# Modulation of Brain Networks Relevant for Schizophrenia

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by
Elyamany, Osama

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From the Centre of Psychiatry
Director / Chairman: Prof. Dr. med. Christoph Mulert
of the Faculty of Medicine of the Justus Liebig University Giessen

First Reviewer and First Supervisor: Prof. Dr. Christoph Mulert (Justus Liebig University Giessen)

Second Reviewer: Prof. Dr. Nina Alexander (Philipps University Marburg)

Vice-chair and Co-supervisor: Prof. Dr. Christoph Rummel (Justus Liebig University Giessen)

Chair: Prof. Dr. Klaus-Dieter Schlüter (Justus Liebig University Giessen)

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# 1. Introduction:

Our current research project entitled “Pharmacological and Electrical Modulation of Disturbed Networks in Schizophrenia and the Clinical High-Risk State for Psychosis” aimed eventually to identify potential treatment targets for specific symptoms of psychosis and schizophrenia, particularly auditory hallucinations and working memory impairment. In a preliminary phase, we investigated the brain networks relevant for these symptoms and their potential for modulation in healthy participants. This initial work assessed the feasibility of our approach and is intended to inform future studies that will employ pharmacological and electrical interventions in clinical populations. This PhD thesis presents two examples (and subprojects) of network investigation and modulation in healthy individuals. In the first, we examined the brain circuits and biomarkers relevant for auditory hallucinations, exploring the influence of top-down attentional resources on these networks. The second study involved an attempt to electrically stimulate brain regions implicated in working memory function to improve task performance. Both studies were conducted in healthy participants as a foundation for future clinical applications in patients with psychosis. Building on that, the following sections of the introduction will outline the scientific rationale, methodological approach, and broader context of this research pipeline. Additionally, a third supporting study is included to further elaborate on the clinical relevance of one of our electrical modulation techniques.

## 1.1. Psychosis:

Psychosis is a syndrome that can be attributed to various diseases and encompasses two main symptoms: hallucinations and delusions, along with additional accompanying symptoms (Arciniegas 2015). Hallucinations involve the conscious perception of stimuli without external input, affecting any sensory modality, with auditory and visual presentations being the most common forms. Delusions are defined as false fixed beliefs, which can occur in different forms such as delusions of persecution, reference, control, grandiosity, and guilt (Gaebel and Zielasek 2015).

Psychosis can be accompanied by a wide range of symptoms and signs covering most domains of the mental state: formal speech disorders (e.g., loss of association, incoherence of thoughts); behavioural disturbances (e.g., bizarre, disinhibited, or inappropriate behaviour); cognitive impairments (e.g., attention and concentration problems); mood disturbances such

as depression or anxiety; and negative symptoms including affective flattening, alogia, anhedonia, asociality, and avolition (Gaebel and Zielasek 2015; Lyne et al. 2018). In other words, psychosis presents a wide range of clinical pictures that can coincide with many psychiatric and organic diseases; however, it is primarily associated with schizophrenia in the psychiatric field (Radua et al. 2018).

## 1.2. Schizophrenia:

Schizophrenia is a chronic, primarily psychotic disorder that affects approximately 0.28% of the global population with a male-to-female ratio of 1.1 (Solmi et al. 2023). The age of onset in males is typically around late adolescence to early adulthood (21–25), while the onset is later in females (25 - 30) (Zhan et al. 2023). The disease typically exhibits a chronic course with relapses and remissions, preceded by a prodromal phase. Relapses are often associated with acute positive psychotic features, most commonly auditory hallucinations and various forms of delusions, followed by episodes of negative symptoms and residual cognitive impairments (McCutcheon et al. 2020). Schizophrenia imposes a significant burden on individuals, their families, and society as a whole. It negatively impacts various life domains, including social, professional, and educational aspects, and causes considerable psychological distress. The disease accounts for 12.1% [9.6–15.2] of disability-adjusted life-years (DALYs) according to the Global Burden of Disease (GBD) 2019 study (GBD 2019 Mental Disorders Collaborators 2022).

## 1.3. Symptomatology:

As previously discussed, psychosis and schizophrenia encompass a broad spectrum of symptoms and signs. In this project, we focused on two primary symptoms: (1) auditory hallucinations, a hallmark positive symptom of psychosis, and (2) working memory impairment, a debilitating cognitive dysfunction.

### 1.3.1. Auditory hallucinations

One of the most prominent clinical features of schizophrenia is auditory hallucinations, which usually involve hearing voices of known or unknown persons (Thakur and Gupta 2025). These voices can take many forms: commenting, criticizing, ordering, or threatening (McCarthy-Jones et al. 2014). They impose significant stress on patients, particularly because they might be resistant to treatment (Bohlken et al. 2017). Additionally, serious consequences

may arise if the patient reacts to these voices, especially in the case of suicidal or homicidal hallucinations (Yin et al. 2023). Although various theories try to explain the pathophysiology of auditory hallucinations, their exact underlying mechanisms are not fully understood (Lawrence and Bernstein 2024). Given their psychological distress and consequences, and their treatment resistance, it is intriguing to investigate the underlying biological correlates of this symptom and discover new more targeted treatment modalities (Bohlken et al. 2017).

### 1.3.2. Working memory impairment:

Another clinically relevant symptom of schizophrenia is working memory impairment, which is usually clinically relevant and disabling cognitive symptom of the disease (Guo et al. 2019). Working memory is a fundamental cognitive function that allow the individuals to temporarily encode, store and then retrieve pieces of information to smoothly function at the daily level (Alloway and Copello 2013). In schizophrenia, the ability is robustly disturbed during the acute psychotic phase and this deficit may persist during the negative phases of the disorder despite the antipsychotic treatment (Forbes et al. 2009). Similar to the auditory hallucinations, many neurobiological associations have been reported without identifying the exact pathophysiology (Lett et al. 2014). Nonetheless, further research is needed to fully discover the exact biological correlates of this symptom, and identify new treatment targets (Lett et al. 2014).

## 1.4. Treatment:

The treatment of schizophrenia includes a number of biological, psychological and social measures, where the biological treatment (most importantly pharmacotherapy) plays an essential role in the management of psychosis (Keepers et al. 2020). Despite the availability of various antipsychotic medications, primarily targeting the dopaminergic and serotonergic systems, these medications can induce serious side effects, such as extrapyramidal symptoms, cognitive adverse events, and metabolic syndrome (Chokhawala and Stevens 2025; Huhn et al. 2019). Additionally, some patients may develop resistance to these medications, making treatment more challenging (Chokhawala and Stevens 2025; Huhn et al. 2019; Faden and Citrome 2019).

Emerging biologically-based approaches include non-invasive brain stimulation (NIBS) techniques, such as transcranial alternating current stimulation (tACS), transcranial direct

current stimulation (tDCS), and transcranial magnetic stimulation (TMS) (Li et al. 2024; Osoegawa et al. 2018). These methods have shown promise in alleviating specific schizophrenia symptoms and offer a safer alternative to pharmacological treatments. As part of our current project, we explore the application of tACS to modulate dysfunctional brain networks, as discussed in subsequent sections.

Psychosocial approaches complement biological treatments in managing schizophrenia, encompassing psychotherapy and social interventions (Bighelli et al. 2021). Psychotherapy offers various modalities, including psychodynamic therapy, cognitive-behavioural therapy (CBT), cognitive enhancement therapy, and psychoeducational interventions (Ruffalo 2023; Barlati et al. 2024). Despite its potential benefits, psychotherapy faces certain challenges, as it requires patient cooperation, adherence, and adequate cognitive functioning. Consequently, it is generally not suitable for individuals experiencing acute or severe psychotic episodes (Fischer et al. 2024). In addition to psychotherapy, social interventions aim to reintegrate patients into their social environments and provide support for daily life activities (Barlati et al. 2024). These interventions foster a protective and supportive environment that can reduce relapse rates and enhance long-term functional outcomes. By addressing the social dimensions of schizophrenia, these interventions play a critical role in improving patients' overall quality of life.

Despite the variety of available treatments, schizophrenia and psychosis remain significant challenges for both patients and society (Solmi et al. 2023). Many individuals continue to exhibit residual symptoms post-treatment, while some suffer from treatment-resistant schizophrenia (Nucifora et al. 2019; Lally and MacCabe 2016). These limitations underscore the need for a deeper understanding of the disease's pathophysiological mechanisms and the development of more targeted therapies. A symptom-based approach, rather than solely a syndromal perspective, may offer a more effective strategy for managing schizophrenia. Four arguments support this approach: (1) Understanding the neurobiological basis of specific symptoms can help better target the disrupted brain networks underlying them (Ye et al. 2025). (2) Schizophrenia presents with substantial heterogeneity in clinical manifestations, necessitating tailored therapeutic strategies for the subclasses of the disease rather than a one-size-fits-all approach (Wang et al. 2023). (3) A symptom-oriented approach aligns with the principles of personalized medicine, enabling treatments to be more precisely adapted to the patient's individual clinical and functional needs (Hill et al. 2024). (4) This approach may

help identify potential treatment options that can be used transdiagnostically, as different diseases often share similar symptoms. In our project, we aimed to follow this approach by focusing on understanding the brain circuits involved in symptom development, with the goal of targeting them pharmacologically or electrically in the future for potential translation into patient treatment.

## 1.5. Brain Oscillations:

To apply a symptom-based approach in schizophrenia research, we focused on the oscillatory patterns of the brain circuits implicated in the pathogenesis of schizophrenia symptoms. To achieve this, we utilized electroencephalography (EEG), a non-invasive method that records the electrical activity of the brain through electrodes placed on the scalp (Britton et al. 2016). EEG provides a large-scale measurement of the electrical potential beneath the electrodes, capturing the firing activity, particularly the postsynaptic potentials, of thousands of pyramidal cortical neurons (Biasiucci et al. 2019). This technique allows the association of brain activity in different regions with various brain functions or states (Light et al. 2010). These brain oscillations can be precisely linked to specific symptoms, potentially leading to new therapeutic targets through their modulation (Sargent et al. 2021; Mathalon and Sohal 2015).

### 1.5.1. Auditory hallucinations:

Many oscillatory fingerprints have been linked to auditory hallucinations (Ford et al. 2012). However, the interhemispheric miscommunication theory provides a reproducible oscillatory finding specifically related to this symptom (Steinmann et al. 2019). According to this theory, the perception of auditory hallucinations is associated with abnormally enhanced interhemispheric communication between the auditory cortices (Steinmann et al. 2019). This finding has been consistently reproduced in previous EEG studies and further supported by diffusion tensor imaging (DTI) measurements and ketamine models of schizophrenia (Steinmann et al. 2017; Steinmann et al. 2014b; Mulert et al. 2012; Thiebes et al. 2018). Building on this evidence, we aimed to investigate the electrophysiological marker of auditory hallucinations (interhemispheric connectivity) first in healthy participants as a foundation for future clinical trials exploring its potential for pharmacological or transcranial electrical modulation.

## 1.5.2. Working memory:

In the case of working memory, theta oscillations play a crucial role, particularly in the frontal regions of the brain (Sauseng et al. 2005; Payne and Kounios 2009; Sauseng et al. 2004; Brzezicka et al. 2019; Itthipuripat et al. 2013; Pomper and Ansorge 2021). Consistent with this role in normal functioning, alterations in theta rhythms contribute to working memory impairments in patients with schizophrenia (Schmiedt et al. 2005; Lynn and Sponheim 2016; Barr et al. 2017; Lett et al. 2014; Liu et al. 2020; Griesmayr et al. 2014). Disruptions in theta oscillations have even been shown to predict working memory deficits in these patients (Kang et al. 2018). This evidence supports targeting theta oscillations as a potential intervention to improve working memory impairments (Lett et al. 2014; Wang et al. 2024). In our project, we aimed to apply electrical modulation to the prefrontal regions in healthy participants to enhance working memory performance, evaluating its feasibility as a preliminary step before investigating its application in patients with schizophrenia.

## 1.6. Modulation tools:

In the current project, we employed two primary interventions to modulate the disrupted networks in schizophrenia: cognitive top-down modulation using attention instructions and electrical stimulation using tACS.

## 1.6.1. Top-down Modulation:

Top-down modulation has been extensively utilised as an effective approach to examine the extent of cognitive control over task performance and its corresponding EEG readouts (Ramsey and Ward 2020). This can be achieved by introducing specific attentional instructions, expectations, or intentions that prompt individuals to deliberately shift their focus toward particular stimuli. Such attentional control not only engages attentional resources but also demands the involvement of working memory (Gazzaley and Nobre 2012). Patients with schizophrenia often exhibit impairments in this top-down control due to disturbances in both cognitive attention and working memory functions (Dima et al. 2010). Therefore, we sought to apply this approach to modulate EEG-based interhemispheric connectivity and its associated auditory perception, first in healthy participants, with plans to extend its application to patients in future studies.

## 1.6.2. Electrical modulation:

tACS offers a unique method to fine-tune brain oscillations by delivering alternating current to target brain regions through scalp electrodes. Although the current intensity is insufficient to directly trigger action potentials, it can entrain endogenous brain oscillations to synchronize with the external current (Wu et al. 2021). This increases the likelihood of neuronal firing at specific phases of the injected current, allowing endogenous oscillations to align in both frequency and phase with the induced current (Tavakoli and Yun 2017). Through this technique, previous studies have successfully modulated a variety of cognitive functions dependent on the targeted brain oscillations and their respective regions (Klink et al. 2020; Grover et al. 2023; Zhang et al. 2024; Liu et al. 2024). In line with these findings, we planned to apply tACS in our project to manipulate the aforementioned brain oscillations and investigate its potential to produce measurable behavioural outcomes.

## 1.7. Readout biomarkers:

We chose specific cognitive tasks to investigate the brain oscillations associated with our target symptoms: auditory hallucinations and working memory impairment. To examine interhemispheric connectivity, we selected the dichotic listening task, which inherently requires intact interhemispheric communication for accurate left-ear reports (Westerhausen and Samuelsen 2020). In the case of schizophrenia, this task is particularly relevant to auditory hallucinations, as patients with auditory hallucinations exhibit increased interhemispheric coupling, resulting in more left-ear reports (Steinmann et al. 2017). Hence, the dichotic listening task was well-suited to our research question.

For investigating theta oscillations in relation to working memory, we used the delayed match-to-sample task, which offers different working memory loads. This task not only engages the three core components of working memory (encoding, storage, and retrieval of information) but also depends on intact theta activity in the frontal brain regions (Griesmayr et al. 2010; Daniel et al. 2016). In schizophrenia, patients typically show lower working memory performance, which is associated with disturbances in theta activity in the frontal regions (Hartman et al. 2003; Haenschel et al. 2009; Lencz et al. 2003). Therefore, the delayed match-to-sample task was an optimal choice for our study.

# 2. Hypotheses:

As part of our project, the attached publications present two examples of successful modulation of target brain oscillations relevant for schizophrenia-related symptoms: auditory hallucinations and working memory impairment. We began by studying these oscillations in healthy participants to examine their functional relevance and to assess the feasibility of specific interventions for future clinical research.

In the first publication, we applied a top-down modulation of the dichotic listening task. We expected to observe the typical enhancement of interhemispheric connectivity in association with left-ear reports. Additionally, we hypothesized that top-down modulation would alter auditory perception and produce corresponding effects on interhemispheric communication.

In the second publication, we applied theta-tACS to the frontal brain regions, aiming to improve working memory performance in the delayed match-to-sample task. We assumed that this stimulation would enhance frontal theta activity and subsequently improve task performance.

The third publication presents a review of tACS and its potential in clinical research. By synthesizing recent findings from a systematic literature search on the application of tACS in clinical populations, this review supports its further investigation as a promising neuromodulatory tool in psychiatric research.

Although the first two publications report experiments conducted on healthy participants, their applications may hold promise for translation into clinical research. By targeting symptom-related brain alterations, these approaches might contribute to the development of innovative treatment strategies for schizophrenia.

# 3. Publications:

## 3.1. Top-down modulation of dichotic listening affects interhemispheric connectivity: an electroencephalography study.

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EDITED BY
Jyrki Ahveninen,
Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, United States

REVIEWED BY
Yayue Gao,
Beihang University, China
Oleg Korzyukov,
University of Nebraska Medical Center, United States
Magda L. Dumitru,
University of Bergen, Norway

*CORRESPONDENCE
Osama Elyamany
✉ osama.elyamany@psychiat.med.uni-giessen.de

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# Top-down modulation of dichotic listening affects interhemispheric connectivity: an electroencephalography study

Osama Elyamany[1,2]*, Jona Iffland[1], Denise Lockhofen[1], Saskia Steinmann[3], Gregor Leicht[3] and Christoph Mulert[1,2]

[1]Centre of Psychiatry, Justus Liebig University Giessen, Hessen, Germany, [2]Centre for Mind, Brain and Behaviour, Marburg, Hessen, Germany, [3]Department of Psychiatry and Psychotherapy, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

**Introduction:** Dichotic listening (DL) has been extensively used as a task to investigate auditory processing and hemispheric lateralisation in humans. According to the "callosal relay model," the typical finding of a right ear advantage (REA) occurs because the information coming from the right ear has direct access to the left dominant hemisphere while the information coming from the left ear has to cross via the corpus callosum. The underlying neuroanatomical correlates and neurophysiological mechanisms have been described using diffusion tensor imaging (DTI) and lagged phase synchronization (LPS) of the interhemispheric auditory pathway. During the non-forced condition of DL, functional connectivity (LPS) of interhemispheric gamma-band coupling has been described as a relevant mechanism related to auditory perception in DL. In this study, we aimed to extend the previous results by exploring the effects of top-down modulation of DL (forced-attention condition) on interhemispheric gamma-band LPS.

**Methods:** Right-handed healthy participants ($n$ = 31; 17 females) performed three blocks of DL with different attention instructions (no-attention, left-ear attention, right-ear attention) during simultaneous EEG recording with 64 channels. Source analysis was done with exact low-resolution brain electromagnetic tomography (eLORETA) and functional connectivity between bilateral auditory areas was assessed as LPS in the gamma-band frequency range.

**Results:** Twenty-four participants (77%) exhibited a right-ear advantage in the no-attention block. The left- and right-attention conditions significantly decreased and increased right-ear reports, respectively. Similar to the previous studies, functional connectivity analysis (gamma-band LPS) showed significantly increased connectivity between left and right Brodmann areas (BAs) 41 and 42 during left ear reports in contrast with right ear reports. Our new findings notably indicated that the right-attention condition exhibited significantly higher connectivity between BAs 42 compared with the no-attention condition. This enhancement of connectivity was more pronounced during the perception of right ear reports.

**Discussion:** Our results are in line with previous reports describing gamma-band synchronization as a relevant neurophysiological mechanism involved

in the interhemispheric connectivity according to the callosal relay model. Moreover, we newly added some evidence of attentional effects on this interhemispheric connectivity, consistent with the attention-executive model. Our results suggest that reciprocal inhibition could be involved in hemispheric lateralization processes.

