Applications of Transcranial Alternating Current Stimulation at Different Frequencies in Psychiatric Disorders

Authors: Siyuan Zhang, Xuebing Li, Li Xuebing

Date: 2022-03-03T15:56:10+00:00

Abstract

In recent years, researchers have begun to apply transcranial alternating current stimulation (tACS) technology in the field of psychiatric disorders, among which γ and α frequencies have attracted the most attention. The potential mechanisms of tACS action in psychiatric disorders include two aspects: directly regulating abnormal brain neural activity and indirectly improving patients' cognitive functions. First, applying tACS at specific frequencies to target brain regions can modulate neural oscillations and brain functional connectivity at corresponding frequencies, thereby directly ameliorating patients' clinical symptoms by acting on disease-related abnormal brain activity. Second, rather than targeting brain activity specifically impaired in a particular disease, tACS is used to activate brain circuits related to cognitive functions, broadly enhancing various cognitive functions such as attention and memory in patients, thereby globally alleviating adverse symptoms.

Currently, there remain unresolved and worthy issues to explore in the field of using tACS to treat psychiatric disorders. Research on tACS mechanisms of action, improvement of stimulation parameters and paradigms, and technological upgrades can become key research directions in psychology, brain science, and clinical medicine.

Full Text

The Application of Different Frequencies of Transcranial Alternating Current Stimulation in Mental Disorders

ZHANG Siyuan[1,2], LI Xuebing[1,2]

[1]Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China

[2]University of Chinese Academy of Sciences, Beijing 100049, China

Abstract: In recent years, researchers have begun applying transcranial alternating current stimulation (tACS) to mental disorders, with gamma- and alpha-band frequencies receiving particular attention. The potential mechanisms through which tACS acts on mental disorders involve two aspects: directly modulating aberrant neural activity and indirectly improving patients' cognitive functions. First, applying tACS at specific frequencies to target brain regions can modulate corresponding neural oscillations and functional connectivity, thereby directly ameliorating clinical symptoms by acting on disease-related abnormal brain activity. Second, rather than targeting disease-specific impaired brain activity, tACS can activate brain circuits associated with cognitive functions to broadly enhance various cognitive abilities such as attention and memory, thereby alleviating symptoms overall.

Currently, several unresolved issues warrant discussion in the application of tACS to treat mental disorders. Research on tACS mechanisms, improvements in stimulation parameters and paradigms, and technological upgrades represent key directions for future investigation in psychology, neuroscience, and clinical medicine.

Keywords: transcranial alternating current stimulation; mental disorders; neural oscillations; cognitive function; intervention

Transcranial alternating current stimulation (tACS) is a non-invasive brain stimulation (NIBS) technique that delivers low-intensity alternating current at specific frequencies to target brain regions via scalp electrodes, thereby modulating cortical neural activity. Due to its non-invasive and safe characteristics, tACS holds broad application prospects in medicine and psychology.

Although tACS belongs to the family of transcranial electrical stimulation (tES) techniques, its mechanism of action differs from that of transcranial direct current stimulation (tDCS). Numerous empirical studies have demonstrated that tDCS can alter neuronal resting potentials, producing excitatory effects under the anode and inhibitory effects under the cathode (Chase et al., 2020; Woods et al., 2016). In contrast, tACS achieves different intervention effects primarily through alternating currents of varying frequencies. Additionally, tDCS studies have reported more side effects, including headache, burning sensations, and even hypomania and epilepsy (Matsumoto & Ugawa, 2016; Antal et al., 2017). These side effects have rarely appeared in existing tACS studies, with only a few subjects reporting transient adverse reactions such as scalp burning, mild tingling, or phosphenes (Matsumoto & Ugawa, 2016; Antal et al., 2017). Consequently, some researchers have shifted their interest toward the safer tACS approach.

Previous research has primarily focused on tACS effects in healthy individuals, revealing that tACS can enhance motor abilities (Joundi et al., 2012) and improve cognitive functions such as perception and memory (Strüber et al., 2014; Hoy et al., 2015). As exploration of this technology continues, researchers have begun investigating tACS applications in mental disorders, hoping it may become a potential therapeutic tool for modulating abnormal brain activity in psychiatric conditions. Currently, abnormal neural oscillations and functional connectivity can be observed in many mental disorders (Başar, 2013; Hinkley et al., 2011). Some tACS intervention results show that applying specific frequency tACS (e.g., 10Hz-tACS, 40Hz-tACS) can directly interact with brain oscillations, modulate abnormal oscillations, and induce normalization of defective inter-regional functional connectivity (Antal & Paulus, 2013; Clancy et al., 2018). This suggests that tACS may alleviate symptoms of various mental disorders through such interactions with brain oscillations, aiding disease treatment.

