paper [24]. Though this RCT had shown a good effect size in reducing hallucinations, the difference between sham stimulation or tDCS group could not be established, probably due to the small sample size. A case study [52], reported improvement in the duration and controllability of auditory hallucinations with weekly tACS, but this could not be replicated in the original RCT by the same group [33]. The open-labelled study targeting the medial prefrontal cortex [48] reported significant improvement in the severity of delusions with the persistence of improvement for at least a month following tACS.

With regards to negative symptoms of schizophrenia, one RCT [53], 2 case series [42,49], and a report [50] noted a reduction in negative symptoms as well as an improvement in cognitive symptoms. Though 2 studies [43, 51] reported no change in working memory with tACS, 3 other studies [41,44,47] reported improvement in working memory along with processing speed.

Adverse effects: Most studies used structured questionnaires to systematically assess the associated adverse effects [41,42,44,45,47-50,52-54]. Nine of the studies used standardised questionnaires to evaluate the adverse effects, and the other 2 used a comfort rating questionnaire [49,50]. The studies suggested good tolerance of tACS by schizophrenia patients, with a few reporting of mild and transient adverse effects like scalp pain, itching and burning sensations, tingling sensation, phosphenes, and increased depth of sleep. Additionally, diarrhoea and muscular pain were noted in one study in 2 participants [54]. Across all studies, approximately 1,180 sessions of tACS were administered with no reports of serious side effects or drop-outs due to intolerability.

DISCUSSION

tACS is a novel non-invasive technique that applies a low-intensity alternating current stimulation leading to modulation of the neuronal oscillations, which in turn affects the cortical processes [55]. Though the role of tACS in modulating cognitive processes has been known for the past decade, its use in psychiatric disorders, especially schizophrenia, began in the last 5 years. Here in this review, we have tried to summarize the protocols used and outcomes of tACS in patients with schizophrenia and it adds on to the earlier review on tACS [56]. There is a paucity of rigorous studies assessing the effects of tACS in patients with schizophrenia, with only 4 sham controlled trials [21,23,32,33] to date. Most of the published studies were either case reports, case series or open-labelled trials. All of these open-label studies showed promising results. In a case study [52], with weekly alpha tACS over left DLPFC and left TPJ reported improvement in auditory hallucinations. An open-labelled study reported significant improvement in delusions following alpha tACS targeting the medial prefrontal cortex [48]. A reduction in negative symptoms along with cognitive symptoms was noted in 2 case series [42,49], and a case report [50] was noted using theta tACS [42] and gamma tACS [49,50]. Moreover, 3 studies [41,44,47] reported improvement in working memory along with processing speed using theta tACS. For RCTs, except for one RCT, which used HD-tACS targeting working memory [53], all others could not demonstrate the superiority of tACS [43,45,54]. The RCT that targeted hallucinations in schizophrenia had a higher effect size with true tACS than the sham with respect to

improvement [45] and showed associated changes in neural oscillatory markers [46]. However, this clinical effect could not be replicated in a recent larger study [54]. The current findings do support the notion that abnormal neural oscillations are associated with symptoms of schizophrenia (Table 2) [21,26,29,31,32,57-63]. The positive symptoms are associated with dysfunctional alpha [57-59], gamma [21,57] and beta oscillations [57], negative symptoms mainly with gamma oscillations [21,57], and cognitive symptoms mainly with theta [32] and gamma oscillations [21,57]. As noted, targeting these abnormal oscillations may lead to the amelioration of symptoms associated with schizophrenia, thus suggesting a potential role of tACS in schizophrenia.

The stimulation parameters for tACS in patients with schizophrenia are still evolving compared to other neuromodulation modalities such as tDCS [64]. The studies in schizophrenia have generally used 2 mA peak-to-peak (−1 mA to +1 mA) intensity current and were found to be tolerable without major adverse effects. Tolerability acts as a decisive factor in determining the current intensity. As tACS involves the transcutaneous application of alternating current, it would become intolerable at higher intensities. A burning sensation is common above ± 1 mA with higher reporting of dizziness, phosphenes, and metallic taste [65]. Thus, balancing effectiveness and safety, a current amplitude of 2 mA is used as optimal stimulation intensity in schizophrenia.

Conventional conductible latex-rubber electrodes (25−35 cm^2) were applied in all except 1 study. These electrodes lack focality but have high tolerability, and the electric field distribution over the brain surface is simpler to predict. To further improve the current density and spatial focality of stimulation, a high-definition montage using multi-electrode configurations was devised for tDCS [66]. Recently high-definition montage has been applied in studies using tACS [13,67]. The only study that used smaller electrodes in schizophrenia had 2 sets of 4 ring-electrodes was designed to provide stimulation in frontoparietal regions with current directed towards each other. This distribution and direction of current flow in high-definition tACS [32] was demonstrated using computer simulation over the modelled brain from neuroimaging data. However, more studies investigating HD-tACS in schizophrenia would assist in exploring the neurobiological basis of schizophrenia. Though HD-tACS optimises the focality of stimulation, it may be less tolerable with a potential of higher current shunting due to decreased inter-electrode distance [65].

The electrodes, as noted in the studies, were in the same phase of the cycle of alternating current with zero phase difference between them leading to synchronization of neuronal activity in the targeted brain area in the studies. However, if electrodes are in the opposite phase, it can lead to desynchronisation [12,68] and the clinical /neurobiological effects of this desynchronisation would be of research interest.