KEYWORDS

**dichotic listening, interhemispheric connectivity, top-down modulation, auditory hallucinations, EEG, lagged-phase synchronisation**

## 1 Introduction

Dichotic listening (DL) has been extensively used as a task to investigate auditory processing and hemispheric lateralisation in humans for more than six decades (Broadbent, 1956). It involves the simultaneous presentation of two different sounds to both ears via headphones. While one sound is presented to the right ear, a different sound is presented simultaneously to the left ear. Then, the participant is asked to report which sound they perceived (Figure 1). People with left-hemispheric dominance normally tend to report more sounds from the right ear than sounds from the left (Kinsbourne, 1970; Cheatham, 1990). This observation is typically called the "right ear advantage" (REA), first discovered in Kimura (1961a, 1961b). According to the "callosal relay model," the REA occurs because the information coming from the right ear has direct access to the left dominant hemisphere (Zaidel, 1983). On the other hand, for the left ear sound to be perceived, auditory information from the left ear reaches first the right hemisphere, from which it travels through the corpus callosum to the dominant left hemisphere. In other words, the left ear report necessitates enhanced interhemispheric connectivity between both auditory cortices (Zaidel, 1983; Hugdahl and Westerhausen, 2016). Interestingly, this enhanced interhemispheric communication was structurally [using diffusion tensor imaging (DTI)] and functionally [using electroencephalography (EEG)] verified (Westerhausen et al., 2006; Westerhausen et al., 2009a; Steinmann et al., 2018a). Another phenomenon, which contributes to REA, is the reciprocal inhibition between both auditory cortices during DL (Brancucci et al., 2004). Since right-handed persons commonly, but not always, possess left-hemispheric dominance, most of them show the typical REA (Cheatham and Herbig, 1992).

Like most psychological tasks involving attention, DL can be modulated by either top-down or bottom-up mechanisms (Andersson et al., 2008). While top-down modulation involves attentional instructions, bottom-up modulation comprises manipulations of sound properties such as sound intensity (Westerhausen et al., 2009b). Attention instructions during top-down modulation are conducted by asking participants to attend actively to either the left or the right ear during DL, resulting in reduction or enhancement of REA, respectively (Bryden et al., 1983). Such instructions allocate higher cognitive resources to interact with the bias toward the right ear sound (i.e., REA) either to increase or decrease it. This interaction is called the "attention-executive model" (Hugdahl and Westerhausen, 2016). Deliberately attending to the right ear increases the REA, while left ear attention decreases it.

Top-down modulation of DL has been investigated using different imaging techniques: functional magnetic resonance imaging (fMRI), EEG, magnetoencephalography (MEG), and functional near-infrared spectroscopy (fNIRS), to describe the neurobiological correlates of its behavioural outcomes. A recent fMRI study observed more activation in the auditory temporal cortex on the left side compared with the right side. However, no certain activation patterns were found while comparing the forced left/right and non-forced conditions to each other (Kazimierczak et al., 2021). Previous fMRI studies suggested activation of the auditory cortex contralateral to the attended ear (O'Leary et al., 1996; Jäncke et al., 2001), while other studies highlighted the involvement of frontal regions in the attentional control (Pugh et al., 1996; Thomsen et al., 2004; Kompus et al., 2012). MEG Studies showed similar results, as an MEG-based study showed higher ipsilateral synchronization in the frontal region (Gootjes et al., 2006). Additionally, the contralateral auditory cortex was more activated during the forced attention conditions (Alho et al., 2012), while the response of the auditory cortex was higher during the active attention compared to passive attention (Tanaka et al., 2021). A single fNIRS study added to the evidence of frontal activation, which was exaggerated upon higher cognitive demand in the left attention condition in comparison to the non-forced condition (Eskicioglu et al., 2019). Finally, the attentional input to lower regions within the auditory system was found to be more implicated in the attentional control of DL, according to a modelling study, demanding more research on the role of auditory temporal cortices (Kuo et al., 2022). These results not only prove the role of the frontal regions in attentional control, but they suggest also the implication of the temporal auditory cortices in this process. Applying EEG, many previous studies discovered other processes involved in attentional control during DL (Payne et al., 2017; Dahl et al., 2019; Teoh and Lalor, 2019; Dahl et al., 2020). An interesting finding was the detection of right frontotemporal alpha modulation only during the right attention condition, compared to passive listening (Payne et al., 2017). Given the callosal relay model, it might be needed to analyse interhemispheric interaction between both auditory cortices via EEG, especially after giving attentional instructions (Berretz et al., 2020). However, only one study investigated interhemispheric interaction during top-down modulation with attention instructions (Razumnikova and Vol'f, 2007), but the study focused on the interaction between frontal and/or parietooccipital areas. To the best of our knowledge, no

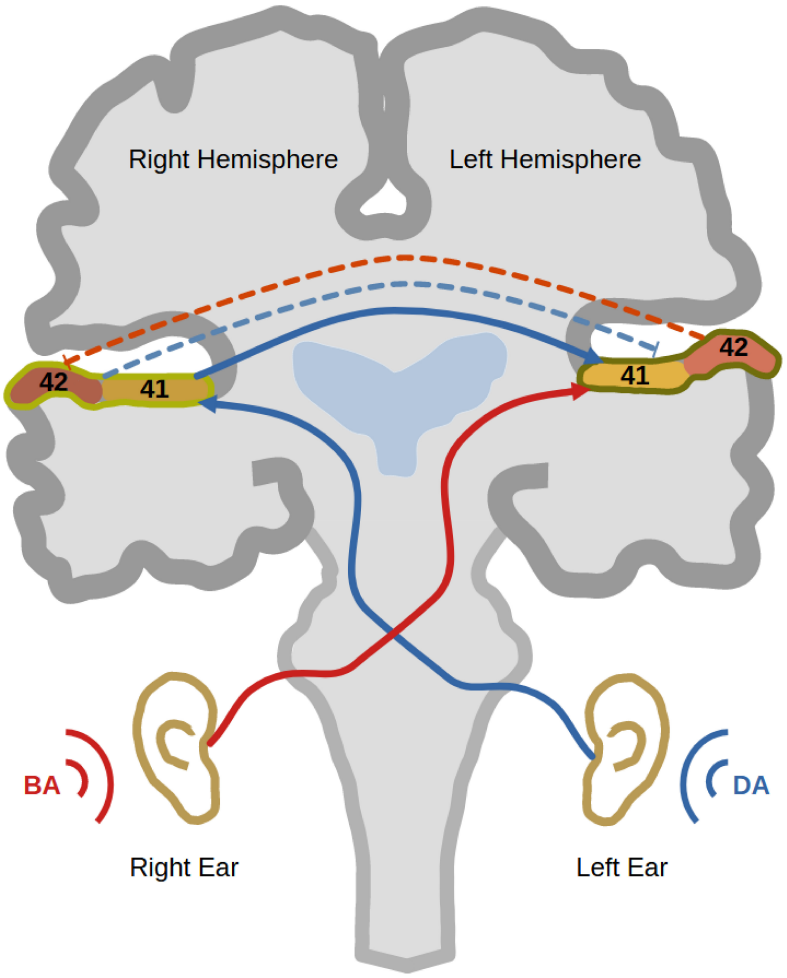


FIGURE 1
Dichotic listening. The figure shows a trial of dichotic listening where the syllable "BA" is presented to the right ear and the syllable "DA" is presented to the left ear. As well, it shows the trajectory of auditory information transfer to the left auditory cortex, where the auditory information from the right ear has direct access to the left dominant hemisphere (red). On the other hand, the auditory information presented to the left ear travels first to the right auditory cortex and then through the corpus callosum to the left hemisphere (blue). That explains why most right-handed participants show a right ear advantage (REA). During a dichotic listening experience, reciprocal inhibition between auditory cortices occurs to inhibit the processing of the ipsilateral sound at the level of auditory cortex (bidirectional dashed lines).

previous studies focused on the interhemispheric communication between both auditory cortices during top-down modulation of DL.

Interestingly, during the non-forced condition, EEG helped to reveal interesting results based on the above-mentioned interhemispheric connectivity between both auditory cortices (Razumnikova and Vol'f, 2007; Steinmann et al., 2014a; Solcà et al., 2016; Steinmann et al., 2017; Steinmann et al., 2018b; Steinmann et al., 2018a; Thiebes et al., 2018; Momtaz et al., 2021). The findings showed that the left ear reports were associated with increased interhemispheric communication in the gamma range (Steinmann et al., 2014a), consistent with the callosal relay model (Hugdahl and Westerhausen, 2016). Additionally, effective connectivity analysis revealed increased right-to-left interhemispheric connectivity only during left precepts (Steinmann et al., 2018b). These results were further substantiated by studies using diffusion tensor imaging showing anatomically stronger interhemispheric connections (Westerhausen et al., 2006; Westerhausen et al., 2009a; Steinmann et al., 2018a). Therefore, examining the interhemispheric communication during top-down modulation of DL would help detect the auditory information transfer during the different attention conditions. In this regard, the previous results did not highlight any relevant difference between the primary and the secondary auditory cortices, while the later could be more involved in integrating the attentional control of auditory processing (Grady et al., 1997; Johnsrude et al., 2002).

No study, so far, addressed attentional control on the neurophysiological mechanisms underlying the callosal relay model in the DL. Accordingly, we aimed to apply a top-down modulation of DL and examine its corresponding effects on interhemispheric connectivity between left and right auditory cortices. We hypothesised that REA would result from non-modulated trials of DL. Upon giving instructions to attend to the right or left ear, we expected to see an increase or decrease in REA, respectively. Using EEG and computing functional connectivity measures between auditory cortices, we extended our hypothesis to predict increased interhemispheric connectivity during left

ear reports. More interestingly, we focused on the effects of the attentional shift, either to the left or to the right ear, on this interhemispheric connectivity. Additionally, we explored the interhemispheric connectivity at the primary and the secondary auditory levels separately, to investigate their individual roles during attentional control.

## 2 Materials and methods

We recruited healthy participants to perform a DL task with top-down modulation. During this task, EEG was simultaneously recorded to evaluate the functional connectivity between both the left and right auditory cortices of the brain during offline analysis.

### 2.1 Participants

This work included the recruitment of human participants after signing an informed consent. The whole work was carried out according to the approval of the ethical committee at the Faculty of Medicine (FB 11 Medizin), Justus-Liebig University Giessen, registered with the project number "AZ 34/19" in May 2019. Native German speakers were invited to take part in the study at the research lab of the Department of Psychiatry at Justus Liebig University Giessen in Germany. The inclusion criteria included both genders, any age between 18 and 65 years and right-handedness. Exclusion criteria were left-handedness, hearing disability, any neurological or psychiatric disorder or taking medications that could affect the brain. According to these criteria, 33 participants (17 females) took part in the study. Two male participants were excluded later: one because of a neurological disorder and the other due to intake of thyroxine. The remaining 31 participants (17 females) were considered for analysis.

### 2.2 Questionnaires

After having given informed consent, each participant filled in three questionnaires: the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971), a questionnaire for sociodemographic data and the schizotypal personality questionnaire (SPQ) (Raine, 1991).

### 2.3 Audiometry

The hearing ability of the participants was investigated using Home Audiometer Hearing Test (Esser Audio Software, 2023). Three different frequencies of sound (500, 1000, and 2000 Hz) were tested. Participants were excluded when they could not hear sounds below 15 dB or when the hearing difference between both ears was more than 9 dB.

### 2.4 Dichotic listening task

Participants performed a special task of DL in a soundproof and electrically shielded room. They listened to sounds through Sennheiser HDA 300 headphones (Sennheiser Audiometers Headphones, 2021). We used one of the most typical DL paradigms, which is the consonant-vowel (CV) version (Shankweiler and Studdert-Kennedy, 1967). Not only is it a simple paradigm, but also its stimuli are devoid of any emotional or semantic valence. The typical CV paradigm contains syllables made of a consonant sound combined with a vowel sound. For example, the Bergen CV paradigm consists of six different consonants (b - d - g - p - t - k) combined with the vowel /a/ to form six syllables (ba - da - ga - pa - ta - ka) (Hugdahl and Andersson, 1986). In this study, we used a German version of the Bergen CV paradigm, where a male German native speaker pronounced the syllables, while we kept the loudness at 70 dB. Three of these syllables are voiced (ba – da – ga) while the other three (pa - ta - ka) are their corresponding unvoiced syllables. Combining these six syllables into sound pairs gives rise to 36 pairs to be presented through headphones (i.e., one syllable for each ear). Considering a dichotic listening paradigm, six identical pairs are excluded resulting in 30 dichotic pairs. However, due to the difference in pronunciation between voiced and unvoiced syllables, it is advisable to use only homologous pairs: voiced-voiced and unvoiced-unvoiced ones (Westerhausen and Kompus, 2018). Therefore, the paradigm can be reduced to twelve pairs of either voiced (ba-ga, ba-da, da-ba, da-ga, ga-da and ga-ba) or unvoiced nature (pa-ka, pa-ta, ta-pa, ta-ka, ka-ta and ka-pa). During each trial, one pair of these 12 combinations was presented simultaneously to both ears: one syllable to the right ear and the other syllable to the left ear, respectively. Before the experiment, participants were not informed that they would hear two different sounds. They were instructed to listen and report after each trial, which sound they heard from the six different syllables.

Each participant had to finish three different blocks with each containing 121 trials. The trials were randomised within each block using Python 3 (Python.org, 2021) so that no pair would be repeated within two successive trials. Each of the selected twelve pairs was repeated ten times within each block. A test (ba-ba) pair was added in the middle of each block. A pause of 1 min was inserted between blocks. During the first block, participants were instructed to listen and report the best perceived sound. However, during the second and the third, they were asked to attend to either the left or the right ear, respectively. Therefore, each participant was subject to three different conditions: no-attention (NA), left-attention (LA), and right-attention (RA). The order of instructions during the second and third blocks was randomised between subjects.

The task was run on a monitor at a 1-m distance from the eyes of participants using Presentation® software from Neurobehavioral Systems (Version 20.1, Neurobehavioral Systems, Inc., Berkeley, CA, USA).[1] At the beginning of each trial, a fixation sign was presented in the middle of the screen for 1 s followed by the auditory presentation of one syllable pair. Afterward, the six used syllables were shown in a circular structure, from which participants could choose the perceived sound. Participants could navigate through the circle and then confirm their choice by clicking the left and the right mouse buttons, respectively (Figure 2). Therefore, after each trial, participants could choose one of two correct reports (i.e., right ear or left ear syllables)

1 https://www.neurobs.com/

or mistakenly select an incorrect report. If a participant showed incorrect reports for more than 25% of the trials, their dataset would be excluded from the analysis.

The log files exported from the Presentation software were analysed using Python 3 (Python.org, 2021). After excluding the incorrect reports, the numbers of right and left ear reports (RE and LE) per block were calculated. From these values, a laterality index (LI), which is a measure of REA, was computed for each block using the following formula:

$$LI = (RE - LE)/(RE + LE) \times 100.$$

## 2.5 EEG recording

The electrical activity of the brain was measured using a 64-channel EEG device. The device contained two (BrainAmp DC) amplifiers: each gave rise to 32 active channels (Brain Products, Munich, Germany). The electrodes were placed over the scalp according to an extended 10/20 configuration. The head circumference of each participant was measured and then a cap with a suitable size and the same configuration was applied to their head (ActiCaps, Brain Products, Munich, Germany). An electro-conductive gel was spread between the electrodes and the scalp to ensure an impedance level below 5 KΩ (ActiCaps, Brain Products, Munich, Germany). Reference and ground electrodes were put on the FCz and AFz positions of the cap, respectively. Four electrodes were dedicated to electrooculography (EOG): two superior and inferior vertical electrodes (VEOGS and VEOGI) and two right and left horizontal electrodes (HEOGR and HEOGL). Brain Vision Recorder software version 1.21.0303 was used for recording with a sampling rate of 1000 Hz (Brain Products, Munich, Germany). Before running the DL task, a 5-min resting EEG was recorded. The task was then run with simultaneous EEG recording.

## 2.6 EEG pre-processing

Brain Vision Analyzer software version 2.2 was used to pre-process the EEG datasets (Brain Products, Munich, Germany). At first, a radial EOG (REOG) channel was created to detect micro-saccades using the following formula (Keren et al., 2010):

$$REOG = \{(VEOGS + VEOGI + HEOGR + HEOGL) / 4)\} - Pz.$$

All EEG channels were then referenced to a new common average reference formed from all EEG channels without the EOG electrodes while retaining FCz as a normal channel. Afterward, an infinite impulse response (IIR) filter was applied to cut off all frequencies below 30 Hz and more than 120 Hz with an order of two. The filtered data were later down-sampled to 500 Hz. To remove the visually obvious artefacts, the whole dataset was inspected semi-automatically. To get rid of special sources of contamination (eye, muscle and sweat artefacts), an independent component analysis was run. The resulting components were scanned according to their topography, frequency composition and the patterns of coarse eye movements and micro-saccades. After removing the suspicious components, the dataset of each participant was segmented around the time point of sound presentation. Each segment extended from 200 ms before to 824 ms after the stimulus presentation. Then, a baseline correction was applied for each segment. After excluding the segments of incorrect reports, the remaining segments were exported for connectivity analysis.

## 2.7 functional connectivity analysis

Depending on EEG data, functional connectivity between distant brain regions stands as a valid method to measure the interaction between these regions (Fingelkurts et al., 2005). One measure of functional connectivity between brain regions is lagged-phase synchronisation (LPS) (Wilmer et al., 2012; Olcay and Karaçalı, 2019). Unlike other measures of functional connectivity, LPS cancels out the effects of artificial artefacts and low spatial resolution (Stam et al., 2007). As well, it could offer clues concerning the spectral domain of brain connectivity, for example, using exact low-resolution brain electromagnetic tomography (eLORETA) (Pascual-Marqui, 2007; Pascual-Marqui et al., 2011).

Afterward, the exported segments were organised into six groups of segments [each attention condition (NA, LA and RA) had two types of reports (LE and RE)]. At the individual level, the numbers of segments per group were matched to obtain comparable connectivity values. So, the six groups of segments from the same participant included the same number, which was equal to the number of segments within the group with the smallest number of segments. To avoid any bias from the sample size, any subject with a number of segments below 20 was excluded from the connectivity analysis.

LORETA software was used (eLORETA, 2021). First of all, a transformation matrix was created according to the configuration of recording electrodes using the exact LORETA method. To assess connectivity between both right and left auditory cortices, Brodmann areas (BAs) 41 (i.e., primary auditory cortex) and 42 (i.e., secondary auditory cortex) on both hemispheres were selected as regions of interest (ROIs) within the computed transformation matrix (Figure 3).

For our eLORETA connectivity analysis, LPS was used, where the frequency band of interest was set to the gamma band (30 Hz – 100 Hz), according to previous studies (Steinmann et al., 2014a). All exported segments belonging to one of the six groups gave rise to one average LPS value, calculated from a specific time interval. In order to have reasonable time resolution, we divided the whole time window of segments (−200 to 824 ms) into ten equal intervals to calculate LPS values, each consisting of 100 ms. So, for each participant, we ended up with one LPS value for each condition/report (e.g., LA-LE for left ear reports during left attention) for each 100 ms interval.