However, the application of tACS in mental disorders remains in the exploratory stage. Although studies have found that stimulating aberrant brain regions in patients with schizophrenia, depression, and obsessive-compulsive disorder using different tACS frequencies can effectively alleviate symptoms (Haller, Senner, et al., 2020; Sreeraj et al., 2020; Klimke et al., 2016), the results have low reproducibility and remain difficult to apply clinically due to limited clinical trials and non-standardized treatment protocols. On one hand, more clinical trials are needed to demonstrate tACS efficacy; on the other hand, mechanism research is needed to guide clinical trials. Elucidating tACS mechanisms of action will facilitate more targeted treatment protocol development, establishment of unified treatment manuals, and translation of clinical trial findings into application and dissemination. Therefore, mechanistic investigation of tACS intervention in mental disorders is particularly important and necessary.

This article reviewed 21 studies on tACS and mental disorders published on PubMed through July 2021, using keywords including "tACS," "transcranial alternating current stimulation," and mental disorder terms such as "depression," "anxiety," "schizophrenia," "ADHD," and "dementia." We aim to review the application of different tACS frequencies in mental disorders and discuss the unique features and innovations of alternating current stimulation. Given that the mechanisms of tACS intervention in mental disorders remain unclear, this article will also discuss possible mechanisms based on current clinical trial status and findings from tACS studies in healthy subjects, hoping to provide ideas for mechanistic research in this field. Additionally, we will outline unresolved issues in the tACS field and recent technological developments to provide references for researchers planning to use tACS.

2. Applications of Different Frequency tACS in Mental Disorders

2.1 Applications of γ-tACS

Unlike tDCS, which uses anodal and cathodal interventions, achieving different effects through different current frequencies is the most important characteristic of tACS. Currently, γ-tACS is most frequently applied in mental disorders.

Gamma-band (approximately 30Hz-80Hz) brain activity is primarily involved in cognitive functions, and abnormal γ activity is commonly observed across various mental disorders (Fitzgerald & Watson, 2018; Farzan et al., 2010; Herrmann & Demiralp, 2005). γ-tACS mainly targets cognitive impairment in mental disorders by stimulating aberrant brain regions, demonstrating significant beneficial effects in schizophrenia, depression, and dementia.

Schizophrenia includes positive symptoms (e.g., hallucinations, delusions), negative symptoms, and cognitive deficits, with negative symptoms and cognitive decline often being refractory to pharmacological treatment (Lally et al., 2016) and severely impairing patients' quality of life. Cognitive impairment in schizophrenia involves multiple levels from gene expression to brain networks (Millan et al., 2012), with patients typically showing reduced activation in the dorsolateral prefrontal cortex (DLPFC) (prefrontal dysfunction) (McGuire et al., 2008; Minzenberg et al., 2009). Lack of γ oscillation inhibition in DLPFC is considered an important cause of common symptoms in schizophrenia (Farzan et al., 2010; Dobbs, 2010). Case reports have documented that 10 days of bilateral DLPFC 40Hz-tACS (20 sessions total) improved cognitive functions including visual attention and verbal fluency, as well as depressive mood, in schizophrenia patients with negative symptoms (Haller, Hasan, Padberg, Brunelin, et al., 2020; Haller, Hasan, Padberg, Valiengo, et al., 2020). The authors suggested that repeated γ-tACS could modulate prefrontal oscillations, thereby improving negative symptoms in schizophrenia. However, another study found that three sessions of 40Hz-tACS targeting left DLPFC did not improve working memory in schizophrenia patients (Hoy et al., 2016), while the same protocol significantly improved working memory in healthy subjects (Hoy et al., 2015). The authors proposed that tACS may be unable to induce neural oscillations when patients lack the capacity to generate or modulate endogenous oscillations.

γ-tACS has also been applied in the treatment and diagnosis of dementia, which is directly related to cognitive impairment. Recent research found that combining left DLPFC 40Hz-tACS with brain training significantly improved memory in mild cognitive impairment (MCI) patients, with tACS-treated patients maintaining cognitive improvements longer than those receiving brain training alone (Kehler et al., 2020). Beyond clinical treatment, Naro et al. (2016) proposed that γ-tACS could assist in diagnosing MCI and Alzheimer' s disease (AD). AD is characterized by progressive cognitive decline (Cornutiu, 2015), severely affecting patients' quality of life, making early identification of at-risk patients crucial. However, current diagnostic methods are complex and often cannot directly differentiate MCI, AD, and MCI patients who may convert to AD (Hugo & Ganguli, 2014; Bertè et al., 2014). Research shows that AD patients exhibit abnormal γ oscillations compared to MCI patients (Babiloni et al., 2013; Herrmann & Demiralp, 2005), with different degrees of impairment in long-range cortico-thalamo-cortical networks between AD and MCI patients (Babiloni et al., 2016). Naro et al. (2016) found that after dorsomedial prefrontal cortex (DMPFC) γ-tACS, EEG results showed significant γ oscillation increases in healthy subjects and some MCI patients, while AD patients and a few MCI patients showed no significant changes. Notably, those MCI patients without changes developed AD within two years. These results suggest that AD patients may completely lack the ability to modulate γ oscillations, and γ-tACS could serve as an effective auxiliary diagnostic method to differentiate MCI from AD and predict AD conversion.