Stimulation in the range of 10−20 minutes duration is required to produce after-effects following tACS [69]. Multiple sessions are known to enhance the plasticity, thereby bringing a longer-lasting effect. In studies investigating the effect of tDCS in schizophrenia, higher frequency (2 sessions per day) and a greater number of sessions (> 10 sessions) were associated with better outcomes [64]. Although currently, data is lacking, a similar result may be anticipated with tACS [12]. Thus, most studies

Table 2. Neural oscillations and symptoms of schizophrenia

Neural oscillations	Frequency range	Functions	Findings in schizophrenia
Theta	4−7 Hz	Memory, spatial navigation, modulation of synaptic plasticity, long-range synchronization across brain regions [57,60,61].	Reduced theta oscillation in frontal regions is associated with impairment in the working memory [32,57].
Alpha	8−12 Hz	Inhibitory control, attention, long-range synchronization across brain regions [31,57,58].	Reduced alpha oscillation associated with positive symptoms [26,57-59].
Beta	13−30 Hz	Motor control, gating, attention, perception, somatosensory processing [57,62].	Beta oscillation dysfunction associated with positive [57] and negative symptoms [29].
Gamma	30−200 Hz	Attention, cognition, memory, perception, movement, consciousness, synaptic plasticity, short-range synchronization across brain regions [57,63].	Reduced gamma oscillations are associated with negative and cognitive symptoms, whereas increased oscillations are associated with positive symptoms [21,57].

with the therapeutic application of tACS have used twice daily sessions. But the exact effects of session duration, number and frequency of sessions of tACS in schizophrenia need systematic evaluation.

Also, the effect of tACS is noted to be state-dependent [70] with effects known to be enhanced with the targeted region in an activated state. As noted, in most of the studies involving cognitive or negative symptoms wherein a working memory task (online) was performed during stimulation to activate the region of interest. However, in studies involving positive symptoms, the participants were mainly in a resting state, as the targeted region was already in an activated state. Thus, based on the symptom domain to be targeted, online or offline stimulation can be planned.

The tACS is well tolerated, with adverse effects being transient. The adverse effects could be linearly related to intensity and stimulus frequency [71]. However, no serious adverse effects have been reported in any single/multi-session tACS study in either healthy volunteers or patients. The common side effects in schizophrenia patients have been phosphene perception, dizziness, skin sensation, pressure perception and increased depth of sleep similar to that of healthy volunteers based studies [71,72]. The phosphene perception is commonly reported with anterior montages and at a higher frequency, while dizziness is associated with posterior montages. Higher frequency and intensity of stimulation may lead to skin sensations (burning and tingling). Phosphene experience can be minimised by watching videos on a television screen during stimulation [45], but it may affect the tACS effect, which may be brain state-dependent. None of the patients discontinued tACS secondary to the adverse side effects. Thus, in patients with schizophrenia, the application of tACS appears to be safe in the short-term, even with multiple sessions, though long-term safety needs further evaluation. The adverse effects were well-documented in the studies using structured adverse effect questionnaires. Given that tACS research is in its early phase, it is advisable to use structured questionnaires to assess the adverse side effects [72].

In summary, we can note that very few studies have assessed the effect of tACS in patients with schizophrenia. Most of the studies had sub-optimal evidence and smaller sample sizes. The studies were heterogeneous, using varied protocols and targeting different symptom domains of schizophrenia. As a result, no robust inference can be drawn regarding the clinical, biological or therapeutic effects of tACS in patients with schizophrenia. Further, it is unclear whether tACS can be used as a stand-alone therapeutic modality or as an add-on option to target residual symptoms. Also, most studies examined only the short-term tolerability of tACS in patients with schizophrenia.

Further research is needed with well-structured double-blind RCTs with a larger sample size to replicate the findings. Drug-naïve/drug-free patients could be recruited to rule out the effects of pharmacological treatment in investigative applications of tACS. Inter-individual variability in response to tACS may happen secondary to differences in neuroanatomy and resultant difference in the electric field inside the brain. Individualisation of stimulation protocol based on dysfunctional neuronal oscillation and neuroimaging-based computational modelling would be advisable. Also, to optimise the effect of tACS various methods have been investigated such as HD-tACS wherein by using smaller electrodes, more focal effects can be provided. Multi-site stimulation brings in complexity but also much scope to understand the neurobiology. Recent studies in healthy individuals using travelling wave tACS have immense potential for investigational and translational applications in schizophrenia [73].

Temporal interferential stimulation is a modification of tACS where high frequency-low amplitude waves are focused onto the deeper brain regions to provide stimulation with frequencies in the range of endogenous oscillations. Early experiments on safety and applicability in human subjects have been promising [74]. This would overcome the major drawback of the transcranial electrical stimulation related to the depth of penetration. We will be able to target the deep-seated brain regions enhancing the applicability of tACS in schizophrenia. Special waveforms of tACS such as amplitude-modulated tACS as described earlier could replicate the intrinsic interactions among different frequencies of neural oscillations and may provide evidence of neuropathology by direct manipulations. Intersectional short pulse stimulations are being attempted to enhance the tolerance to higher intensity of current targeting deeper brain regions. Here multi-electrode montage will be used but targeting a common specific brain region through short pulses of alternating currents administered from different electrodes sets placed at

multiple scalp locations shifting from one set to the other. Additionally, methods like transcranial electrical theta burst stimulation (te-TBS) is another promising development in this field and awaits application in neuropsychiatric conditions [75]. These advancements in the methods need to be investigated further to improve the effect of tACS. Additionally, clinical studies should target long-duration follow-ups to assess the long-term effects and safety of multi-session tACS.

CONCLUSION

tACS, a novel neuromodulation technique, modulates neuronal oscillations as well as causes long-term neuroplastic changes. It is a safe technique with minimal side effects. The initial studies have shown improvement in aberrant brain oscillations associated with schizophrenia with associated improvement in clinical symptoms. Though the current findings are promising, further studies are required to confirm these findings.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

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