## 2.8 Statistical analysis

For descriptive purposes, mean and standard deviation (SD) were used with continuous data. For categorical data, numbers and

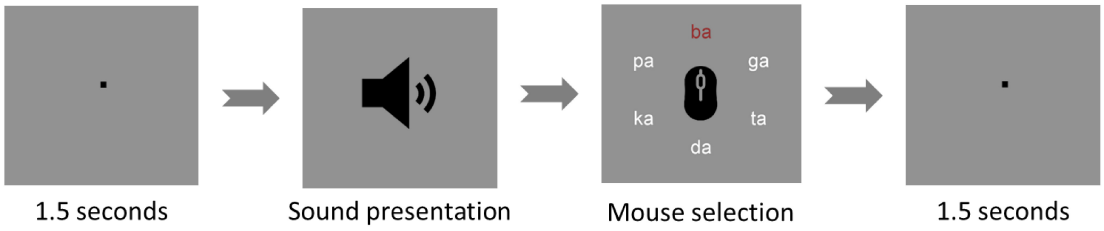


FIGURE 2
Dichotic listening trial. The figure shows one of the dichotic listening trials used during the experiment. The trials start with a fixation point for 1.5 s and then, the sound is presented. Afterward, the participant must select - with a left click of the mouse - the best-heard syllable out of six different options (ba - da - ga - pa - ta - ka). After confirmation of the selection with a right click, the next interval of 1.5 s is presented.

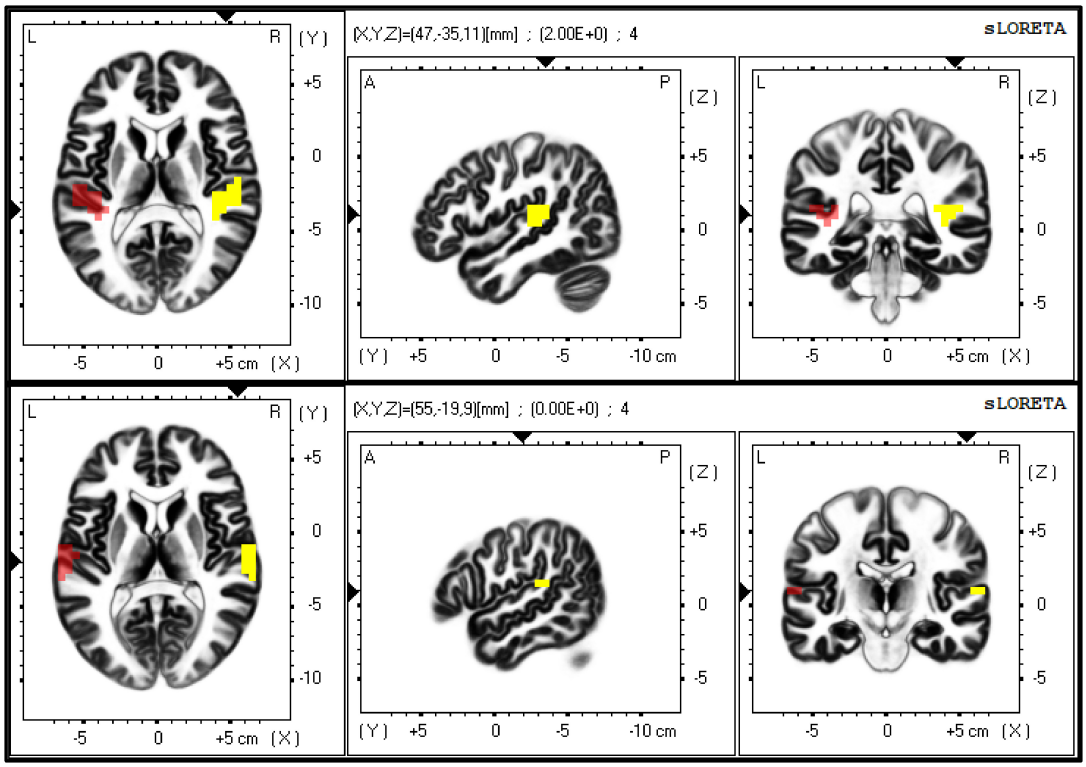


FIGURE 3
The figure shows the exact localisation of Brodmann areas (BAs) 41 **(upper panel)** and 42 **(lower panel)**, as extracted by eLORETA. These two regions of interest (ROIs) were used as seeds to calculate the lagged-phase synchronisation (LPS) between primary and secondary auditory cortices on both sides, respectively.

percentages were calculated. All figures of comparisons show mean and 95% confidence intervals.

For inferential statistics, one-way repeated-measures ANOVA tested the difference in laterality index between different conditions (NA, LA and RA). To test LPS differences between both LE and RE, a paired-sample *t*-test was used. In the case of condition comparison (NA, LA and RA), one-way ANOVA was suitable. To compare LPS values between different conditions (NA, LA and RA) and reports (LE and RE), a two-way repeated-measures ANOVA (Condition x Report) was applied for each 100ms-interval. The Greenhouse-Geisser correction was applied whenever Mauchly's sphericity test showed significance. A Student's paired-sample *t*-test was selected for two-variable comparisons with normal distributions, while the Wilcoxon signed-rank version was considered in the case of abnormal distributions. Normality was investigated via the Shapiro-Wilk test and Q-Q plots.

Both JASP (JASP Team, 2022) and SPSS (IBM Corp, 2022) software packages were used throughout the analysis. A significant result would mean a *p*-value below 0.05. The full statistical analysis is available in the "Supplementary material 1 inferential statistics".

# 3 Results

## 3.1 Sociodemographic data

We included 31 participants (17 females) for further analysis. Their age ranged from 20 to 38 years old (mean = 24.161,

SD = 4.124). All of them were right-handed according to EHI. No participant reached the threshold of clinical significance for schizotypal personality (i.e., a total score of 41) (Raine, 1991).

## 3.2 Audiometry

All participants, who took part in the study, were able to hear sounds below 15 dB and their interaural differences were less than 9 dB.

## 3.3 Dichotic listening task

All participants reported correct reports for more than 75% of all 363 trials (mean = 330.258, SD = 19.026), so the behavioural analysis included all of them. During the first condition NA, 24 (77 %) participants exhibited a positive LI (i.e., REA).

Upon applying one-way repeated-measures ANOVA on these laterality indices of the three conditions (NA, LA and RA), the analysis yielded a significant within-subjects effect (df = 1.580, $F$ = 15.803, $p < 0.001$, $\eta^2p = 0.345$). Post hoc test with Holm correction revealed that the three conditions differed significantly among participants in terms of laterality index (LA VS NA: $t = -3.254$, Cohen's d = −0.517, $p = 0.004$; NA VS RA: $t = -2.343$, Cohen's d = −0.373, $p = 0.022$; LA VS RA: $t = -5.597$, Cohen's d = −0.890, $p = 1.715 \times 10-6$) (Figure 4A).

## 3.4 EEG and connectivity results

One participant had a matching number of samples equal to eight, so his datasets were excluded from further connectivity analysis.

A) LPS between BAs 41:

Two-way repeated-measures ANOVA was conducted to compare the groups of two factors: conditions (NA, LA and RA) and reports (LE and RE) at each interval level (Figure 4B). The test showed a significant effect (df = 1, $F = 6.732$, $p = 0.015$, $\eta^2p = 0.188$) only for reports (LE VS RE) and only at the interval 200 ms – 300 ms after stimulus presentation. This significance indicates that LE showed significantly higher LPS than RE in all three conditions.

B) LPS for BA 42:

At each interval, two-way repeated-measures ANOVA was conducted to compare the groups of two factors: conditions (NA, LA and RA) and reports (LE and RE). The test showed a significant effect for both reports (LE VS RE) (df = 1, $F = 5.204$, $p = 0.03$, $\eta^2p = 0.152$) and conditions (NA, LA and RA) (df = 2, $F = 3.211$, $p = 0.048$, $\eta^2p = 0.100$) at the interval 200 – 300 ms after the stimulus (Figure 4C). The former significance meant that LE showed significantly higher LPS than RE in all three conditions. A *post hoc* test with Holm correction was applied to compare the three conditions (NA, LA and RA). Only RA revealed a significant difference in comparison with NA ($t = -2.532$, Cohen's d −0.406, $p = 0.042$) (Figure 4C). To explore which side of ear reports resulted in the significant difference in LPS between RA and NA, two paired-sample Student's $t$-tests were applied (NA LE VS RA LE, and NA RE VS NA RE). In comparison to NA, RA showed significantly higher LPS values only during RE ($t = -2.153$, Cohen's d = −0.393, $p = 0.04$). On the other hand, the corresponding comparison during LE did not reach the significance level ($t = -2.032$, Cohen's d = −0.371, $p = 0.051$).

# 4 Discussion

## 4.1 Summary of results of the current study

In the current study, a top-down modulation was applied to a dichotic listening task using three attention instructions: no, left ear and right ear attention instructions (NA, LA and RA) with simultaneous EEG recording. LIs were computed from behavioural datasets of the three conditions while gamma-range LPS values were calculated from EEG data to compare the conditions (NA, LA and RA) and reports (LE and RE). Similar to previous results, 24 (77 %) participants exhibited a positive LI (i.e., REA) during the neutral NA condition. As well, all participants on average showed the typical REA (i.e., more reports from the right ear). LA and RA conditions managed to significantly decrease and increase REA, respectively.

In accordance with the previous literature, LPS between BAs 41 and between BAs 42 on both hemispheres revealed significantly more connectivity between the ROIs during LE than during RE at the interval of 200 ms to 300 ms after stimulus. Our novel results showed a discrepancy between BAs 41 and BAs 42 in terms of interhemispheric LPS during top-down modulation of DL. For the same interval, RA and LA showed increased connectivity between only BAs 42 in contrast to NA. However, only the difference between RA and NA was statistically significant. This increase during RA, in comparison to NA, could be detected only in the case of RE, but not LE.

## 4.2 Results of the right ear advantage (replication of previous studies)

The current study showed behavioural results during NA, which are in line with previous literature (Westerhausen et al., 2015a; Westerhausen et al., 2015b; Westerhausen and Kompus, 2018). Our study showed that 77 % of a sample of right-handed participants exhibited REA, quite close to the pool's results (70.6 % - 75.3 %). To some extent, this right ear advantage can be explained by the callosal relay model (Zaidel, 1983). In that sense, left-hemispheric dominance, in most right-handed people, promotes bias to perceive the right ear sound easier than the left ear one (Westerhausen and Hugdahl, 2008). However, the callosal relay model cannot fully explain REA since the percentage of left-hemispheric dominance in the right-handed population is 96% (Rasmussen and Milner, 1977). This yields a difference of around 20% of right-handed individuals who do not show REA. To further explain this observation, another model (the attention-executive model) is introduced, where attentional control can interact with the built-in REA (Hugdahl and Westerhausen, 2016). This model predicts that the participants would report more from the ear they attend to. This process might interfere with the built-in right ear

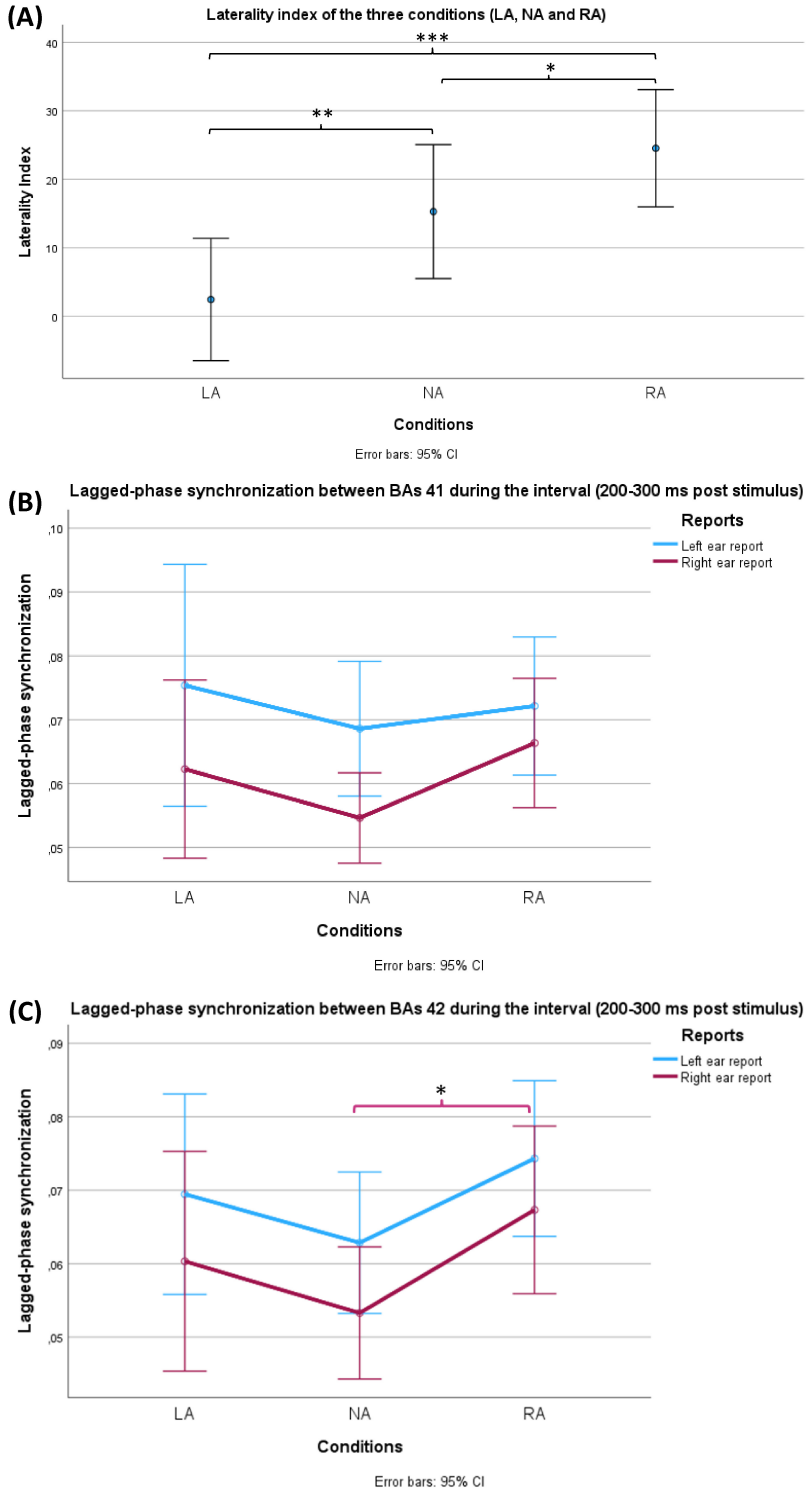


FIGURE 4
Behavioural **(A)** and EEG **(B,C)** results of the current study. **(A)** Shows a comparison between the laterality indices during the three conditions (LA: left-attention, NA: No-attention and RA: right-attention). The bars represent standard 95% confidence intervals. Using repeated measures ANOVA, the conditions factor showed significance ($p < 0.001$). All pairwise comparisons were significant after Holm correction. **(B,C)** Show a comparison of lagged-phase synchronisation (LPS) values between Brodmann areas (BAs) 41 and 42 of the groups of two factors, respectively. LPS values represent the interval (200 ms – 300 ms after the stimulus) between BAs 41 and 42 of the groups of two factors: conditions (LA, NA and RA) and reports (LE: left ear reports in blue and RE: right ear reports in red). The bars represent 95% confidence intervals. **(B)** LPS during LE was significantly higher than LPS during RE ($p = 0.015$) in the case of BAs 41. **(C)** LPS during LE was significantly higher than LPS during RE ($p = 0.03$) in the case of BAs 42. In the same case, the conditions factor (NA, LA and RA) reached a significance level ($p = 0.048$) where a *post hoc* test showed significantly higher LPS during RA in comparison with NA ($p = 0.042$). Only during RE, RA revealed significantly higher LPS compared with NA ($p = 0.04$). On the other hand, the corresponding comparison during LE did not reach the significance level ($p = 0.051$). The asterisk (*) is used to indicate the statistical significance (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$), while the error bars represent the confidence intervals (CI).

advantage, notably when the participants deliberately focus on the left ear. Although the participants were not instructed to attend to any ear during NA, they might idiosyncratically or randomly pay attention to one ear or another from trial to trial. This would lead to intra-individual, trial-to-trial fluctuations and therefore interfere with the right ear advantage. In addition to this interference, other stimulus-related factors (stimulus parameters such as the phonological properties) could contribute to this deviation from the right ear advantage (Westerhausen and Kompus, 2018).

## 4.3 Results of top-down modulation of dichotic listening (replication of previous studies)

As expected, this study showed REA during the NA condition, which was attenuated and potentiated during LA and RA conditions, respectively. This observation stands as a replicable finding upon top-down modulation of DL using attentional instructions (Hiscock and Kinsbourne, 2011). Again, the attention-executive model can justify the attentional effects on DL (Hugdahl and Westerhausen, 2016). Moreover, this proves that intra-individual inter-trial variation takes place within the same individual and it is not an absolute advantage of one ear per individual. In other words, the momentary interaction between higher cognitive control and the anatomical bias of REA dictates which ear sound would take advantage in each trial. According to the attention theory, when two competing stimuli reach the brain, one would be attenuated and the other would be perceived due to the limited capacity of the brain (Hiscock and Kinsbourne, 2011). Considering this theory in the DL context, one sound is ignored, while the other is further processed at higher levels. By default, a bias is dedicated to the right ear sound in the case of left-hemispheric dominance. However, attentional conditions, either deliberately or stochastically, can play a role in controlling the competition between two different sounds. In the case of uncontrolled attention (i.e., free-report condition, like NA condition), the attentional resources can fluctuate between the right and left ears. This describes the inter-trial variability during NA. On the other hand, when attention instructions are given, deliberate allocation of attentional resources to the left ear (LA condition) would compete with the lower level of hemispheric asymmetry and attenuate the built-in REA. In the case of right-attention instructions, the attentional processes would further potentiate the bias toward the right ear.

## 4.4 EEG results during the left and right ear reports (replication of previous studies)

Based on the callosal relay model, for the left ear sound to be perceived, the auditory information of the left ear should travel first to the right hemisphere, from which it should cross through the corpus callosum to the dominant left hemisphere (Steinmann et al., 2014b). Thus, it is a must to a establish connection between both auditory cortices to perceive the left sound, which was proven in subjects with the surgical section of commissures (Sparks and Geschwind, 1968). Therefore, it is expected that LE should show higher connectivity between both auditory cortices than RE. In accordance with this theory, our study managed to show more LPS during LE than during RE in all conditions, more specifically after 200 ms of stimulus presentation. This increase was observed between both BAs 41 and BAs 42 on both sides. These results go along with previous similar results of increased connectivity values during LE (Steinmann et al., 2014a; Steinmann et al., 2018b; Steinmann et al., 2018a). Additionally, this interhemispheric communication, in the form of gamma-band synchrony, was shown to be associated with structural components using diffusion tensor imaging (Steinmann et al., 2018a). Although every study showed different time points, at which the significant LPS difference is found, this can be explained by different technical equipment and delivery of stimuli. All of these studies addressed LPS within the gamma range, whose synchronisation is thought to be essential for the interaction between brain regions underlying cognitive functions and cortical computation (Fries, 2009). Noteworthily, these studies showed enhanced gamma-band interhemispheric connectivity at a more or less late time point after the stimulus presentation, which was the case in our results as well (200 ms – 300 ms after the stimulus). An interesting review has already addressed the timing pattern of the auditory processing at different stages based on event-related potentials (Joos et al., 2014). The review indicates that top-down modulation is mostly synchronised with P300 component. Since dichotic listening, in contrast to diotic listening, involves two competing sounds, it should exhibit a later stage of auditory processing integrating both top-down and bottom-up processes (Westerhausen et al., 2009b). In this regard, the frontal regions are involved in modulating the perception at the auditory cortices and their interhemispheric connectivity, notably the reciprocal inhibition. These mechanisms could explain the late timing of this enhanced interhemispheric connectivity.