In addition to improving cognitive abilities, γ-tACS also demonstrates emotional benefits. Recent studies have examined bilateral prefrontal cortex γ-tACS for major depressive disorder (MDD) treatment. Repeated 40Hz-tACS improved depressive symptoms and cognitive task performance (Haller, Senner, et al., 2020). The authors suggested that γ-tACS may simultaneously induce changes in other neural oscillations, such as emotion-related α oscillations, and alter cortical neuroplasticity with repeated use (Tavakoli & Yun, 2017), thereby improving clinical symptoms in depression patients. Furthermore, Wilkening et al. (2019) first applied γ-tACS to a pregnant woman with depression. The patient received nine sessions of bilateral DLPFC 40Hz stimulation and reported symptom relief and improved cognitive functions including memory during treatment and up to three months post-treatment. Depression is the most common mental disorder during pregnancy, and many women avoid pharmacological treatment due to fear of teratogenic side effects (Kurzeck et al., 2018; Ross et al., 2013). This case report suggests γ-tACS may become a safe and effective treatment for depression during pregnancy.

γ-tACS has also been applied in obsessive-compulsive disorder (OCD) treatment. OCD is characterized by recurrent intrusive thoughts and impulses, with individuals engaging in repetitive thoughts or behaviors to reduce anxiety. Research indicates that OCD patients exhibit hypoactive DLPFC, difficulty controlling neuronal activity in the striatum and thalamus, leading to imbalanced activity in DLPFC-orbitalfrontal cortex (OFC) circuits and causing OCD symptoms (Nakao et al., 2014). Klimke et al. (2016) applied fronto-temporal 40Hz-tACS to seven OCD patients unresponsive to cognitive behavioral therapy (CBT), with all patients showing significant symptom improvement after several treatment sessions. This clinical result suggests γ-tACS may induce γ activity in DLPFC while reducing hyperactive OFC activity associated with anxiety.

Overall, applying γ-tACS to abnormal γ activity in schizophrenia, Alzheimer's disease, and other mental disorders may help restore normal γ oscillations and improve cognitive functions such as working memory. γ-tACS may also indirectly induce other frequency band activities, such as emotion-related α oscillations in depression treatment, demonstrating emotional benefits like reduced depression and anxiety. However, not all γ-tACS effectively alleviates cognitive impairment; for example, early AD patients show no response to γ-tACS. This may relate to patients' capacity for γ oscillation modulation—tACS may not enhance brain activity in patients who lack or have completely lost this ability. Whether γ-tACS can modulate other frequency oscillations and whether its effects are influenced by disease severity are important questions for future mechanistic and therapeutic research.

2.2 Applications of α-tACS

Alpha oscillations are the most prominent rhythmic activity in the human brain during resting wakefulness. Typically, α oscillations (approximately 8Hz-12Hz) originate from thalamo-cortical networks (Hughes & Crunelli, 2005; Bollimunta et al., 2011), exerting inhibitory effects on various cognitive processes including attention and perception (Foxe & Snyder, 2011; Klimesch, 2012) and influencing communication between long-range resting-state networks (RSNs), particularly the default mode network (DMN) and salience network (SN) associated with emotion, arousal processes, and mood disorders (Mantini et al., 2007; Mo et al., 2013). Currently, α-tACS has been applied in clinical trials for various mental disorders related to perceptual impairment and emotional abnormalities by modulating aberrant α oscillations and network connectivity.

α-tACS can alleviate positive symptoms such as auditory hallucinations and delusions in schizophrenia. Research has found that schizophrenia is directly associated with reduced α oscillations (Omori et al., 1995), with weakened functional connectivity between frontal and temporal lobes during resting state (Hinkley et al., 2011). Patients with auditory hallucinations show abnormal temporo-parietal junction (TPJ) and DLPFC activity (Vercammen et al., 2010; Lawrie et al., 2002), while delusions may result from impaired frontal α oscillations leading to hyperactive DMPFC (Lariviere et al., 2017; Jia et al., 2019). Mellin et al. (2018) found that 10Hz-tACS applied to left DLPFC and TPJ reduced auditory hallucination symptoms. High-density EEG showed enhanced α oscillations and α-band modulated functional connectivity in frontoparietal networks (Ahn et al., 2019). Force et al. (2021) similarly applied 10Hz-tACS to left DLPFC and TPJ for 20 weeks, with the patient reporting reduced hallucination duration, improved controllability over hallucinations, and positive cognitive effects starting from week nine. Sreeraj et al. (2020) applied 10Hz-tACS to DMPFC, demonstrating that α-tACS could reduce delusional symptoms while also improving other positive symptoms like auditory hallucinations and negative symptoms. These results suggest α-tACS may improve positive symptoms in schizophrenia by modulating abnormal α oscillations and brain network connectivity.

α-tACS has also been applied in clinical trials for MDD and anxiety reduction. MDD patients typically show higher α oscillations in left frontal regions, with left-right α asymmetry reflecting reduced neuronal activity in left DLPFC and weakened emotional processing capacity (Leuchter et al., 2012). Alexander et al. (2019) applied 10Hz-tACS to bilateral frontal regions in MDD patients, finding significantly reduced α oscillations in left prefrontal regions. At two-week follow-up, tACS-treated patients showed lower depression levels compared to 40Hz-tACS and sham stimulation groups. Following the main experiment, one patient from the 10Hz-tACS group continued with 40-minute weekly tACS sessions for 12 weeks at the patient's request. After completing 12 weeks of stimulation, the patient achieved remission, reporting good and lasting treatment effects for two weeks, but complete relapse at six weeks post-treatment (Riddlea et al., 2020). This suggests weekly bilateral frontal 10Hz-tACS may become an effective treatment for depressive symptoms, being more manageable and feasible than daily stimulation. Additionally, Clancy et al. (2018) examined α-tACS effects on anxiety in healthy subjects using anxiety induction. They found that occipitoparietal α-tACS persistently enhanced α-band connectivity from occipital to frontal regions, with this connectivity enhancement accompanying reduced anxiety induction. This study indicates tACS may have the capacity to induce plasticity in long-range brain connections, which would benefit treatment of mental disorders with abnormal functional connectivity, such as post-traumatic stress disorder (PTSD) (Sripada et al., 2012; Clancy et al., 2017).

α-tACS can enhance not only local α-band activity but also brain functional connectivity. Applying α-tACS to various diseases closely related to abnormal α oscillations and functional connectivity represents a feasible new clinical treatment approach. However, whether α-tACS-induced functional connectivity changes have long-term benefits remains unresolved. Some studies report enhanced α-band functional connectivity 24 hours post-stimulation (Clancy et al., 2018), while others report complete symptom relapse after stimulation cessation (Riddlea et al., 2020). Therefore, investigating the scope of α-tACS effects using neuroimaging techniques and examining whether tACS can induce functional connectivity plasticity are important future research directions.

2.3 Applications of Other tACS Frequencies

In addition to the common γ and α stimulation frequencies, a few studies have used and δ band alternating currents for therapeutic stimulation. Some research has also attempted using higher current intensity of 15mA. This section briefly introduces these studies.

Neuroimaging findings suggest that schizophrenia negative symptoms may relate to abnormal functional connectivity among prefrontal cortex, ventral tegmental area, and hippocampus (Sanfilipo et al., 2000; Tregellas et al., 2014), with these connections modulated by oscillations (approximately 4.5Hz) (Fujisawa & Buzsáki, 2011). In a case report using tACS for clozapine-resistant schizophrenia, researchers placed electrodes on bilateral DLPFC and applied 4.5Hz-tACS for 20-minute sessions across 20 treatment courses. Results showed improved negative symptoms and reduced confusion post-treatment (Kallel et al., 2016). Similarly, in cognitive enhancement treatment for mental disorders, Sreeraj et al. applied -tACS while subjects performed n-back and facial emotion recognition tasks. Results showed -tACS improved working memory, attention, processing speed, and emotion processing, with effects persisting 50 days post-treatment (Sreeraj et al., 2019). Another researcher applied one session each of -tACS and γ-tACS to a paranoid schizophrenia patient, with electrodes placed on left DLPFC and left posterior parietal region while patients completed cognitive tasks during stimulation. Only -tACS improved working memory, while γ-tACS showed no significant change (Sreeraj et al., 2017). This finding that -tACS improves cognition while γ-tACS does not aligns with Kallel et al. (2016)

and Hoy et al. (2016).

Additionally, one study used tACS to modulate P300 amplitude in attention deficit hyperactivity disorder (ADHD). Compared to healthy individuals, ADHD patients show reduced P300 during Oddball and similar cognitive tasks (Hasler et al., 2016; Itagaki et al., 2011). If event-related potential (ERP) components are considered part of event-related oscillations (EROs), P300 corresponds to δ and frequency oscillations (Herrmann et al., 2014; Başar-Eroglu et al., 1992). Dallmer-Zerbe et al. (2020) applied tACS coinciding with P300 oscillation peaks in ADHD patients, finding increased P300 amplitude and better task performance in the stimulation group compared to sham.