## 4.5 Comparison of EEG results between brodmann areas (BAs) 41 and 42 (core results)

More surprisingly, RA (and in a non-significant way LA) showed higher LPS between both BAs 42, but not BAs 41 in comparison to NA. The discrepancy in findings between BAs 41 and BAs 42 could be attributed to their functional specificity. While BA 41 (i.e., primary auditory cortex) is responsible for primary properties of sounds such as frequency and intensity, BA 42 processes complex sounds and voices (Grady et al., 1997; Binder et al., 2000; Khalil, 2020). Therefore, BA 41 should show more activation for the fundamental properties of sounds, which could be translated into interhemispheric connectivity to perceive the left sound and block the right one. On the other hand, BA 42, as an auditory association hub, could be more affected by attentional input, and thus show a contrast between different attentional conditions (Grady et al., 1997). Another possibility could be the limited spatial resolution of EEG and eLORETA (Burle et al., 2015). An interesting new result was the significant difference between different attentional conditions, more specifically RA showed higher connectivity than NA. It is noteworthy that auditory cortices are affected by attentional instructions, especially BAs 42

(Grady et al., 1997; Johnsrude et al., 2002). As well, top-down modulation of DL affects frontal activity underlying attentional processes, which may, in turn, modulate auditory cortical activity (Gootjes et al., 2006). Based on that, during RA, attentional input to the auditory cortex is enhanced to promote the right ear sound, which is favoured by default. In such a case, this increased interhemispheric communication during RA might reflect higher right-to-left-hemispheric information transfer, which helps, in turn, to overcome the attentional input - concentrating on the right ear - especially during LE. Another explanation might be the reciprocal inhibition between bilateral auditory areas, where the left hemisphere extensively inhibits the right hemisphere information, notably during RE (Brancucci et al., 2004). Our results would support the second explanation, since the enhanced interhemispheric communication during RA, in comparison to NA, could be attributed to the contribution of RE, rather than LE. This agrees with the previous finding of enhanced parietal and right frontotemporal alpha modulation during RA (Payne et al., 2017). Moreover, during deliberate attention, sound processing was promoted within the hemisphere contralateral to the side of attention (O'Leary et al., 1996; Jäncke et al., 2001; Alho et al., 2012).

### 4.6 Auditory hallucinations outlook

The current findings may not only add to the current understanding of speech lateralisation but might also help to clinically investigate patients with schizophrenia, especially those with auditory hallucinations. Auditory hallucinations have been associated with increased interhemispheric communication during DL in either patients with schizophrenia, schizophrenia-like models, or individuals at clinical high-risk for psychosis (Steinmann et al., 2017; Thiebes et al., 2018; Langhein et al., 2023). These findings are consistent with the interhemispheric miscommunication theory of auditory hallucinations (Ćurčić-Blake et al., 2017; Steinmann et al., 2019; Weber et al., 2021). This disrupted circuitry can serve in the future as a potential neurostimulation target for non-invasive brain stimulation in patients with schizophrenia (Elyamany et al., 2021), as it has already been investigated in healthy participants with some promising results (Meier et al., 2019; Preisig et al., 2020; Preisig et al., 2021).

### 4.7 Limitations of the current study

Despite the new findings of this study, it possesses some limitations that could be improved in future research. First, we recruited a relatively small number of participants, so it would be recommended to replicate the experiment with a bigger sample size. Second, a limitation of this study is the limited spatial accuracy of the LORETA approach, although several cross-validation studies using simultaneous EEG and fMRI have suggested sufficient validity of the LORETA approach in general (Mulert et al., 2004). Third, LPS, though being valid for functional connectivity in general, does not give a clue about the direction of connectivity. Effective connectivity analysis should be applied to assess the directionality of information flow. Fourth, the results represent associative rather than causal relationships. However, some studies have already discovered the causal effect of interhemispheric connectivity and validated the callosal relay model (Zaidel, 1983).

## 5 Conclusion

During the neutral NA condition of DL, the right-handed population shows the typical right ear advantage. This is attributed to REA explained by the callosal relay model. The model shows that left ear information should cross to the dominant left hemisphere to be perceived, unlike right ear information, which has direct access to the dominant hemisphere. This REA could be manipulated by top-down modulation giving attentional instructions, which affect the behavioural outcome by increasing the reports from the ear attended to. RA and LA conditions managed to increase or decrease REA, respectively. Such manipulation is considered in terms of the attention-executive model, which implies an interaction between the attentional input to auditory cortices and the built-in anatomical REA.

Using EEG and computing LPS, LE showed higher interhemispheric connectivity between BAs 41 on both sides than RE in all conditions. This reflects the transfer of auditory information from the right to the left hemisphere according to the callosal relay model. Attentional condition RA showed more interhemispheric connectivity between BAs 42, compared to NA. This might result from reciprocal inhibition between bilateral auditory cortices, especially during RE. Finally, this study might help in the future to modulate interhemispheric connectivity between both auditory cortices aiming to reset abnormal communication during auditory hallucinations.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by the Ethical Committee at the Faculty of Medicine (FB 11 Medizin), Justus-Liebig University Gießen, registered with the project number "AZ 34/19" in May 2019. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

OE: Writing – review and editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. JI: Writing – review and editing, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization.

DL: Writing – review and editing, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization. SS: Writing – review and editing, Validation, Methodology, Formal analysis, Data curation, Conceptualization. GL: Writing – review and editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. CM: Writing – review and editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2024.1424746/full#supplementary-material

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## 3.2. Theta transcranial alternating current stimulation over the prefrontal cortex enhances theta power and working memory performance.

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EDITED BY
Yuanjun Xie,
Fourth Military Medical University, China

REVIEWED BY
Stevan Nikolin,
University of New South Wales, Australia
Xueli Chen,
University of Science and Technology of China, China
Kai Guan,
Information Science Academy of China Electronics Technology Group Corporation, China
Lukas Diedrich,
University Medical Center Göttingen, Germany

*CORRESPONDENCE
Ranjan Debnath
ranjan.debnath@psychiat.med.uni-giessen.de

†These authors share first authorship

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# Theta transcranial alternating current stimulation over the prefrontal cortex enhances theta power and working memory performance

Ranjan Debnath[1*†], Osama Elyamany[1,2†], Jona Ruben Iffland[1], Jonas Rauh[3], Michael Siebert[1], Elisa Andraes[1], Gregor Leicht[3] and Christoph Mulert[1,2]

[1]Centre for Psychiatry and Psychotherapy, Justus-Liebig University Giessen, Giessen, Germany, [2]Centre for Mind, Brain and Behaviour (CMBB), University of Marburg and Justus-Liebig University Giessen, Marburg, Germany, [3]Department of Psychiatry and Psychotherapy, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

**Introduction:** Transcranial alternating current stimulation (tACS) is a promising tool for modulating brain oscillations. This study investigated whether 5 Hz tACS could modulate neural oscillations in the prefrontal cortex and how this modulation impacts performance in working memory (WM) tasks.

**Method:** In two sessions, 28 healthy participants received 5 Hz tACS or sham stimulation over the left dorsolateral prefrontal cortex (DLPFC) while performing tasks with high and low WM loads. Resting-state EEG was recorded before and after stimulations for 5 minutes. EEG power was measured at electrodes surrounding the stimulation site.

**Results:** The results showed that tACS significantly improved reaction time (RT) compared to sham stimulation. This effect was task-specific, as tACS improved RT for hit responses only in high WM load trials, with no impact on low-load trials. Moreover, tACS significantly increased EEG power at 5 Hz and in the theta band compared to pre-stimulation levels.

**Discussion:** These findings demonstrate that tACS applied over left DLPFC modulates post-stimulation brain oscillations at the stimulation sites – known as tACS after-effects. Furthermore, the results suggest that 5 Hz tACS enhances response speed by elevating task-related activity in the prefrontal cortex to an optimal level for task performance.

**Conclusion:** In summary, the findings highlight the potential of tACS as a technique for modulating specific brain oscillations, with implications for research and therapeutic interventions.

KEYWORDS

**transcranial alternating current stimulation, EEG, working memory, theta power, dorsolateral prefrontal cortex**

# 1 Introduction

Working memory (WM) is a complex cognitive process that temporarily stores and manipulates information required for various cognitive functions including language comprehension, learning, problem-solving, and decision-making (1, 2). Deficits in WM leading to diminished cognitive activities have been observed in several neuropsychiatric and neurological disorders, such as depression (3, 4), schizophrenia (5–7), ADHD (8, 9), and Alzheimer's disease (10, 11). Neuroimaging studies have identified brain regions, including the prefrontal cortex, superior and inferior parietal lobules, and the inferior temporal cortex, that underlie different components of WM (12–15). Moreover, electroencephalography (EEG) and magnetoencephalography (MEG) studies have demonstrated that neural oscillations within these brain regions play a major role in facilitating WM processing. WM is associated with enhanced oscillations and neural synchrony across multiple frequencies (16–19). However, there is evidence that specific frequency bands are particularly relevant to aspects of working memory. Notably, theta oscillations in the dorsolateral prefrontal cortex (DLPFC) have been found to be associated with WM performance (20–22). Alekseichuk et al. (16) found that synchronized theta and high gamma oscillations in the prefrontal cortex are essential for efficient spatial working memory function, particularly under higher cognitive demands. Theta appears to act as a coordinating rhythm and a potential organizer of working memory processing (16, 23).

The association between DLPFC theta oscillations and WM has been investigated by attempting to modulate oscillations within DLPFC using non-invasive brain stimulation techniques. Among brain stimulation techniques, transcranial alternating current stimulation (tACS) emerges as a promising tool in research and therapeutic endeavors due to its ability to modulate cortical excitability using low-intensity electrical currents (24). tACS delivers alternating electric current to specific brain regions through scalp electrodes affecting the neural oscillations at a particular frequency (25–28). tACS is believed to interact with ongoing rhythmic cortical activities and directly influence cognitive processes by entraining underlying neural oscillations at the frequency of stimulation (29, 30). The ability of tACS to modulate endogenous oscillations at stimulated frequency allows more direct and selective enhancements of processes underlying cognitions. Indeed, numerous studies reported that tACS enhanced performance in working memory (31–33), learning (34, 35), and decision-making (36, 37). Moreover, selective entrainment of specific neural oscillations through tACS has significant clinical implications as it could aid individuals with psychiatric and neurological disorders. Recent clinical applications of tACS have shown encouraging results in alleviating negative symptoms in several psychiatric conditions such as depression (38–40) and schizophrenia (28, 41).

Previous studies investigating the effects of tACS over DLPFC on working memory have produced mixed results (for details review Booth et al. (42); Senkowski et al. (43)). Several studies have reported that tACS applied simultaneously over frontal and parietal areas significantly improved WM performance in healthy individuals (18, 19, 30, 31, 44–47). However, studies examining the effects of tACS applied solely or separately over brain areas overlying the DLPFC are limited and the findings are inconsistent. For instance, Jaušovec et al. (45) observed positive effects of theta tACS on WM performance across different paradigms of WM when delivered over the frontal or parietal cortex. Jaušovec and Jaušovec (31) found that theta tACS over the left parietal brain area significantly increased WM capacity compared to sham tACS; however, no such effect was observed for tACS over the left frontal region. Our previous study found that 5 Hz tACS over the left DLPFC significantly improved performance in high-load WM tasks whereas tACS did not affect performance in low-load tasks (Rauh et al. (33)). These varying findings highlight the complexity of tACS effects on working memory and suggest that its impact may depend on multiple factors. Further research is needed to better understand the conditions under which tACS might influence WM performance and cognitive function.

Besides the effects of tACS on cognitive functions, a key area of research in tACS is its after-effects - lasting changes in brain activity and cognitive performance after the stimulation ends. Among the various frequencies used in tACS, theta and alpha frequencies have garnered particular interest due to their association with working memory, attention, and other cognitive functions. However, the existence and nature of tACS after-effects are debated, with studies reporting both positive and null results. For instance, Zaehle et al. (30) and Vossen et al. (29) found that alpha tACS improved cognitive performance and significantly increased alpha power compared to sham stimulation even 30 minutes after the stimulation ended. In contrast, Lafleur et al. (48) found no after-effects following 10 Hz and 20 Hz tACS applied over sensorimotor regions. Although many studies have explored tACS after-effects at alpha frequency (for a detailed review see De Koninck et al. (49)), research on tACS after-effects at theta frequency is scarce. D'Atri et al. (50) applied 5 Hz tACS to bilateral frontotemporal areas and observed significant increases in theta power in the parietooccipital area compared to the sham stimulation. Conversely, Pahor and Jaušovec (32) found a decrease in theta power measured 25 minutes after theta tACS stimulation. Briley et al. (51) reported increased task-related frontal theta power following theta tACS but observed no significant differences in resting theta power at 5 and 12 minutes post-stimulation compared to sham. These disparate findings highlight the need for further research to explore how to achieve sustained after-effects with theta tACS.

The present study investigates how targeted modulation of oscillations in the DLPFC influences task performance in healthy individuals. Building on our previous findings (Rauh et al. (33)), we applied 5 Hz (theta) tACS over the left DLPFC and examined its effects on performance in WM tasks. We hypothesized that theta tACS applied to the DLPFC would enhance performance in WM tasks compared to sham stimulation. Additionally, we explored whether theta tACS induces lasting changes in neural oscillations beyond the stimulation period - referred to as tACS after-effects. To this end, resting-state EEG was collected before and after the stimulations, and spectral power was measured from the EEG data. We anticipated an increase in post-stimulation theta power

compared to pre-stimulation (baseline) levels. Furthermore, we investigated whether this enhancement in power was specific to the frequency of tACS.

# 2 Materials and methods

## 2.1 Participants

Twenty-eight healthy individuals participated in this study (Male = 10, Mean age = 32.5, SD = 13.22). Individuals with a history of neurological or psychiatric disease were excluded. All had normal or corrected-to-normal vision. They received compensation for their participation in the study. Each participant gave written informed consent to participate in the study. The Ethics Committee of the Justus-Liebig University Giessen reviewed and approved the study protocol.

## 2.2 Working memory tasks

The delayed match-to-sample task that examines load effects in visual WM was used in this study (33). The stimuli consisted of non-natural visual objects, specifically blurred outlines of random Tetris shapes (BORTs), presented under two conditions with varying WM loads. BORTs were chosen for their novelty and difficulty in verbalizing. The high-load condition featured four visual objects, while the low-load condition included two. To prevent recognition of previously viewed stimuli and subsequent ceiling effects, a large set of 504 BORTs was generated using a custom MATLAB script (448 for the experimental session and 56 for training). Within each session, no stimulus was repeated except for matching probe stimuli.

## 2.3 Procedure

The experiment was conducted in an electrically shielded and acoustically attenuated cabin. Participants were seated at a table, and the stimulus was presented using Presentation software (Neurobehavioral Systems, Berkeley, United States). They performed the delayed match-to-sample task described above. Each trial consisted of three phases: encoding, maintenance, and retrieval (Figure 1). During the encoding phase, either two (low-load condition) or four (high-load condition) different visual objects were shown sequentially for 600 ms each, resulting in an encoding phase duration of 1.2 to 2.4 s depending on the condition. Following the encoding phase, a fixation cross was displayed for 2 s, during which participants were instructed to memorize the displayed items (maintenance phase). In the retrieval phase, a probe stimulus was presented for 2 s, and participants were asked to indicate as quickly and accurately as possible whether this probe stimulus had been shown during the encoding phase. Responses were made via button press with the left index finger for a mismatch and the right index finger for a match. The intertrial interval was set to 3.5 s. The position of the target stimulus (first, second, third, or fourth in the encoding phase) was equally distributed and remained constant within each trial set. Each experimental session consisted of two blocks of 80 trials (40 trials per condition), presented in a randomized order. At the beginning of each experimental session, a training session of 16 trials was conducted to familiarize participants with the task. This study employed a cross-over design in which each subject participated in both sham and theta tACS - spaced 7 days apart. The same procedure was repeated for both sham and theta sessions. The order of the sham and tACS sessions was pseudo-randomized and balanced across participants. Each experimental session lasted approximately 50 minutes.

## 2.4 tACS parameters

A DC Stimulator MC (neuroConn GmbH, Ilmenau, Germany) was used for the electrical stimulation. The stimulation was delivered to the scalp area overlying the left DLPFC at 5 Hz. The 5 Hz stimulation frequency was chosen because, as discussed above, the effects of tACS at a slow theta frequency on brain rhythms have not been extensively studied. Moreover, 5 Hz oscillation has been used as an approximation of theta activity in previous studies employing the visual delayed match-to-sample paradigm, which is comparable to the task used in the present study (33, 52). We

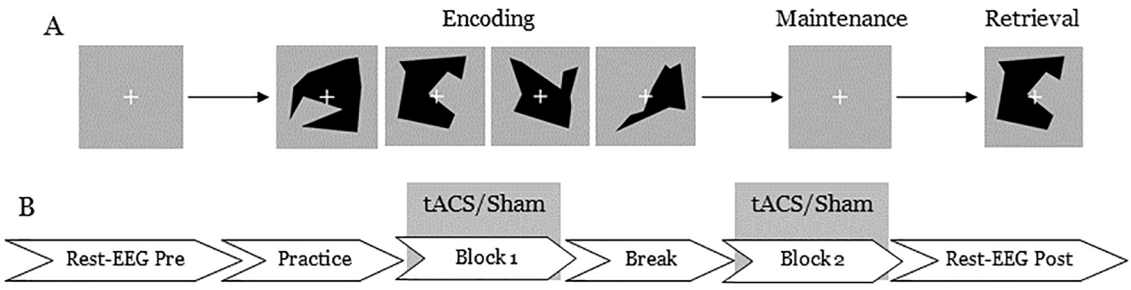


FIGURE 1
An illustration of **(A)** the delayed match-to-sample task used in the experiment and **(B)** stimulation and EEG data recording protocol. **(A)** Each trial began with a fixation cross for 2 seconds, followed by either 2 (low-load) or 4 (high-load) visual objects. Then, another fixation cross was presented for 2 seconds, followed by a probe stimulus. Participants responded by pressing a button to indicate whether they had seen the probe stimulus earlier. Each block lasted approximately 20 minutes. **(B)** Resting state EEG was collected for 5 minutes before and after the stimulation.

targeted the left DLPFC at coordinates (x, y, z = −40, 37, 24) in MNI space, identified in a previous study by Rauh et al. (33). Consequently, we deployed a "left frontal" high-definition model comprising three return electrodes positioned at F1, FC5 and AF3, and one stimulating electrode at F3. The anodal rubber electrode had a diameter of 2 cm and was surrounded by 3 "cathodal" Ag/AgCl electrodes. First, an EEG cap was placed on the participant's head, and the target position for the rubber electrode was marked with a pen. The cap was then removed, and the rubber electrode was attached to the marked position using Ten20 paste (Weaver and Company, Aurora, USA). Subsequently, the EEG cap was refitted onto the head, with the remaining stimulation electrodes integrated directly into the cap. To minimize impedance, Signagel® Electrode Gel (Parker Laboratories, Fairfield, USA) was applied. To achieve a stimulation current of 1.5 mA (peak-to-peak for tACS) at F3, the stimulation currents were weighted -690 μA at F1 and -405 μA at both FC5 and AF3. The 5 Hz stimulation included a 10-second ramp-up and a 10-second ramp-down period. For the sham condition, the stimulation protocol included a 10-second ramp-up, 10 seconds of stimulation, and a 30-second ramp-down. In the sham stimulation, the current was turned off after the ramp-down period and remained off for the rest of the stimulation period. The stimulation session lasted 21 minutes.

## 2.5 EEG data recording and preprocessing

EEG data were recorded with 64 Ag/AgCl electrodes mounted on an elastic cap (ActiCaps, Brain Products, Munich, Germany), using the Brain Vision Recorder software version 1.21.0303 (Brain Products, Munich, Germany). The TP10 electrode was used as reference and the EEG data were sampled at 5000 Hz. Impedances were kept below 10 kΩ. EEG data were collected in three blocks: (1) baseline resting EEG for 5 minutes, (2) active or sham stimulation, (3) post-stimulation resting EEG for 5 minutes. For the resting EEG, the participants were instructed to close their eyes for 5 minutes. During the stimulation, they performed the task described above.

EEG data were preprocessed using the EEGLAB toolbox (53). EEG data were down-sampled to 500 Hz and bandpass filtered (0.5–100 Hz). The cleanLine plugin of EEGLAB was used to remove the 50 Hz electrical line noise. Channels containing excessive noise or artifacts were identified and removed using the EEGLAB plug-in FASTER (54). Across all participants, on average 2.10 (SD = 1.09, range 0–5) channels per subject were removed. Independent component analysis (ICA) was performed on continuous EEG data to remove ocular artifacts and generic noise. Artifactual independent components (ICs) were identified and removed from the data using the ICLabel plug-in (55) of EEGLAB and through visual inspection of individual ICs. On average, 13.2 ICs (SD = 5.62, range 7-29) per subject were removed from the data. EEG data were then segmented into 1-s epochs. Epochs containing artifacts were removed using a voltage threshold (± 100μV) rejection. This procedure removed on average 21.2 (SD = 40.3) epochs per subject. After artifact rejection, any missing channels were interpolated using spherical interpolation. The epoched data were then re-referenced to the average of all channels.

## 2.6 Spectral power analysis

The EEG epochs were processed using Welch's method to estimate the PSD for each channel. Specifically, we applied a Hanning window of 0.5 seconds with a 0.25-second overlap to each epoch. The resulting PSD values ($\mu V^2/Hz$) were averaged across all epochs for each channel and log-transformed (log10). To avoid negative values, 1 was added to the power values before the log transformation.

Power was extracted at 5 Hz and for the theta (4–6 Hz), delta (1–3 Hz), and alpha (7–12 Hz) bands. Finally, power was averaged across a cluster of electrodes (FC1, FC3, F5, Fz) surrounding the stimulation site (F3) in each frequency band of interest. Since the FC1, FC3, F5, and Fz electrodes surround the stimulation site (F3), analyzing power across this cluster allows for a more comprehensive assessment of the effects of stimulation on the targeted region. Although the primary frequency of interest was 5 Hz, we also analyzed power in the delta, theta, and alpha bands to assess whether the power modulation was specific to the stimulation frequency.

## 2.7 Statistical analyses procedure

We recorded response accuracy and reaction time for behavioral data analysis. We used d-prime values as outcome measures for response accuracy. D-prime, a discriminability index adapted from signal detection theory (56), measures the ability to correctly identify targets while minimizing false alarms and has been shown to have high sensitivity to detecting true signals or targets (57). Participants' responses were categorized as either hits, misses, false alarms, or correct rejections. These response types were used to calculate d-prime metrics. Hit rate (H) was calculated as the proportion of correctly identified targets (i.e., H = Hits/Hits +Misses), and false alarm rate (FA) was the proportion of incorrect identifications (FA = False Alarms/False Alarms +Correct Rejections). To avoid issues with extreme values (e.g., hit rates of 1.0 or false alarm rates of 0), values were adjusted following standard practices: if H or FA equaled 1.0 or 0, they were adjusted by 1/2N, where N represented the number of trials. The d-prime index was then computed as the difference between the z-transformed hit rate and false alarm rate (d' = Z(H)−Z(FA)). A repeated measures ANOVA was conducted with factors of Stimulation (Sham, tACS) and Task-load (Low, High) on d-prime scores. Reaction time (RT) was defined as the interval between the probe stimulus and the button press. RTs were also calculated for the 4 categories of responses. We performed a repeated measures ANOVA with factors of Stimulation (Sham, tACS), Task-load (Low, High), and Response (Hit, Miss, False Alarm, Correct Rejection). Baseline and post-stimulation EEG spectral power were compared using a repeated measures ANOVA with factors of Stimulation (Sham, tACS) and Time (Baseline, Post-stimulation). ANOVA was performed separately for each measured frequency. Follow-up analyses were performed to compare baseline and post-stimulation EEG spectral power using paired two-tailed t-tests.

Power and behavioral data were normally distributed according to Shapiro-Wilk tests. Throughout the analyses, extreme scores (values exceeding ±3 SD from the mean) were excluded as outliers. Statistical analyses were performed using R.

# 3 Results

## 3.1 D-prime

Table 1 presents the means and standard deviations of the d-prime score. The ANOVA with factors Stimulation (Sham, Theta) and Task-load (Low, High) on d-prime scores revealed a main effect of Task-load ($F(1, 26) = 131.66$, $p < .001$, $\eta^{2p} = .835$). *Post hoc* comparison with Bonferroni corrections showed that performance was significantly higher in low-load trials compared to high-load trials in both Sham ($T(26) = 11.31$, $p < .001$) and tACS ($T(26) = 8.90$, $p < .001$) conditions. Neither the main effect of Stimulation ($F(1, 26) = .13$, $p = .725$, $\eta^{2p} = .005$) nor the Stimulation x Task-load interaction ($F(1, 26) = .09$, $p = .769$, $\eta^{2p} = .003$) was significant. The results suggest that participants had higher accuracy in low-load trials and made more errors in high-load trials regardless of stimulation conditions (Figure 2A).

## 3.2 Reaction time

The three-way repeated-measures ANOVA of reaction time revealed the main effect of Task-load ($F(1, 27) = 41.13$, $p < .001$, $\eta^{2p} = .604$), resulting from overall faster response for low load trials compared to the high load trials. The main effect of Response was also significant ($F(3, 81) = 4.71$, $p = .004$, $\eta^{2p} = .148$). The main effect of Stimulation was not significant ($F(1, 27) = 1.73$, $p = .199$, $\eta^{2p} = .060$). However, the Stimulation x Task-load x Response interaction was significant ($F(3, 81) = 4.31$, $p = .007$, $\eta^{2p} = .138$). To explore the interaction, follow-up Stimulation x Task-load ANOVA was performed within each response category. The ANOVA for Hit response revealed a main effect of Stimulation ($F(1, 27) = 4.93$, $p = .035$, $\eta^{2p} = .154$) and Task-load ($F(1, 27) = 30.82$, $p < .001$, $\eta^{2p} = .533$). The Stimulation x Task-load interaction was also significant ($F(1, 27) = 4.52$, $p = .043$, $\eta^{2p} = .143$). *Post hoc* comparisons after the Bonferroni correction showed that participants made significantly faster hit responses in high-load trials during active tACS than Sham stimulation ($T(27) = 3.58$, $p = .008$) (Figure 2B). In contrast, there was no significant difference in RTs for hit responses in low-load trials between Sham and active tACS stimulation conditions ($T(27) = .86$, $p = .395$) (Figure 2B). Table 1 presents a summary of RTs for hit responses. The ANOVA for Miss response revealed a main effect of Task-load ($F(1, 27) = 11.64$, $p = .002$, $\eta^{2p} = .301$), resulting from faster overall RT in Low-load ($M = 1027$) compared to High-load ($M = 1101$) trials across stimulations. The main effect of Stimulation ($F(1, 27) = .81$, $p = .375$, $\eta^{2p} = .029$) and Stimulation x Task-load interaction ($F(1, 27) = .37$, $p = .55$, $\eta^{2p} = .013$) were not significant. The ANOVA for False alarms response revealed a main effect of Task-load ($F(1, 27) = 10.26$, $p = .003$, $\eta^{2p} = .277$), resulting from higher overall RT in High-load ($M = 1207$) compared to Low-load ($M = 937$) trials across stimulations. The main effect of Stimulation ($F(1, 27) = .77$, $p = .388$, $\eta^{2p} = .028$) and Stimulation x Task-load interaction ($F(1, 27) = .003$, $p = .953$, $\eta^{2p} = .00$) were not significant. The ANOVA for Correct rejections response revealed a main effect of Task-load ($F(1, 27) = 63.53$, $p < .001$, $\eta^{2p} = .702$), resulting from higher overall RT in High-load ($M = 990$) compared to Low-load ($M = 878$) trials across stimulations. The main effect of Stimulation ($F(1, 27) = .44$, $p = .51$, $\eta^{2p} = .016$) and Stimulation x Task-load interaction ($F(1, 27) = .69$, $p = .414$, $\eta^{2p} = .025$) were not significant. In summary, the RT analyses revealed that participants responded faster overall in low-load trials, and tACS stimulation specifically accelerated responses when participants correctly recognized stimuli presented during the encoding phase in the high-load trials. However, tACS did not affect error response times and the RTs related to the correct rejection of the stimuli. These behavioral results suggest that tACS may enhance the speed of accurate responses, particularly in high-load trials. However, the results should be interpreted cautiously rather than as conclusive evidence of a load-specific effect. Instead, they point to a promising trend that warrants further investigation, with additional data needed to confirm the reliability and replicability of the observed effects.

TABLE 1 Means and standard deviations (in parentheses) of d-prime scores and reaction times (ms) for correct responses in low- and high-load trials for Sham and tACS conditions.

| | Low Load | High Load |
|---|---|---|
| d-prime | | |
| Sham | 2.41 (.57) | 1.28 (.41) |
| tACS | 2.41 (.55) | 1.27 (.42) |
| Hit RT | | |
| Sham | 1074 (254) | 1165 (253) |
| tACS | 1052 (251) | 1102 (226) |

## 3.3 Spectral power

For power at the stimulation frequency of 5 Hz, the ANOVA revealed a main effect of Time ($F(1, 27) = 7.15$, $p = .013$, $\eta^{2p} = .210$). Neither the main effect of Stimulation ($F(1, 27) = .13$, $p = .723$, $\eta^{2p} = .005$) nor the Stimulation x Time interaction ($F(1, 27) = .003$, $p = .952$, $\eta^{2p} = .00$) was significant. We further explored the main effect of Time by comparing baseline and post-stimulation power. Based on our *a priori* hypotheses, we conducted paired t-tests within each condition to investigate potential condition-specific effects. In the active tACS condition, post-stimulation power ($M = .814$, $SD = .29$) was significantly higher than baseline power ($M = .778$, $SD = .28$) at the stimulation frequency of 5 Hz ($T(27) = 2.78$, $p = .01$, Cohen's $d = .526$). In contrast, no significant difference was observed between baseline ($M = .805$, $SD = .30$) and post-stimulation ($M = .770$, $SD = .27$) powers in the sham condition ($T(27) = 1.71$, $p = .098$, Cohen's $d = .324$). The ANOVA comparing baseline and post-stimulation theta band power in sham and tACS stimulation conditions also

revealed a main effect of Time ($F(1, 27) = 5.17$, $p = .031$, $\eta^{2p} = .160$). The main effect of Stimulation ($F(1, 27) = .28$, $p = .601$, $\eta^{2p} = .01$) and Stimulation x Time interaction ($F(1, 27) = .306$, $p = .585$, $\eta^{2p} = .011$) were not significant. In the active tACS condition, post-stimulation ($M = .847$, $SD = .24$) theta power was significantly higher than baseline ($M = .806$, $SD = .23$) theta power ($T(27) = 2.49$, $p = .019$, Cohen's $d = .470$). However, theta power did not differ between baseline ($M = .802$, $SD = .22$) and post-stimulation ($M = .829$, $SD = .26$) in the sham condition ($T(27) = 1.26$, $p = .218$, Cohen's $d = .239$). Comparisons of baseline and post-stimulation power did not show significant differences in the delta and alpha bands for either the active tACS or sham conditions (all $p > .05$). Spectral power analyses demonstrated that 5 Hz tACS induced a significant increase in power and the power modulation was specific to the stimulation frequency (Figure 3).

## 4 Discussion

This study investigated how tACS at a slow theta frequency (5 Hz) modulated brain rhythms and task performance. Sham or 5 Hz tACS was applied to the left DLPFC while participants performed WM tasks with varying cognitive loads. RT and accuracy were measured during both tACS and sham conditions to assess task performance. Resting state EEG was collected before and after the stimulations, and spectral power was computed from EEG data. The results showed that tACS significantly enhanced task performance, particularly in high-load trials, as demonstrated by faster reaction times. Additionally, there was a significant increase in post-tACS spectral power at 5 Hz and in the theta band. This study builds on our previous work (33), in which we demonstrated that tACS at a slow theta frequency (5 Hz) over the left DLPFC improved working memory performance under high cognitive load conditions. In the present study, we found selective enhancement of RT in WM tasks. Additionally, we extend our earlier research by showing a significant increase in post-tACS spectral power, indicative of after-effects.

Our findings demonstrated that tACS improved RT in WM tasks selectively for cognitively demanding tasks. Specifically, response speed in high-load trials was significantly faster in the tACS condition compared to the sham condition. Notably, there were no effects of any stimulation on accuracy, suggesting that the improved response speed in high-load trials in the tACS condition did not involve a speed-accuracy trade-off. In a previous study, we found that 5 Hz tACS preferentially enhanced performance on high WM load tasks (33). Furthermore, our results are consistent with numerous previous studies reporting that tACS administered in the alpha (25, 36), theta (19, 33), and gamma (58, 59) ranges positively impacted cognitive functions. Hoy et al. (58) found that gamma-tACS improved WM performance only for stimuli that required greater cognitive load. The selective improvement of cognitive functions following tACS has also been reported in other domains (36, 59). The selective improvement in WM performance induced by tACS may result from the enhanced synchronization of neural oscillations. tACS is believed to entrain endogenous oscillations by enhancing coherence and synchronization of neuronal oscillations within and across brain regions (60, 61). The improved synchronization facilitates more efficient neural communication, which is particularly beneficial for cognitively demanding tasks in which the need for coordinated neural activity is higher. Furthermore, neural synchronization is considered pivotal in representing information in WM (62–64).

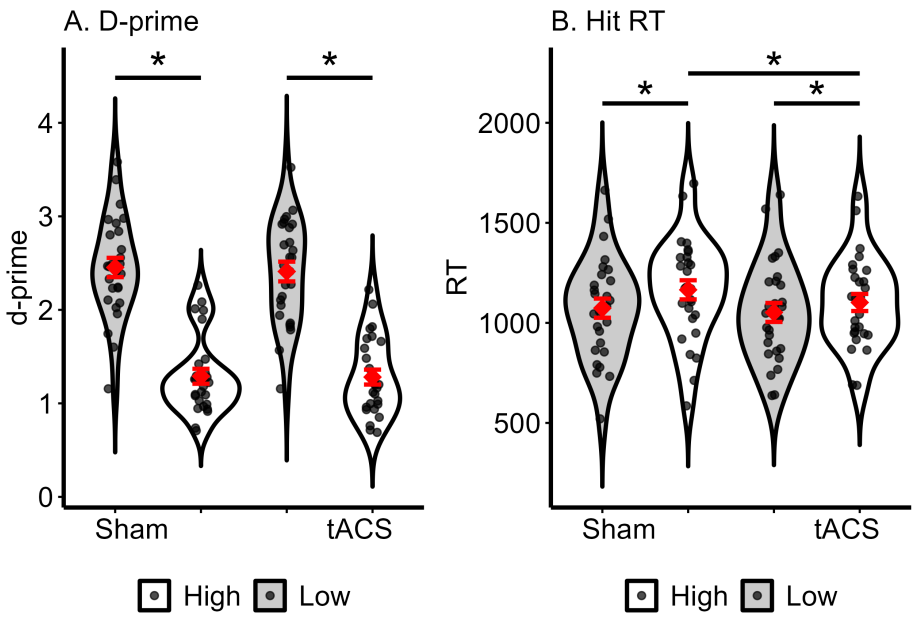


FIGURE 2
Effects of Sham and tACS stimulations on working memory performance, measured by d-prime **(A)** and reaction time (RT) for hit responses **(B)**. The violin plots display the distribution of individual data points shown as jittered dots. Red diamonds mark the mean and red error bars show the standard error. Significant differences between specific conditions are denoted by asterisks above the plots. * $p < .05$.