Furthermore, domestic researchers have used 15mA, 77.5Hz-tACS to treat MDD and chronic insomnia. tACS is typically a low-frequency, low-current transcranial electrical stimulation method with applied currents around 1-2mA. As this is the first use of high-intensity current in mental disorder treatment and does not conform to the general definition of tACS, it is introduced in this "Other tACS" section. Previous studies have shown that 77.5Hz-tACS over prefrontal cortex and bilateral mastoids may increase concentrations of β-endorphins and other neurotransmitters such as serotonin in cerebrospinal fluid and hypothalamus-related brain regions (Zaghi et al., 2010; Lebedev et al., 2002). Serotonin is an important neurotransmitter affecting depression (Porter et al., 2004) and also influences chronic insomnia (Riemann et al., 2015; Morin & Benca, 2012). Wang et al. (2020) used prefrontal and bilateral mastoid 77.5Hz-tACS in MDD patients, finding immediate depression reduction compared to non-tACS groups. Although depression levels rebounded somewhat after tACS cessation, antidepressant effects were maintained up to four weeks post-treatment. Using the same protocol for chronic primary insomnia patients, results showed significant symptom relief at post-treatment and four-week follow-up, with significantly higher remission rates than the sham stimulation group (Wang et al., 2020). These results indicate that 15mA, 77.5Hz-tACS can effectively and safely alleviate MDD and chronic insomnia, and this stimulation protocol may be applicable to mental disorders related to abnormal neurochemical concentrations.

3. Mechanistic Discussion of tACS Effects

Currently, the mechanisms through which tACS acts on mental disorders remain unclear. Exploring potential mechanisms will provide references for clinical applications. One possible mechanism is the direct modulation of abnormal neural activity to alleviate mental disorder symptoms. As described above, many mental disorder symptoms relate to abnormal brain activity—for example, auditory hallucinations in schizophrenia relate to abnormal TPJ and DLPFC activity, while delusions relate to abnormal frontal α oscillations. Applying α-tACS to these abnormal brain regions can directly modulate aberrant oscillations and connectivity, reducing symptom occurrence. Additionally, tACS demonstrates cognitive benefits. Many studies have found tACS can enhance memory

(Sreeraj et al., 2017; Kehler et al., 2020), improve attention (Dallmer-Zerbe et al., 2020; Wilkening et al., 2019), and reduce negative emotions (Sreeraj et al., 2020; Sreeraj et al., 2019). Previous intervention studies in mental disorders have shown that cognitive training such as working memory training (Pan & Li, 2017) and mindfulness (Bulzacka et al., 2018) produce good effects. tACS may possess cognitive benefits similar to cognitive training, improving disease symptoms by enhancing patients' cognitive functions. A few studies also suggest high-intensity tACS can promote release of neurotransmitters such as serotonin and endorphins as a possible symptom relief mechanism. However, evidence for tACS promoting neurotransmitter release is insufficient, so this section focuses on detailed discussion of the first two mechanisms and related issues.

3.1 Modulating Brain Neural Activity

One possible mechanism of tACS intervention in mental disorders is directly inducing restoration of abnormal neural oscillations and brain functional network connectivity, thereby improving clinical symptoms.

Neural oscillations are rhythmic or repetitive neural activities that exist throughout the nervous system (Koepsell et al., 2010; Zhang, 2011), regulating long-range communication between cortical and subcortical regions (Buzsáki & Draguhn, 2004). Among them, α oscillations are the most prominent neural oscillations during resting wakefulness, typically generated in thalamo-cortical networks (Hughes & Crunelli, 2005; Bollimunta et al., 2011) and spreading to frontal regions. Research shows schizophrenia is directly associated with reduced α oscillations (Omori et al., 1995), while depression patients show higher frontal α oscillations with left-right asymmetry (Leuchter et al., 2012). γ oscillations relate to transient connectivity in information processing (Colgin et al., 2009), primarily generated in inhibitory interneuron networks. Abnormal γ oscillations mainly relate to cognitive impairment in mental disorder patients, with severe γ oscillation abnormalities in AD patients (Babiloni et al., 2013; Herrmann & Demiralp, 2005). In schizophrenia, DLPFC lacks inhibition of γ oscillations, with aberrantly active γ oscillations causing cognitive impairment and other common symptoms (Farzan et al., 2010; Dobbs, 2010).

α-tACS and γ-tACS targeting prefrontal regions have achieved good results. Ahn et al. (2019) EEG results showed that 10Hz-tACS applied to DLPFC and TPJ in schizophrenia patients enhanced α oscillations and α-band modulated functional connectivity. Alexander et al. (2019) found that 10Hz-tACS applied to bilateral frontal regions in depression patients significantly reduced left frontal α activity. Naro et al. (2016) found that some MCI patients and healthy subjects showed enhanced γ activity after 40Hz-tACS. These results demonstrate that applying tACS at frequencies corresponding to abnormal oscillations to impaired brain regions can directly induce restoration of abnormal oscillations and functional connectivity.