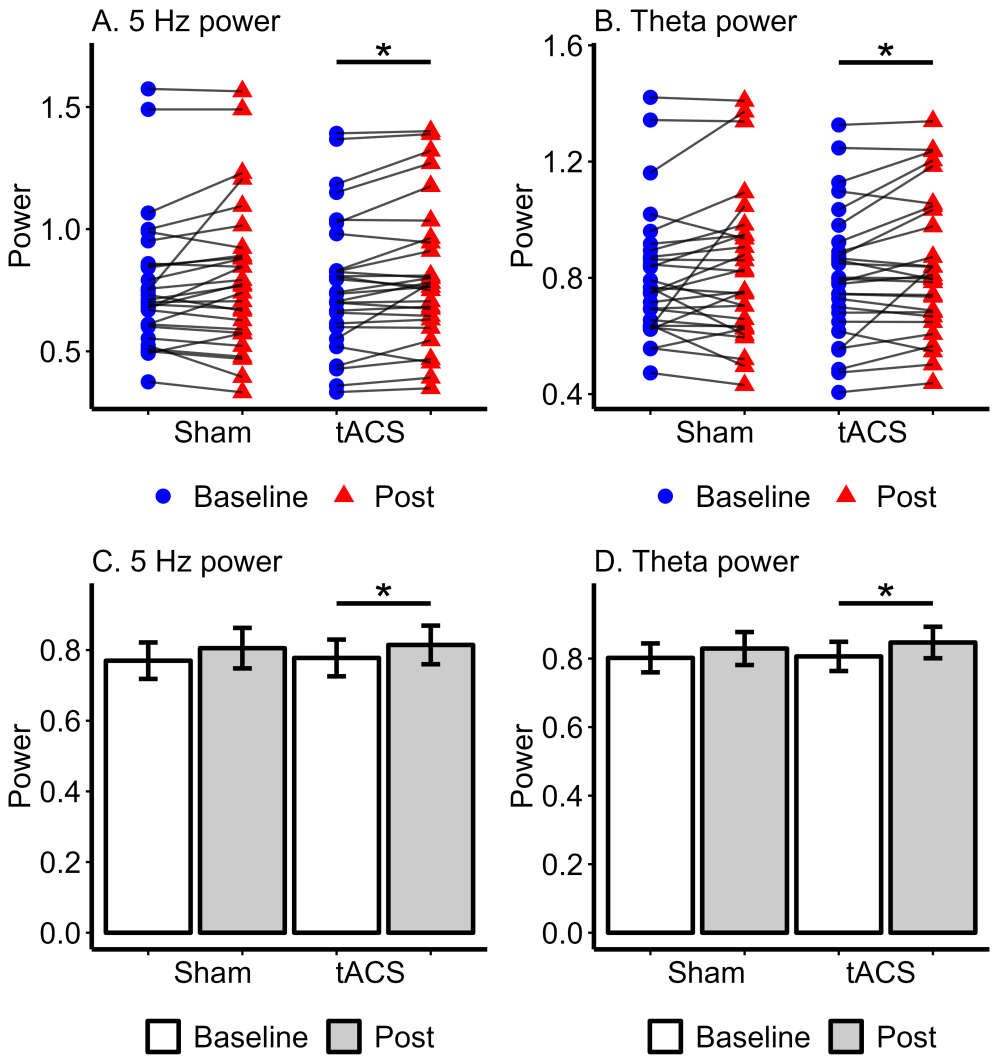


FIGURE 3
Spectral power at 5 Hz and theta band in Sham and tACS stimulation conditions. The upper **(A, B)** show individual power values with lines connecting baseline (pre-stimulation) and post-stimulation powers for each participant. **(A)** represents 5 Hz power, while **(B)** shows Theta power, with statistical significance indicated by an asterisk (*) between the baseline and post-stimulation powers in the tACS condition. The lower **(C, D)** present bar plots of mean power with standard error for each condition. **(C)** shows 5 Hz power, and **(D)** shows Theta power, with an asterisk (*) highlighting significant differences between baseline and post-tACS power. * p <.05.

The complex cognitive processes underlying WM are mediated by oscillatory activity across multiple frequency bands, involving both independent contributions and cross-frequency coupling (16–18, 21, 22). However, evidence suggests that specific frequency bands may play a more critical role in certain aspects of WM. Notably, frontal theta power is associated with memory load, with increased power correlating with the number of items maintained (65, 66). These findings highlight the facilitatory role of increased theta power in WM performance under higher cognitive load. Moreover, the absence of effects in the low-load condition is not surprising, given that low cognitive demand often leads to high performance and may cause ceiling effects. Therefore, the mechanism of tACS in enhancing neural synchrony likely accounts for the selective improvement of performance in WM tasks observed in this study. Our results illustrate the involvement of DLFPC in visual WM and the importance of theta oscillations in WM processes.

We found that 5 Hz tACS over the left DLPFC significantly increased spectral power post-stimulation compared to the pre-stimulation baseline level. The power enhancement, known as after-effects, was limited to the theta band and did not occur in the adjacent delta and alpha frequency bands. Our findings are consistent with the idea that tACS modulates brain oscillations in the frequency band corresponding to the stimulation frequency (25, 29, 30, 50). Although the exact neuronal mechanism of tACS is not fully understood, current research suggests that the after-effects may be primarily driven by neuronal entrainment or synaptic plasticity (26, 67, 68). The neuronal entrainment theory suggests that continuous stimulation with an oscillating current causes more individual neurons to synchronize their activity with the external

rhythm, leading to a power increase across the entire network (68). It further suggests that neurons oscillating within the stimulation frequency range will become synchronized and entrained, while those with intrinsic frequencies outside this range will remain unaffected (68). Our findings may be explained by neuronal entrainment, as elevated power was observed specifically in the theta band while power in surrounding frequency bands did not change.

### 4.1 Limitations

Although this study was carefully designed and conducted, some limitations should be noted. The placement of the stimulation electrodes was based on previous studies, which may not be ideal. Given that tACS is more localized, individual differences in head anatomy could affect the results. Future studies using imaging techniques could address this issue. Additionally, we were unable to analyze the EEG data recorded during tACS due to artifacts introduced by the electrical stimulation. Currently, there is no established method to eliminate this noise effectively. Overcoming this challenge would provide crucial insights into the underlying processes of tACS and its effects on brain function. Our evaluation of working memory performance was based solely on reaction time (RT), accuracy and spectral power in the theta band. While these metrics are commonly used to assess task performance and neural activity, working memory is influenced by a range of factors, including cognitive strategies and individual differences in processing speed. Therefore, relying exclusively on RT and spectral power may not capture the full complexity of the cognitive processes involved in working memory tasks. Finally, we did not observe any effects of tACS on accuracy. While this outcome was not anticipated, previous research indicated that tACS may selectively improve task performance.

### 4.2 Conclusion

Our findings demonstrated that the application of tACS at a slow theta frequency (5 Hz) over left DLPFC improved performance in WM tasks preferentially in the higher cognitive load condition. Furthermore, the results showed a significant increase in post-tACS spectral power, known as after-effects. Our findings highlight the potential of tACS as a non-invasive brain stimulation method for modulating brain activity and enhancing cognitive function. Given that cognitive deficits are common in psychiatric and neurological conditions, these findings have significant implications for the clinical application of tACS in enhancing cognitive functions and overall wellbeing in clinical populations.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by the ethics committee of Justus-Liebig University Giessen. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

RD: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Validation. OE: Data curation, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. JI: Data curation, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. JR: Conceptualization, Methodology, Supervision, Writing – review & editing. MS: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. EA: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. GL: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. CM: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare no conflicts of interest, financial interests, or personal relationships that could have influenced the findings reported in this paper.

## Publisher's note



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## 3.3. Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry.

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INVITED REVIEW

# Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry

**Osama Elyamany**[1,2] · **Gregor Leicht**[3] · **Christoph S. Herrmann**[4,5] · **Christoph Mulert**[1,2]

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## Abstract

Transcranial alternating current stimulation (tACS) is a unique form of non-invasive brain stimulation. Sinusoidal alternating electric currents are delivered to the scalp to affect mostly cortical neurons. tACS is supposed to modulate brain function and, in turn, cognitive processes by entraining brain oscillations and inducing long-term synaptic plasticity. Therefore, tACS has been investigated in cognitive neuroscience, but only recently, it has been also introduced in psychiatric clinical trials. This review describes current concepts and first findings of applying tACS as a potential therapeutic tool in the field of psychiatry. The current understanding of its mechanisms of action is explained, bridging cellular neuronal activity and the brain network mechanism. Revisiting the relevance of altered brain oscillations found in six major psychiatric disorders, putative targets for the management of mental disorders using tACS are discussed. A systematic literature search on PubMed was conducted to report findings of the clinical studies applying tACS in patients with psychiatric conditions. In conclusion, the initial results may support the feasibility of tACS in clinical psychiatric populations without serious adverse events. Moreover, these results showed the ability of tACS to reset disturbed brain oscillations, and thus to improve behavioural outcomes. In addition to its potential therapeutic role, the reactivity of the brain circuits to tACS could serve as a possible tool to determine the diagnosis, classification or prognosis of psychiatric disorders. Future double-blind randomised controlled trials are necessary to answer currently unresolved questions. They may aim to detect response predictors and control for various confounding factors.

**Keywords** Transcranial alternating current stimulation (tACS) · Non-invasive brain stimulation (NIBS) · Psychiatry · Schizophrenia · Depression · OCD

## Abbreviations

| | |
|---|---|
| AD | Alzheimer's disease |
| ADAS-Cog | The 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale |
| ADHD | Attention deficit hyperactivity disorder, |
| AHRS | Auditory Hallucination Rating Scale |
| ASSR | Auditory steady-state response |
| BACS | Brief assessment of cognition in schizophrenia |
| BDI | Beck Depression Inventory |
| CES | Cranial electrotherapy stimulation |
| CGI | Clinical Global Impression Scale |
| DLPFC | Dorsolateral prefrontal cortex |
| DMPFC | Dorsomedial prefrontal cortex |
| DTI | Diffusion tensor imaging |
| EEG | Electroencephalography |
| FAA | Frontal alpha asymmetry |
| HAMA | Hamilton Anxiety Rating Scale |
| hdEEG | High-density electroencephalography |
| HDRS | Hamilton Depression Rating Scale |
| LTD | Long-term-depression |
| LTP | Long-term-potentiation |
| M1 | Primary motor |
| MADRS | Montgomery–Asberg Depression Rating Scale |

✉ Christoph Mulert
Christoph.Mulert@psychiat.med.uni-giessen.de

1 Centre of Psychiatry, Justus-Liebig University, Klinikstrasse 36, 35392 Giessen, Hessen, Germany

2 Centre for Mind, Brain and Behaviour (CMBB), University of Marburg and Justus-Liebig University Giessen, Marburg, Germany

3 Department of Psychiatry and Psychotherapy, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

4 Experimental Psychology Lab, Centre for Excellence "Hearing4all," European Medical School, University of Oldenburg, Oldenburg, Lower Saxony, Germany

5 Research Centre Neurosensory Science, University of Oldenburg, Oldenburg, Lower Saxony, Germany

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|---|---|
| MCI | Mild cognitive impairment |
| MDD | Major depressive disorder |
| MEG | Magnetoencephalography |
| NIBS | Non-invasive brain stimulation |
| OCD | Obsessive–compulsive disorder |
| PANAS | Positive and Negative Affect Schedule |
| PANSS | Positive and Negative Syndrome Scale |
| PMA | Premotor area |
| PSYRATS | Psychiatry rating scale |
| SANS | Scale for the Assessment of Negative Symptoms |
| SAPS | Scale for the Assessment of Positive Symptoms |
| SMA | Supplementary motor area |
| STDP | Spike-timing-dependent plasticity |
| SUMD | Scale to Assess Unawareness of Mental Disorder |
| tACS | Transcranial alternating current stimulation |
| tDCS | Transcranial direct current stimulation |
| TMS | Transcranial magnetic stimulation |
| TMT | Trail Making Test |
| WM | Working memory |
| YBOCS | Yale–Brown Obsessive–compulsive Scale |

## Introduction

Transcranial alternating current stimulation (tACS) is a widely used non-invasive brain stimulation (NIBS) method. It has been used for more than a decade in different fields, such as cognitive neuroscience [1, 2]. However, its use in psychiatric clinical research began with case reports [3], and only recently have the first well-structured double-blind randomized controlled trials examined its efficacy for the treatment of psychiatric disorders [4]. tACS involves direct delivery of alternating electric currents to the scalp. The current travels through the skull to affect mostly cortical neurons. Such alternating current has a sinusoidal waveform where the voltage changes gradually from positive to negative every half-cycle. Therefore, the current flows from an anodal electrode to a cathodal electrode in one half-cycle and in the reverse direction in the second half-cycle [5].

The concept underlying alternating current is to simulate the naturally occurring rhythmic pattern of electrophysiological activity of the brain, which can be detected by electroencephalography (EEG) and magnetoencephalography (MEG) [6]. Such rhythmic patterns, oscillating at a certain frequency, are called brain oscillations. Various specific brain oscillations have been coupled with diverse brain functions and states [7]. Moreover, connectivity and communication between distant cortical regions were shown to be associated with the synchronization of brain oscillations within these regions [8, 9]. In that sense, tACS is also used to couple or decouple two connected neuronal circuits by synchronizing or desynchronizing their oscillations, respectively. Accordingly, tACS might represent a potential therapeutic tool by modifying altered brain oscillations and connectivity patterns that were previously identified in various psychiatric disorders.

The typical setup of tACS involves the application of electrodes onto the scalp, whose position and size can be modified to specifically target a certain brain region [10, 11]. For this purpose, positioning of the electrodes is designed according to computational models to optimize the stimulation parameters [12, 13]. Furthermore, the parameters of the alternating current itself can be customized in terms of frequency, amplitude, phase shape, phase timing, and the duration and number of stimulation sessions. The stimulation frequency is usually set to EEG frequencies to modulate the brain processes associated with them. Other parameters may vary according to the study question and brain electric activity to be modulated (some examples are discussed below; for more details, see this review: [14]).

## Mechanism of action

Although the exact mechanisms of action of tACS are still not well understood, there is growing evidence of possible explanations. Electrophysiological methods have been extensively used to elucidate these mechanisms, as well as the effects of tACS, mostly EEG and, to a lesser degree, MEG, in humans, and intracranial and local field potential recordings in animals [15, 16]. Those methods have shown two main categories of tACS effects: online effects (those that coincide with the stimulation duration), and offline effects or after-effects (those that outlast the stimulation period). Both involve entrainment of brain oscillations to the stimulation frequency and coupling or decoupling of long-range oscillatory connectivity between distant brain regions [17, 18]. To understand these effects and their underlying electrophysiological processes, we summarize previous literature bridging the gap between cellular and whole network levels.

Upon tACS application to the skull, some of this alternating current reaches the brain. As a result, it causes the cell bodies and dendrites of the cortical neurons to alter their membrane potential towards depolarization or hyperpolarization in an oscillatory fashion [16]. This alternating change in the membrane potential is thought to be sufficient to alter the probability of a neuron generating action potentials [19]. However, it is not strong enough to change the rate of action potentials, as it controls only their timing in a frequency- and location-specific manner [20]. That is why this stimulation seems to be a type of sub-threshold stimulation that does not directly fire neuronal spikes [14, 21].

The influence of tACS depends not only on the amplitude and frequency but also on the three-dimensional orientation of both neurons and the penetrating current [22]. Its effects result from manipulating the membrane potential of neurons that are aligned with the introduced electric field, mostly pyramidal cells in layer V. These cells are extremely sensitive to current changes due to their elongated soma-dendritic axis [22, 23]. Moreover, they have characteristic properties, including intrinsic resonance, neuroplastic activity and cortico-cortical projections [24–26]. Therefore, these cells, once stimulated by tACS, show specific frequency resonance, long-term after-effects and long-range oscillatory cortical connectivity (more details on resonance and after-effects are discussed below). Similarly, the direction of the electric stimulation substantially changes the properties of the resulting field, and thus, its effects on the neurons [27].

In 2018, Liu et al. suggested five different neuronal mechanisms that could translate the previously mentioned cellular effects of tACS into whole network activity at a larger scale [28]. First, stochastic resonance: a wide range of tACS-affected neurons, differing in their momentary probability to generate action potentials, will react stochastically to be either polarized or hyperpolarized. This leads to the absence of a theoretical 'minimum effective threshold'. Second, rhythm resonance: this occurs when the tACS frequency is the same as that of the endogenous oscillations. This ends with the stimulatory current wave striking the endogenous one at a similar phase every cycle. Third, temporal biasing of spikes: the spike timing of neurons is regulated by the interaction between the stimulation and internal currents, which may work synergistically to excite the same group of neurons during each cycle of stimulation. Fourth, network entrainment: the entrainment of an endogenous irregular activity necessitates an external current with sufficiently stronger amplitude. Finally, imposed pattern: to overcome endogenous regular oscillations and introduce a new oscillation, the strongest stimulation is required [28].

These mechanisms support the explanation by Vosskuhl et al. [14] of the large-scale effects of tACS. The authors attributed the online and offline tACS effects to two synergistic phenomena: entrainment and neuroplasticity, respectively. Entrainment, by definition, takes place when an external rhythmic system affects another naturally occurring one, forcing it to follow its own oscillating frequency. During tACS, the external driving current forces the endogenous brain oscillations to follow in terms of frequency and phase [14, 29]. Such entrainment has two crucial properties: "Arnold tongue", and harmonics. Arnold tongues describe the relationship between the stimulation amplitude and its corresponding range of frequencies at which tACS can entrain endogenous brain oscillations. When the amplitude of this stimulation increases, it entrains brain oscillations in a wider range of frequencies [30]. Harmonics describe the preference of an intrinsic oscillator to be trained by tACS at multiple frequencies that have an n:m relationship to the endogenous frequency, e.g., at twice or half the endogenous frequency [23, 31].

For the neuroplasticity to elicit offline effects, long-term plasticity should occur in one form among two primary mechanisms: Long-term-potentiation (LTP) and long-term-depression (LTD), two results of spike-timing-dependent plasticity (STDP) [32]. LTP is the potentiation of a synaptic connection when the presynaptic action potential comes before the post-synaptic potential. In contrast, LTD is the weakening of the synapse if the presynaptic action potential follows the post-synaptic one. Therefore, these phenomena are the primary culprits that elicit offline tACS effects by increasing or decreasing neural synchronization [33]. This explanation has been confirmed by many studies [33–36], which may explain why the offline effects of tACS have been shown to last for 70 min after one stimulation session lasting 20 min [37].

From this standpoint, we try to refer to some unique features of tACS as a neuromodulator in contrast to other forms of NIBS, yet it is relatively new and the least studied form. Transcranial direct current stimulation (tDCS), a closely related type of NIBS that constantly depolarizes or hyperpolarizes the affected neurons [38], specifically changing axonal membrane potential [39]. In fact, tACS is a specific version of tDCS where the current is set to fluctuate sinusoidally between the electrodes rather than exhibiting constant polarity. Similar to tACS, tDCS effects depend on the orientation of the neurons relative to the current direction [40, 41], and it can induce both online and offline neuroplastic effects [42, 43]. Equivalently, tDCS does not directly affect the neuronal firing rate, but rather its probability and spontaneous activity via subthreshold voltage changes [44]. Although tDCS is shown to modulate oscillatory brain activity [45], tACS is more effective at entraining the endogenous brain oscillations as it mimics the alternating nature of brain oscillations [2, 14, 46] (For more details about the mechanisms of action of tDCS, see these reviews: [47–51]).

Another more studied method of NIBS is transcranial magnetic stimulation (TMS), which is approved for the treatment of some psychiatric disorders [52–54]. In TMS, a magnetic field is produced by a coil applied to the scalp and then travels through the skull to elicit electric fields in the cortical neurons [55]. Compared to tACS, TMS, a suprathreshold stimulator, produces action potentials in silent neurons [56] in the form of two successive volleys. While the first volley (direct waves) represents direct activation of pyramid tract axons, the second (indirect waves) reflects synaptic activation of the same neurons [57]. As expected, TMS evokes long-term synaptic changes and thus after-effects beyond the stimulation period [58] (For more details about the mechanisms of action of TMS, see

these reviews: [59–63]). However, practically, tACS exhibits superior cost, portability, tolerability, and safety profiles [64, 65]. In other words, tACS is a feasible tool that reshapes or re-synchronizes intrinsic brain rhythms, manipulating the associated brain functions without adding extra excitatory or inhibitory burden. Given that (1) tACS clinical research is still in its infancy, and (2) tACS possesses such unique features, we aim, in this review, to encourage more tACS usage in psychiatric research.