Some studies have also targeted   oscillations.   oscillations relate to conflict processing and inhibitory control, with enhanced activity observed in various conflict tasks. oscillations originate from dorsal anterior cingulate cortex (dACC) covered by medial prefrontal cortex (mPFC), thus also called frontal midline theta (FMT). Unlike α and γ oscillations that directly target prefrontal cortex, oscillations originate from deeper locations, raising questions about whether scalp electrical stimulation can affect deeper structures like ACC. Current studies primarily use indirect frontal targeting of ACC, with some targeting DLPFC (Lehr et al., 2019) and more stimulating the frontal midline region (van Driel et al., 2015; Fusco et al., 2020; 2018). Klírová et al. (2021) found that -tACS applied to mPFC could target ACC activity through mPFC, enhancing dACC activity and improving Stroop task performance. Therefore, frontal -tACS is applicable to various mental disorders related to abnormal dACC activity, such as schizophrenia with reduced ACC activity (Carter et al., 2001) and OCD with higher ACC activity (Fitzgerald et al., 2005). Additionally, frontal -tACS can alter emotional evaluation processes (Onoda et al., 2017) or make subjects feel calmer (Klírová et al., 2021), possibly related to ACC integration functions. Current theory suggests dACC influences cognitive activity while rostral ACC (rACC) is closely related to emotional processing (Bush et al., 2000). Thus, future research could explore -tACS for mental disorders with emotional abnormalities due to ACC dysfunction.

These studies using various frequencies show that tACS can affect not only local brain regions but also induce inter-regional functional connectivity. For example, α-tACS studies found enhanced α-band functional connectivity after stimulation (Ahn et al., 2019), and -tACS targeting mPFC enhanced mPFC-ACC circuits (Klírová et al., 2021). These findings indicate tACS can target abnormal brain connections while also affecting other normal brain activities through diffusion. Visual phosphenes are the most commonly reported adverse effect in tACS experiments, possibly because substantial current shunts through the skin to the eyes, affecting retinal cells or optic nerves (Kar & Krekelberg, 2012). However, no controlled experiments have excluded tACS effects on other specific cortical activities (Woods et al., 2016). This suggests that tACS current targeting specific brain regions may also transmit through scalp and cortex to affect other normal brain activities. How to precisely target abnormal brain regions without affecting normal activity is an important question for discussion.

Notably, current research primarily focuses on immediate modulation effects of tACS on abnormal brain activity during or immediately after stimulation. Although some clinical trials have used 4-week or longer follow-ups to investigate symptom relief, few studies have examined long-term changes in brain activity. Whether tACS modulation of abnormal brain regions has long-term benefits and whether tACS can induce brain plasticity are important questions. This relates to control of tACS dosage and treatment courses, as well as feasibility and economy of incorporating tACS into daily treatment. Some studies found that depression patients showed sustained improvement in depressive symptoms and cognitive levels for weeks or months after tACS treatment (Wilkening et al., 2019; Alexander et al., 2019; Wang et al., 2020), and schizophrenia patients receiving -tACS showed persistent improvements in attention and working memory 50 days post-treatment (Sreeraj et al., 2019). These results suggest tACS may change brain structure or function, producing long-term intervention effects. However, other studies found tACS treatment effects may rebound over time, with some patients experiencing complete symptom relapse (Wang et al., 2020; Riddlea et al., 2020). Currently, only Clancy et al. (2018) found enhanced α-band functional connectivity persisted 24 hours post-stimulation, while local α activity enhancement disappeared, suggesting tACS may have the capacity for long-term brain activity changes. Future studies using neuroimaging techniques are needed to clearly and intuitively observe whether tACS-induced brain activity changes can persist for weeks or longer post-treatment, exploring tACS long-term benefits.

3.2 Improving Cognitive Function

Many tACS experiments in healthy subjects demonstrate cognitive benefits that also exist in mental disorder interventions. Another possible mechanism of tACS intervention in mental disorders is indirectly alleviating psychiatric symptoms by improving cognitive functions such as memory and attention.

Memory improvement is an important indicator of tACS intervention. Many experiments incorporate memory tasks like n-back to examine tACS cognitive benefits in memory. Sreeraj et al. found -tACS could improve 2-back performance in schizophrenia patients while γ-tACS could not (Sreeraj et al., 2019; 2017). Hoy et al. found γ-tACS improved working memory in healthy subjects but not in schizophrenia patients (Hoy et al., 2015; 2016). Haller, Senner et al. (2020) found γ-tACS improved n-back task performance in depression patients. Other studies using Wechsler Memory Scale (WMS-IV) and verbal Digit Span forward tests found γ-tACS improved memory in dementia patients (Naro et al., 2016; Kehler et al., 2020). These studies demonstrate that selecting appropriate tACS frequencies for different diseases can improve memory.