## Altered brain oscillations and tACS applications in psychiatric disorders:

Given the association between EEG brain oscillations and various brain functions, many researchers have managed to successfully modulate normal cognitive functions by manipulating brain oscillations or connectivity patterns using tACS (for more details see these reviews [7, 14, 65–67]). Motivated by successful tACS applications in cognition, future investigations could aim to normalize pathological brain oscillations, and identify beneficial tACS roles in the management of psychiatric disorders. In this section, we focus on such electrophysiological alterations that could benefit researchers in designing tACS clinical trials in psychiatric patients. Moreover, we review previous clinical trials that have already examined the role of tACS in psychiatry. Six psychiatric disorders are discussed, where a subsection is devoted to each disorder.

It is noteworthy to state two caveats here to properly understand the current state of the literature regarding disturbed brain oscillations in psychiatry. First, this is not a comprehensive overview of disturbed brain oscillations in all psychiatric disorders, but rather, it presents six of the most studied and major disorders. Hence, this section is intended to provide only a glimpse of this interesting electrophysiological approach in psychiatric pathophysiology. Second, because of the heterogeneity of the studies and the limited knowledge of some disturbed oscillations, we tried to selectively focus on some of the more replicated and reproduced findings supported by different studies. Therefore, the following electrophysiological changes should be extrapolated with extreme caution before building around them to design tACS protocols.

The results of tACS clinical studies were identified according to a systematic search on PubMed using two keywords with the Boolean operator "AND". The first keyword was "tACS" or "alternating current stimulation" throughout the search process. The second term was changeable to signify several psychiatric disorders ("ADHD", "Insomnia", "Depression", "Schizophrenia", "Bipolar", "OCD", "Anxiety", "PTSD", "Dementia", and "Alzheimer"). The search process, last performed in June 2020, yielded a total of 151 records, including 68 duplicates. The original 83 publications were screened to exclude 31 non-tACS relevant articles and 15 reviews. After a careful assessment of the remaining 37 studies, a stroke-related article and 18 non-clinical experiments were excluded. Five publications actually applied cranial electrotherapy stimulation (CES) rather than tACS, and thus were excluded. The remaining 13 eligible articles, which show the experimental application of tACS in patients with any psychiatric disorder, were included (see Fig. 1 [68]).

The included articles comprise study designs with different levels of evidence: three randomized double-blind controlled trials, two single-blind randomized controlled trials, an open-label non-controlled clinical trial, a longitudinal case–control study, two case series, and four case reports (see Table 1). They cover five different psychiatric disorders: one study on attention-deficit/hyperactivity disorder (ADHD), three publications on depression, seven on schizophrenia, one on dementia, and one case series on OCD. Some of the included articles conducted a relatively non-robust study design, such as case reports. However, we will consider them in further discussion due to the limited number of clinical trials and the variety of investigated psychiatric disorders. Accordingly, the reader could appreciate the shortage of evidence to apply tACS in psychiatry. After discussing the included articles for each disorder, we state some general remarks on the application of tACS in participants with psychiatric illnesses.

### Schizophrenia

With the aid of EEG and MEG, a great bulk of research has already identified characteristic alterations of brain oscillations in patients with schizophrenia [69]. These electrophysiological fingerprints of schizophrenia have been shown to be heterogeneous but task-/state-, location, and frequency-specific, where they, in turn, correlate with the severity of certain symptoms [70]. However, such heterogeneity is not surprising given the heterogeneity of clinical presentations in schizophrenia [71]. Pertaining to the task/state aspect, three distinctive patterns of brain oscillations were identified: evoked, induced and resting-state [69]. Each type could be compromised peculiarly in schizophrenia, so tACS strategies should precisely consider which one/ones to modify.

Regarding the frequency and location domains, the results might be harmonious in the low-frequency range (alpha and theta), whereas they are not in the high-frequency range (beta and gamma). A general persistent finding in schizophrenia is reduced alpha power, especially in the resting-state, which might be linked to the increased state of arousal and abnormal self-referential processing [70, 72–76]. Delta and theta waves are mostly elevated [77–79], but only theta activity is decreased, especially in the frontal lobe [80], correlating

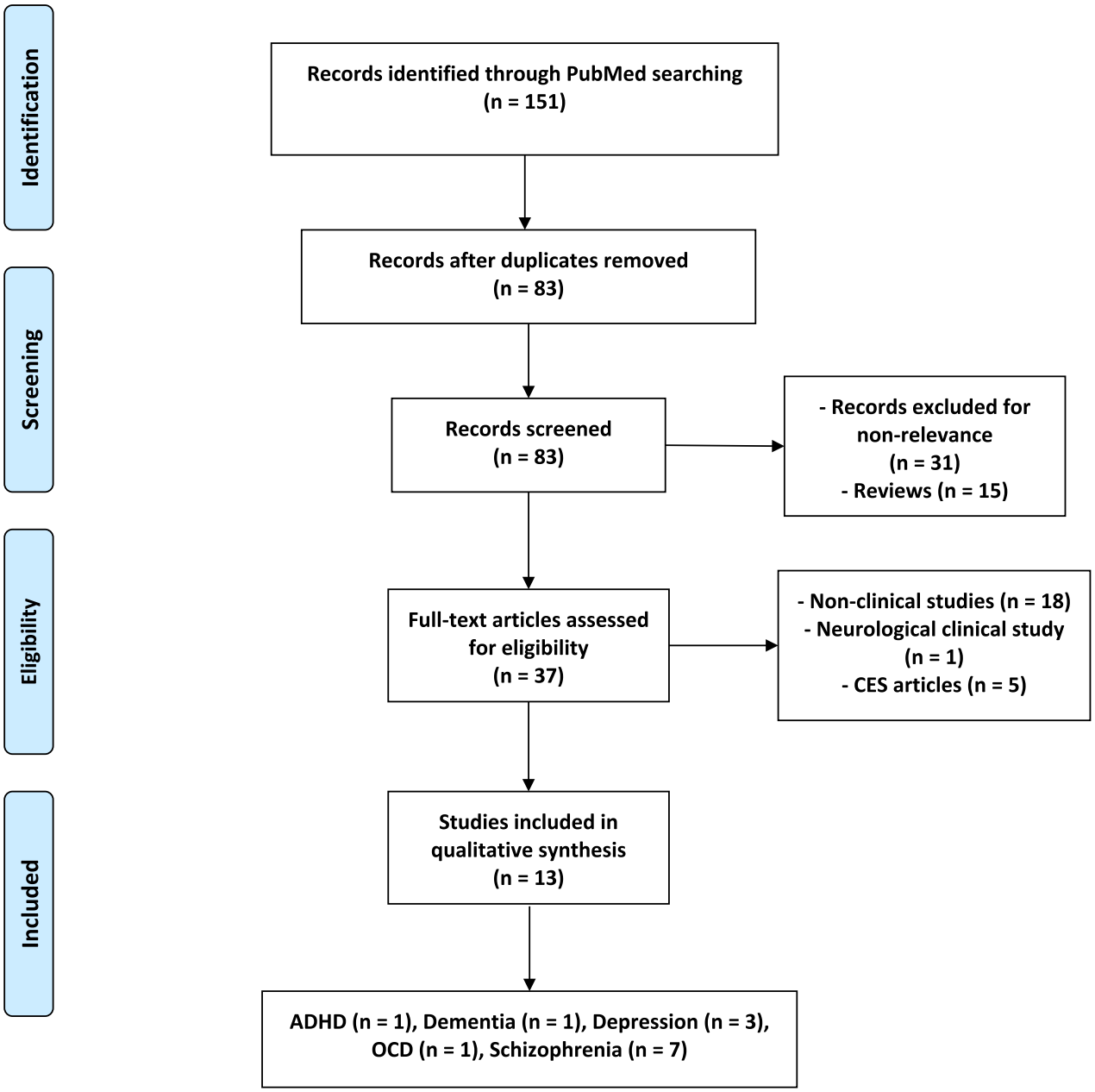


**Fig. 1** PRISMA Flow Diagram of the included articles [68]. *ADHD* attention deficit hyperactivity disorder, *CES* cranial electrotherapy stimulation, *OCD* obsessive-compulsive disorder

with an impairment in working memory [81, 82]. Furthermore, theta-band connectivity was shown to be increased, especially between the frontal and parietal regions, during the resting state [83, 84]. Although beta activity in schizophrenia is not well-studied, some studies showed that it was decreased in both resting-state and task-related brain activity [85, 86]. Alterations of gamma-band oscillations have been extensively investigated as a neurobiological correlate of different stages and symptoms of schizophrenia [87] and are commonly interpreted as an imbalance between excitation and inhibition (E/I-balance), which is considered a crucial mechanism in the pathophysiology of schizophrenia [88].

A major and often replicated finding in schizophrenia is the reduction of stimulus-evoked task-related gamma power and coherence between different brain regions [85, 89–95], which, besides the chronic illness, appears across different stages and models of the disease, including in patients with their first episode of psychosis [95, 96], in healthy relatives of patients [97, 98], in subjects at high risk for developing psychosis [99], and in the ketamine model of schizophrenia

**Table 1** Included articles on psychiatric applications

| Publication | Study design | Participants | Stimulation protocol | | | | | Study outcomes | Main Findings |
|---|---|---|---|---|---|---|---|---|---|
| Author, Year | | | Sessions' number | Session duration | Current amplitude (Peak-To-Peak) | Frequency | Electrode Location | | |
| A. Schizophrenia | | | | | | | | | |
| Sreeraj et al. [125] | Case report | One patient with paranoid schizophrenia | Two sessions with 2 days apart | 20 min | Session 1: 2 mA, session 2: 1 mA | Session 1: 6 Hz, session 2: 40 Hz | Left DLPFC (F3) and the left posterior parietal region (P3) | WM task | Improved performance in the WM task only with 6 Hz tACS |
| Sreeraj et al. [126] | Case report | One patient with paranoid schizophrenia | 5 sessions for 5 consecutive days | 20 min | 2 mA | 6 Hz | Left DLPFC (F3) and the left posterior parietal region (P3) | WM task | - Improved working memory<br>- Improvement in other cognitive domains<br>- Persistence of improvement for 50 days |
| Kallel et al. [127] | Open case series | 3 clozapine-resistant patients with schizophrenia | 20 daily on weekdays for 4 consecutive weeks followed by 4-week follow-up | 20 min | 2 mA | 4.5 Hz | Both DLPFCs | SANS; PANSS; SUMD; HAMA; and side effects | Reduction in negative symptoms, anxiety and general psychopathology symptoms, and improvement in insight |
| Sreeraj et al. [128] | Open-label non-controlled clinical trial | 12 patients with schizophrenia and persistent delusions | Twice daily for 5 days, 9 patients continued for 5 more days, and another patient continued for 4 more days | 20 min | 2 mA | 10 Hz | Two electrodes on AFz and Cz | PSYRATS—Delusions, SAPS and SANS | - Reduction in the delusion severity, positive and negative symptoms as well as tolerance of tACS<br>- Maintained effect for one month |
| Hoy et al. [129] | Single-blind randomized controlled trial | 10 patients with schizophrenia | Three separate sessions at least 3 days apart | 20 min | 2 mA | 40 Hz-tACS, tDCS and sham stimulation | Left DLFPC | WM task | No significant tACS effects |
| Mellin et al. [4] | Double-blind randomized controlled trial | 22 patients with schizophrenia | Twice daily for 5 consecutive days | 20 min | 2 mA | 10 Hz, tDCS or sham | Left frontal and temporal lobes | Primary outcome: AHRS, secondary outcome: PANSS, BACS | No significant results |

**Table 1** (continued)

| Publication<br>Author, Year | Study design | Participants | Stimulation protocol | | | | | Study outcomes | Main Findings |
|---|---|---|---|---|---|---|---|---|---|
| | | | Sessions' number | Session duration | Current amplitude (Peak-To-Peak) | Frequency | Electrode Location | | |
| Ahn et al. [131] | Double-blind randomized controlled trial | 22 patients with schizophrenia | Twice daily for 5 consecutive days | 20 min | 2 mA | 10 Hz, tDCS or sham | Left frontal and temporal lobes | AHRS, hdEEG | - 10 Hz-tACS showed modulated functional connectivity, and enhanced alpha oscillations and 40 Hz ASSR<br>- This enhancement correlated with the reduction of auditory hallucinations |
| B. Depression | | | | | | | | | |
| Alexander et al. [150] | Double-blind, randomized pilot clinical trial | 32 MDD patients | 5 consecutive days | 40 min | 4 mA at Cz, 2 mA at F3 and F4 | 10 Hz-tACS, 40 Hz-tACS); or sham | Bifrontal: Two electrodes over F3 and F4, and a third over the vertex | Primary outcome: MADRS at 4-week follow-up, secondary: hdEEG, HDRS, BDI | - No significant primary outcome<br>- Two weeks after completion of the intervention, the 10 Hz-tACS group had more responders compared with 40 Hz-tACS and sham groups as well as a significant reduction in alpha power over the left frontal regions at day 5 |
| Riddle et al. [151] | Case report (extension of (Alexander et al., 2019)) | One female MDD patient | 12 weekly sessions | 40 min | 4 mA at Cz, 2 mA at F3 and F4 | 10 Hz-tACS | Bifrontal: Two electrodes over F3 and F4, and a third over the vertex | Daily self-reported 10-point Likert scale, and monthly MADRS | Remission (MADRS = 1 7) after twelve weeks |

**Table 1** (continued)

| Publication Author, Year | Study design | Participants | Stimulation protocol | | | | | Study outcomes | Main Findings |
|---|---|---|---|---|---|---|---|---|---|
| | | | Sessions' number | Session duration | Current amplitude (Peak-To-Peak) | Frequency | Electrode Location | | |
| Wilkening et al. [152] | Case report | One female pregnant MDD patient | 9 weekly sessions | 20 min | 2 mA | 40 Hz-tACS with DC offset | Bifrontal: Two electrodes over F3 and F4 | HDRS, BDI, PANAS, and TMT | Improved scores after 9 stimulations, and after two-week follow-up. Remission after three months |
| C. OCD: | | | | | | | | | |
| Klimke et al. [3] | Cases series | 7 OCD treatment-resistant patients | 3 session per week. Treatment duration varied across patients<br>Follow-up duration was 58 days and one year for 4 patients and the other three, respectively | 20 min | 650 µA | 40 Hz | Fp1-T3 and Fp2-T4 | YBOCS, CGI | The symptoms improved in all patients, and the improvement lasted throughout the follow-up duration |
| D. ADHD | | | | | | | | | |
| Dallmer-Zerbe et al. [185] | Randomized single-blind controlled study | 18 ADHD patients | One stimulation or Sham | 20 min | 1 mA | Timing and frequency personalized to coincide the stimulation peaks with P300 oscillation peaks | Multiple electrodes on the central, parietal and temporal lobes | EEG, visual oddball task | Increase in P300 amplitude in the stimulation group accompanied by a behavioural improvement defined by a decrease in omission errors |
| E. Dementia: | | | | | | | | | |

**Table 1** (continued)

| Publication | Study design | Participants | Stimulation protocol | | | | | Study outcomes | Main Findings |
|---|---|---|---|---|---|---|---|---|---|
| Author, Year | | | Sessions' number | Session duration | Current amplitude (Peak-To-Peak) | Frequency | Electrode Location | | |
| Naro et al. [194] | Longitudinal case–control study | 35 AD and 25 MCI individuals and 27 age-matched health participants | Both sham and one of five verum stimulation sessions on a weekly basis | 10 min | 1 mA | A range between 40 and 120 Hz at steps of 20 Hz | Left M1, PMA, SMA, DLPFC, or DMPFC | EEG and different neuropsychological tests (see text) | - Enhancement of gamma-band oscillations and a clinical improvement in MCI, but not AD patients<br>- tACS predicted the progression from MCI to AD |

[100]. Most of the studies showing reduced task-related gamma oscillations examined impaired cognitive function [101]. However, there are also reports linking increased stimulus-related gamma-synchrony to positive schizophrenia symptoms [102]. As well, in terms of gamma power, the evoked visual gamma-band response is correlated with positive and disorganised schizophrenia symptoms [103], and even with positive schizotypal personality traits [104]. Moreover, spontaneous gamma oscillations and/or gamma-band connectivity measured in resting state conditions are enhanced in patients with schizophrenia [105–113], especially in patients with positive or reality distortion symptoms (hallucinations and delusions) [114].

Revisiting the binding theory of mental representations [115], which assigns mental imagery to the interaction between distant brain regions (a synchronization in the gamma range) [116], such an increase or decrease in gamma oscillations may explain different phenotypes of schizophrenia. For example, the increase in gamma-band power and phase locking (i.e., connectivity) could be related to the emergence of new perceptual representations that are normally absent in healthy individuals, such as auditory hallucinations. In contrast, the decrease in gamma oscillations could be a sign of brain disintegration, and thus, the cause of the impairment or deterioration of normal cognitive functions in normal people. According to these observations, we consider schizophrenia a combination of different clinical presentations that are associated with dysconnectivity [117], not disconnectivity, of the brain, where the differential contributions of different dysconnectional (connection or disconnection) patterns of the patients' brain determine their explicit clinical picture. This functional dysconnectivity is also confirmed by the aberrant underlying anatomical and cellular dysconnectivity [117–119].

In accordance with this assumption, cognitive impairments and negative symptoms in schizophrenia have been linked to reductions in gamma power and phase coherence, whereas positive symptoms are associated with increased gamma activity. In this regard, tACS may help with the diagnosis of and differentiation between different schizophrenic clinical syndromes, in addition to its role in treatment. Future research could exploit tACS-directed characterization of specific oscillatory endotypes in distinct schizophrenic presentations.

One of the main positive symptoms of Schizophrenia is the presence of auditory hallucinations that are sometimes treatment-resistant [120]. In EEG studies, auditory hallucinations in people with schizophrenia are significantly correlated with functional connectivity between both primary auditory cortices. Such enhanced functional connectivity is manifested in the phase synchronization between brain oscillations in both auditory cortices in the range of gamma-band frequencies [102, 121]. Interestingly, this phenomenon was

further confirmed by structural changes using diffusion tensor imaging (DTI) [122]. These findings, in turn, support the interhemispheric miscommunication hypothesis of auditory hallucinations [123]. In the light of these discoveries, tACS was able to manipulate auditory perception in healthy participants by decoupling this interhemispheric connectivity. A remarkable finding was that the individual indigenous brain oscillations prior to stimulation dictated the resulting effects of tACS, favouring the use of individually tailored stimulation paradigms [124].

### Clinical tACS studies

Seven publications studied the application of tACS in patients with schizophrenia. They ranged widely in terms of the evidence-based medicine hierarchy. Two case reports and a case series were reported, while the other four publications were clinical trials. Two of them were an open-label non-controlled trial and a single-blind randomized controlled trial. Finally, two publications comprised a well-structured double-blind randomized controlled study.