Some studies have also examined tACS effects on other cognitive abilities like attention. Researchers used Trail Making Test A and B (TMT-A/B) (Haller, Hasan, Padberg, Brunelin, et al., 2020; Haller, Senner, et al., 2020; Wilkening et al., 2019), visual oddball tasks (Dallmer-Zerbe et al., 2020) to examine attention changes, and Regensburg Word Fluency Test (RWT) (Haller, Hasan, Padberg, Brunelin, et al., 2020; Haller, Senner, et al., 2020), emotion matching and labeling tasks to measure social cognition. Results show tACS can significantly improve attention, language communication, and various cognitive functions.

Previous research found that cognitive training improving attention, memory, and problem-solving can not only directly enhance target abilities but also improve other related abilities, thereby overall alleviating clinical symptoms. For example, anhedonia is a typical negative symptom of schizophrenia. Li et al. found that working memory training could not only improve working memory performance but also enhance hedonic processing and reward sensitivity (Li et al., 2016). Mindfulness-based interventions (MBI), which primarily train attention maintenance, can affect practitioners' learning and memory (Mrazek et al., 2013; Konjedi & Maleeh, 2020; Youngs et al., 2021) and effectively regulate emotional responses in depression and anxiety patients (Bulzacka et al., 2018). Neuroimaging results show that schizophrenia patients receiving working memory training exhibit enhanced neural network activity in DLPFC and anterior cingulate cortex related to working memory (Subramaniam et al., 2012), with enhanced medial prefrontal cortex activity associated with sustained improvement in psychosocial function and working memory performance (Subramaniam et al., 2014). Healthy subjects show activity changes in parietal and DLPFC regions (Lawlor-Savage & Goghari, 2014). ERP results show that high-anxiety individuals receiving working memory training show significantly reduced P3 amplitude in negative face Stroop tasks, closely related to reduced negative attention bias (Pan et al., 2020). These findings demonstrate that working memory training can change brain regions closely related to memory, attention, and emotion, producing multiple cognitive benefits including memory enhancement and anxiety reduction.

Similarly, tACS studies also show these brain activity changes, which are not disease-specific—cognitive benefits of tACS can also be observed in healthy individuals. For example, bilateral parietal and right frontoparietal -tACS can reduce resting-state oscillations and decrease P3 latency in n-back tasks (reflecting faster item matching speed) (Pahor & Jaušovec, 2018). -tACS targeting DLPFC can reduce functional connectivity of brain networks closely related to cognitive function like DMN during working memory tasks (Abellaneda-Pérez et al., 2020). Prefrontal α-tACS can enhance whole-brain α oscillations and frontoparietal attention network activity, significantly increasing P2 and P3 amplitudes in emotional face tasks, thereby improving early and late emotional attention levels to modify negative emotional cognitive bias and enhance emotional processing capacity (Hu et al., 2021). It can be speculated that, analogous to other cognitive training, some tACS does not target disease-specific impaired brain activity but broadly improves multiple cognitive functions by activating or inhibiting brain circuits related to memory, attention, and emotion, thereby overall alleviating symptoms.

4. Issues and Prospects

Current research on tACS treatment for mental disorders is limited, primarily consisting of case reports. To explore tACS therapeutic effects and mechanisms, larger sample sizes and more randomized controlled double-blind experiments are needed. Additionally, both tACS research and the technology itself are under exploration and development. This section introduces and discusses unresolved issues in the tACS field and different tACS technologies, which will help achieve clearer understanding of tACS.

First, tACS stimulation parameter settings are not standardized. As seen in the studies reviewed here, different research has used different frequencies, durations, and treatment courses. Regarding stimulation frequency, some researchers use fixed frequencies like 10Hz or 40Hz for all subjects, while others collect individual oscillation frequencies as personalized stimulation frequencies—for example, Clancy et al. (2018) used each subject' s peak α frequency during eyes-open resting state as the stimulation frequency, and Sreeraj et al. (2019) used individual α peak frequency minus 5Hz as the stimulation frequency. Some researchers use variable frequencies, such as Naro et al. (2016) who applied stimulation at 20Hz intervals across 40-120Hz. Regarding treatment protocols, different studies have inconsistent session durations and total treatment courses, particularly in daily stimulation frequency and session length. Haller, Senner et al. (2020) found that twice-daily 10-minute tACS was more effective than once-daily 20-minute tACS for MDD treatment. However, no other studies have compared different stimulation protocols, representing a possible future research focus. Meanwhile, as tACS research expands, standardized stimulation protocols need to be developed based on empirical study designs and results to provide references for clinical trials and treatment.

Second, current tACS experiments use different paradigms, mainly differing in whether subjects are at rest during stimulation. Notably, most intervention studies only require subjects to watch a screen or view task-unrelated videos during stimulation, using pre-post measurement methods to evaluate stimulation effects—that is, measurement or tasks are separate from electrical stimulation. However, some studies have used "online" tACS (Sreeraj et al., 2019; Hoy et al., 2016). Online tACS requires subjects to complete tasks simultaneously with stimulation. Some research suggests tACS effects depend on brain state, with enhanced effects when target brain regions are activated (Feurra et al., 2013). α oscillations dominate during resting state, while , γ and other band activities can be observed during task execution (Klimesch, 1999; Burgess & Ali, 2002). Therefore, applying γ and other frequencies closely related to cognitive activity while requiring subjects to complete cognitive tasks simultaneously may achieve better therapeutic effects. Since few studies have used online tACS, comparative analysis of its effectiveness and use of various neuroimaging techniques to observe whether online tACS produces greater activation are noteworthy issues.

Additionally, as a technology-dependent intervention, attention to technological development itself is important. Current device development primarily focuses on improving stimulation precision, with researchers beginning to use high-definition tACS (HD-tACS) technology. HD-tACS belongs to the high-definition transcranial electrical stimulation (HD-tES) family and has been applied in tACS research (Deng et al., 2019; Meier et al., 2019; Ghafoor et al., 2021). Traditional tACS uses 25-35cm^2 sponge electrodes based on the international 10-20 EEG electrode positioning system, which has difficulty precisely localizing deep brain structures and may affect structures surrounding and connected to target regions. HD-tACS uses multiple electrodes, establishes computational models of electric field distribution in brain regions, and applies personalized multi-electrode stimulation based on structural neuroimaging to precisely target brain tissues with different conductivities (Alam et al., 2016).

Research shows that multi-electrode stimulation achieving greater current density can penetrate deeper brain structures, making electrical stimulation more directional and focused (Fernández-Corazza et al., 2016; Dmochowski et al., 2011). Studies have found HD-tACS superior to conventional tACS in inducing brain activity changes (Klírová et al., 2021). Using HD-tACS will help more precisely target abnormal brain activity in mental disorder patients without affecting other normal brain regions and can be used to intervene in deeper brain regions such as ACC closely related to cognition and emotion.

Simultaneous EEG recording during tACS application is another important issue. Since applied current creates substantial high-frequency, nonlinear artifacts that obscure low-frequency EEG activity, researchers typically cannot observe brain activity changes during stimulation and must rely on pre-post EEG measurements to assess tACS effects on EEG activity. However, delayed recording has many shortcomings, and recording brain activity during stimulation can more directly reflect immediate tACS effects and clearly observe its mechanisms. Therefore, algorithmic removal of current artifacts is crucial. Regarding tACS artifact removal techniques, Kasten and Herrmann (2019) have provided detailed reviews of existing methods, theories, and limitations. Recently, researchers have also proposed applying machine learning to artifact removal (Kohli & Casson, 2020). Attention to and application of these methods will help better understand tACS mechanisms.

Additionally, based on the concept of simultaneous EEG recording, Boyle and Fröhlich (2013) first proposed feedback-controlled tACS to regulate cortical activity. Feedback-controlled tACS is a brain stimulation system that monitors EEG signals in real-time, dynamically adjusts and optimizes stimulation frequency, amplitude, and duration through adaptive control optimization algorithms, and evaluates stimulation effects to further adjust parameters until abnormal EEG returns to normal (Zhang, 2021). This approach not only more intuitively observes tACS effects at the brain activity level but also more effectively and personally optimizes stimulation protocols for different individuals. Using EEG feedback-controlled tACS, Boyle and Fröhlich (2013) found that parieto-occipital EEG feedback-controlled 40Hz-tACS better controlled α oscillations in visual cortex than randomly applied 40Hz-tACS. Recently, Zhang (2021) also found this system could significantly increase α-band power and decrease δ-band power, making subjects feel clearer and more creative. Further research found that after presetting sleep patterns and undergoing feedback, adjustment, adaptive control, and optimization cycles, β and α waves were suppressed while and δ waves were greatly enhanced, suggesting the system could potentially provide treatment for sleep disorders. Applying these technologies in future research will help better understand tACS technology and promote its clinical application.

tACS holds promise as a safe and effective method for treating and identifying mental disorders, with broad application prospects. Future research should deeply investigate tACS mechanisms to treat various diseases more targetedly.

Meanwhile, different stimulation protocols and experimental paradigms should continue to be explored, with close attention to technology and equipment upgrades to apply more efficient and personalized tACS technology in psychology, cognitive neuroscience, and medical research.

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Note: Figure translations are in progress. See original paper for figures.