The two case reports were published by the same research group to examine the feasibility of tACS in schizophrenia. They were based on previous findings of reduced theta and gamma oscillation in relation to working memory, especially on the frontal region. One of them showed that one session of 20 min tACS applied to the left DLPFC (F3) and the left posterior parietal region (P3) in theta frequency (6 Hz), but not gamma (40 Hz), was able to improve performance in WM task [125]. The same tACS protocol was replicated in the other case report but for five consecutive days, resulting in improved working memory after 6 Hz-tACS, as well as an improvement in other cognitive domains. After 50 days of follow-up, these effects remained observable [126].

Similarly, the open case series in schizophrenia investigated the efficacy and safety of theta tACS, as theta waves are reduced in the frontal region. The study applied 20 daily tACS sessions for 4 weeks on working days in three subjects with clozapine-resistant schizophrenia. 4.5 Hz-tACS targeted both right and left DLPFCs with an amplitude of 2 mA for 20 min per session. Patients were assessed according to their psychiatric clinical symptoms (positive, negative and anxiety), and illness insight, as well as tACS adverse events. They showed a reduction in negative symptoms, anxiety and general psychopathology symptoms with improvement in illness insight [127].

Although the abovementioned case reports obtained results from only a few patients, they may support the feasibility of tACS in schizophrenia research. These effects might be long-term and frequency specific. Furthermore, the case series succeeded in reducing the schizophrenia symptoms and improving insight into treatment-resistant patients without serious side effects. However, well-structured controlled clinical trials are necessary to confirm these findings and to control for the placebo effect. Further research may need to verify modulation of the targeted oscillations using pre- and post-stimulation EEG recordings.

Motivated by the replicated finding of decreased frontal alpha activity in schizophrenia, the open-label non-controlled trial attempted to assess the safety and efficacy of alpha tACS on persistent delusions [128]. The trial recruited 12 patients with schizophrenia who exhibited persistent delusions, despite pharmacological treatment. All patients received two 20-min sessions per day separated by 3 h for 5 days. Nine of them received stimulations for five more days, and only one participant continued for four more days. tACS of 10 Hz was applied with 2 mA intensity via two electrodes over AFz and Cz. The study aimed to decrease persistent delusions by normalizing alpha oscillations in the medial prefrontal region. The patients were monitored by the Psychiatry Rating Scale (PSYRATS)—Delusions, the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS) and were followed up for one month. The results showed a reduction in the delusions, as well as positive and negative symptoms, which was maintained for one month. Interestingly, the patients tolerated the twice-daily regiment without serious side effects.

This study supports the feasibility of twice-daily stimulation and opens the door for the replication of frontal alpha tACS effects on persistent delusions as an add-on option. However, major limitations still exist that should be controlled for in further research. The sample size was small without a placebo control group, and patients were taking different medications, which might have affected the results.

One included publication was a single-blinded, randomized, controlled trial, which attempted to target frontal gamma oscillations that are reduced in schizophrenia. Ten patients with schizophrenia participated in three separate 20-min sessions at least three days apart. They randomly received one of three stimulation protocols: 40 Hz tACS, tDCS and sham stimulation. 40 Hz tACS was delivered on the left DLPFC with an amplitude of 2 mA. Meanwhile, they performed a working memory task before, during and after every stimulation session. The study did not report any significant effects of tACS on the task parameters or any serious side effects [129].

Given the small sample size, this study did not exclude the potential rule of gamma tACS on working memory in subjects with schizophrenia. More interestingly, the trial obtained neither pre- nor post-EEG recordings and did not utilize field modelling tools. The lack of an observed effect in response to tACS may be attributed to the difficulties of gamma stimulation per se or to different brain dynamics in patients, especially since the same group managed to

improve working memory in healthy controls using the same stimulation protocol [130].

The remaining two publications on schizophrenia addressed the first well-structured randomized, double-blind, controlled clinical trial in patients with psychiatric disorders [4, 131]. It investigated the role of alpha tACS based on abnormalities in alpha oscillations over the frontal and temporal regions in schizophrenia. Twenty-two hallucinating participants with schizophrenia were randomized into three groups. While one control group received sham stimulation, the other active ones received either 10 Hz tACS (2 mA) or tDCS. Both were applied to the left frontal and temporal lobes. All groups received two 20 min sessions per day for five consecutive days. The primary outcomes were the improvement of auditory hallucinations calculated by the Auditory Hallucination Rating Scale (AHRS) and High-Density Electroencephalogram (hdEEG). Meanwhile, the secondary outcomes included the Positive and Negative Syndrome Scale (PANSS) and the Brief Assessment of Cognition in Schizophrenia (BACS). Only the group that received 10 Hz tACS exhibited modulation of functional connectivity, and enhancement of alpha oscillations and the 40 Hz auditory steady-state response (ASSR). Such enhancement correlated with a reduction in auditory hallucinations as measured by AHRS [131]. However, the primary and secondary clinical outcomes did not reveal significant effects.

This trial is not only the first clinical trial conducted in patients with schizophrenia, but it revealed the ability of tACS to modulate disturbed alpha oscillations in schizophrenia as well [72, 74]. Interestingly, such a modulation correlated with a reduction in auditory hallucinations as a clinical parameter. Despite this correlation, the clinical outcome did not reach significance. This might be attributed to the small sample size and/or the significant inter-group variation in age, especially since tACS showed the largest effect size for AHRS. Hence, this study requires further replications with a larger sample size and longer duration of follow-up to verify the efficacy of normalization of disturbed alpha oscillations in improving schizophrenia symptoms. Having reported no serious side effects, this study may justify the twice-daily stimulation protocol.

## Depression

Depression, similar to schizophrenia, shows a comparably complex picture of altered brain oscillations [132]. The electrophysiological features of depression manifest some heterogeneity, as well as a greater dependence on the frequency [132, 133]. Either in terms of the power or the coherence, the low-frequency bands (delta, beta and alpha) were enhanced during the resting-state in depression, in particular, alpha oscillations, which persist even after the transition from closed-eyes to open-eyes states [85, 133–136]. Additionally, the same waves indicated specific connectivity, interhemispheric asymmetries, and even probable prognostic patterns.

In the alpha-band synchrony, the dorsolateral prefrontal cortex (DLPFC) is more connected to the anterior cingulate gyrus [137] and temporal and parietal occipital regions [136]. Alpha-band interhemispheric comparisons revealed frontal alpha asymmetry (FAA) and parietotemporal alpha asymmetry, where the left hemisphere shows more alpha power and local synchrony than the right hemisphere [132, 138, 139]. Interestingly, enhanced alpha activity in depression was associated with better response to antidepressant therapies [140, 141]. Though theta waves were also mostly increased in depression, especially within the frontal short-range functional connections [142], in contrast to alpha waves, the enhanced frontal theta waves were correlated with decreased response [143].

Gamma oscillations differ significantly depending on the state, as they were reduced in the anterior cingulate cortex and in the frontal regions during the resting state and emotional tasks, respectively [144, 145]. Nevertheless, they were enhanced in the frontal and temporal lobes in response to spatial and arithmetic tasks [146]. Interestingly, gamma activity differentiated unipolar depression from bipolar depression according to its power in two different tasks: an auditory task augmented gamma ASSR power in unipolar depression, while an emotional task enhanced temporal and suppressed frontal gamma powers in unipolar depression with respect to bipolar depression [147–149]. Different antidepressant options exhibited either increased or decreased gamma oscillations: serotonergic medications, cognitive therapy and deep brain stimulations dampened them; and in contrast, noradrenergic drugs, ketamine and TMS induced them [145].

### Clinical tACS studies

Three eligible articles examined the application of tACS in depression: one of them is a well-structured double-blind randomized controlled trial, while the other two present two case reports. In the double-blind randomized clinical trial, tACS targeted pathologically increased alpha waves on the left frontal region compared to the right frontal region (i.e., FAA). The study aimed to restore the frontal alpha oscillations by synchronously stimulating both frontal regions. Therefore, 32 patients with Major Depressive Disorder (MDD) were randomly recruited to three study groups: two groups were given two verum tACS protocols (10 Hz-tACS or 40 Hz-tACS) with an amplitude of 4 mA at Cz and 2 mA at F3 and F4, and the third group received active sham stimulation. The session took 40 min and was repeated for five consecutive days. The left DLPFC was the stimulation target area, aiming to improve clinical symptoms by retaining its normal alpha frequencies. The primary and secondary

outcomes included the clinical symptoms applying Montgomery–Asberg Depression Rating Scale (MADRS) at 4-week follow-up and the normalization of alpha oscillations using hdEEG, respectively. Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI) were chosen as exploratory outcomes. The study found no significant results regarding the primary outcome. In terms of MADRS and Hamilton Depression Rating Scale (HDRS), there were more responders at the two-week follow-up in the group that received 10 Hz-tACS. Concerning hdEEG, the same group showed significantly decreased alpha power in the left DLPFC on day 5. Moreover, there were no serious adverse events, manic shift or suicidal ideation induction [150].

This is the first well-structured clinical trial to record an effect of tACS stimulation in some patients with depression who were treated for two weeks by resetting the oscillatory brain disturbances. Such an effect was confined to alpha stimulation but not 40 Hz stimulation. This supports the idea that only stimulation at a specific frequency alters the oscillatory pattern and thus the behavioural outcome. However, this effect was not maintained after the 4-week follow-up and did not involve the primary outcome. Therefore, a larger number of stimulation sessions and longer follow-up periods should be encouraged since no serious adverse events were detected. Although no FAA was detected in the study sample at baseline, five sessions of 10 Hz-tACS managed to decrease the alpha power over the left frontal region. This might contradict that alpha tACS is supposed to enhance the alpha power as an immediate after-effect. Therefore, further research is needed to identify the possible mechanisms through which alpha tACS decreased the alpha power as a long-term effect. Given the small number of participants in this study, further research should be conducted with a larger sample size.

One of the included case reports on depression was an extension of the previous clinical trial where one participant received extra 12 weekly sessions of 10-Hz tACS. After the original study, the patient showed a response to the treatment without remission. After the 12 sessions, remission was achieved and maintained for at least a 2-month follow-up [151]. Despite being performed on a single participant, this study might support the feasibility of long-term tACS as a potentially safe tool in MDD treatment research.

The other case report examined the effect of frontal tACS at the gamma frequency band, which is reduced frontally in depressed patients [152]. A pregnant female MDD patient was recruited into the study at week 6 of pregnancy. She received 40 Hz-tACS of 2 mA over both DLPFCs (F3 and F4) for 20 min per session. After nine weekly stimulation sessions, she was followed-up at two weeks and three months (week 27 of the pregnancy) after the intervention. Her depression condition was monitored by HDRS, BDI, Positive and Negative Affect Schedule (PANAS) and Trail Making Test (TMT). The study only reported phosphenes without serious side effects. At the end of the nine stimulation sessions and 2-week follow-up, the patient showed improvement in her symptoms and experienced remission after three months. However, it is noteworthy that the same patient showed remission on tDCS used to treat a previous depressive episode. Therefore, the outcome could be attributed to a placebo effect or the stimulation per se, especially because no EEG recordings were done throughout the study [152]. Nonetheless, this case report may encourage further application of tACS in research on pregnant patients as a relatively safer option compared to pharmacotherapeutic agents.

## Obsessive–compulsive disorder

An enormous body of evidence has shown decreased alpha activity in resting state, task-based and symptom-provocation studies in obsessive–compulsive disorder (OCD), especially in frontal areas (hyper-frontality), reasoning the mental overactivity in OCD [139, 153–158]. Interestingly, the location of the resting alpha reduction was subtype-specific: within the frontotemporal areas in doubting OCD subtype; while over the parietooccipital regions in the checking subtype [159]. Unlike depression, alpha asymmetry is not a stable finding in OCD. Nevertheless, it is more pronounced in the doubting OCD with decreased left alpha waves [139, 159]. The decreased alpha activity during the task state may reflect the augmented readiness and/or the preoccupation of OCD patients by obsessions [160]. Surprisingly, alpha synchronization in working memory was reinforced, proposing a compensatory mechanism to inhibit irrelevant information [139, 161].

Theta and delta power, especially in frontal regions [157, 162–165], are augmented in OCD [154, 157, 159, 166, 167], where theta augmentation, similar to in depression, is correlated with poor response to treatment [168, 169]. The findings of beta oscillations were broadly inconsistent [169], but it is thought to be frontally elevated, originating from the anterior cingulate gyrus [166, 167]. Moreover, the frontal beta showed interhemispheric asymmetry with increased activity on the left side [166]. Although gamma-band oscillations are not well studied in OCD, they are thought to be generally decreased [85]. TACS might be used to normalize the altered oscillations, to potentiate the compensatory changes, and to differentiate subtypes in OCD.

### Clinical tACS studies

Only one publication on OCD was included, which discussed a case series of seven treatment-resistant OCD patients. The authors suggested that "DLPFC activity in OCD might be

pathologically reduced", and thus gamma tACS might lead to its activation. 40 Hz tACS was administered at both frontotemporal sites (Fp1-T3 and Fp2-T4) to stimulate DLPFC. Patients received three 20-min sessions per week, while the duration of treatment varied across patients from two to seven weeks. All patients were clinically evaluated via the Yale-Brown Obsessive–compulsive Scale (YBOCS) and Clinical Global Impression Scale (CGI) on day 1 before tACS stimulation, and 28 and 56 days later. Three patients were followed up for 1 year. Symptoms improved in all patients, and the improvement lasted throughout the follow-up duration [3].

The study successfully reduced clinical symptoms of OCD, opening the door for further tACS research in OCD. However, it lacks EEG recordings to evaluate the effect of gamma stimulation on DLPFC. More importantly, it addressed only seven patients with different ages and medication parameters, and the placebo effect cannot be ruled out. Further double-blind controlled studies are necessary to investigate the reproducibility of such an empirical finding.

## Bipolar disorder

Generally, alpha oscillations are inhibited in bipolar patients in many aspects: both resting and evoked alpha waves, with eyes closed or open, and in euthymic or manic participants [170–172]. In contrast, theta and delta oscillatory activity is enhanced [170, 173–175]. Likewise, an enhancement in the beta power response to different stimuli was recorded, which differentiated bipolar disorder from schizophrenia [171, 176–178]. Nonetheless, the beta synchronization was decreased at rest and in response to an auditory stimulation [179, 180]. Both manic and euthymic patients showed a decreased gamma coherence as evoked by diverse stimuli [96, 148, 181–183]. In summary, the oscillatory changes in bipolar disorder curb the resting-related alpha waves, as well as beta and gamma synchronization, leading to restrained connectivity between brain regions. These two principal findings may explain the disturbed racing thoughts and the distractibility in patients [184] and could be targeted by tACS for normalization. So far, no clinical study investigating the role of tACS in bipolar disorder has been reported according to the systematic search.

## Attention-deficit/hyperactivity disorder (ADHD)

Only one included article addressed ADHD as a single-blind randomized controlled trial. In ADHD, the target P300 amplitude shows some reduction, which is associated with typical cognitive performance deficits in ADHD. Therefore, the trial investigated the role of tACS in potentiating the target P300 amplitude as disturbed brain oscillations in the theta and delta range. In addition, it aimed to improve cognitive performance in patients with ADHD by such P300 amplification. Therefore, EEG was used to examine brain activity in 18 patients with ADHD underlying a visual oddball paradigm. During the task, 1 mA tACS was applied for 20 min through multiple electrodes on the central, parietal and temporal lobes. The stimulation timing and frequency were personalized so that the stimulation peaks could coincide with P300 oscillation peaks to amplify them. The study found P300 amplitude to be significantly augmented in the verum group compared to the sham condition. Interestingly, this P300 amplification was accompanied by a behavioural improvement in task performance. No serious adverse events were reported [185].

This clinical trial is not only the first study to support research on the role of tACS in ADHD, but it also substantiates tACS applicability to modulate event-related potentials for clinical relevance. Nonetheless, future studies could replicate it with more patients and compare tACS effects in patients and healthy controls, especially because a similar stimulation protocol did manage to alter P300 parameters in healthy participants [186]. However, this study paved the way for the feasibility of tACS to modulate event-related potential components with subsequent behavioural improvement without serious side effects.

## Dementia

To the best of our knowledge, there is no available study using tACS as a treatment in either Alzheimer's disease (AD) or dementia. Only a single included study examined the role of tACS as a prognostic factor in predicting the progression of patients with mild cognitive impairment (MCI) to AD. The study was based on findings of decreased gamma-band connectivity in AD [187–192] and increased local gamma-band power in contrast to MCI during resting and task conditions [193]. The study questioned whether the response to gamma tACS could differentiate MCI from AD and predict the progression of MCI to AD. The authors recruited 35 AD and 25 MCI individuals, as well as 27 age-matched healthy participants, and followed them up for 2 years. On a weekly basis, each participant randomly received both sham stimulation over the left primary motor area (M1) and five verum stimulation sessions. Gamma-band tACS was applied for 10 min to one of the following sites per verum session: M1, premotor area (PMA), supplementary motor area (SMA), DLPFC, or the dorsomedial prefrontal cortex (DMPFC). Stimulation of 1 mA was set to vary continuously and randomly in a range between 40 and 120 Hz at steps of 20 Hz, with zero-degree phase-lag. EEG was recorded before and after each session in addition to a follow-up EEG after 2 years.

tACS caused enhancement of gamma-band oscillations and a clinical improvement according to different

neuropsychological tests in MCI patients. AD patients, however, showed neither. After 2 years, a group of MCI patients progressed to AD. Interestingly, this group did not report any tACS after-effects before the 2-year follow-up period [194]. The sessions were well tolerated by the patients.

This is the first publication to report the use of tACS on dementia. Its results might help to identify the potential role of tACS in the differential diagnosis of MCI and AD and in prognosis prediction for MCI. Nevertheless, it is still far from providing a biomarker for dementia progression given the discrepancy between connectivity within and local power of gamma oscillations. Further research should replicate this study in larger sample sizes to verify the reproducibility of these findings. Moreover, follow-up time points should be encouraged with EEG recordings to obtain electrophysiological markers of the disease progression.

## General discussion

To the best of our knowledge, this is the first systematic literature search to report studies that apply tACS in clinical psychiatric research. tACS publications on five different psychiatric disorders were reported. First, in schizophrenia, frontal alpha tACS was promising as an add-on treatment for persistent delusions [128] and was capable of normalizing disturbed alpha oscillations correlated with a decrease in auditory hallucinations [4, 131]. On the other hand, frontal gamma tACS has not shown effects so far [125, 129]. Case reports revealed that frontal theta tACS could be helpful for improving clinical symptoms, even in schizophrenia with clozapine resistance [125–127]. Second, in depression, bifrontal alpha tACS was able to normalize alpha oscillations and concurrently showed a higher response rate for at least two weeks [150]. Two case reports showed that tACS might be safely tolerated, even for a large number of sessions or during pregnancy [151, 152]. Third, a case series in OCD with seven patients revealed an empirical improvement in symptoms after frontal gamma tACS [3]. Fourth, a single-blind trial managed to amplify P300 in ADHD patients with subsequent improvement in working memory task [185]. Finally, frontal gamma tACS might support a potential role for tACS as a diagnostic or prognostic tool in MCI and AD [194]. All the studies reported neither serious side effects nor exacerbation of clinical symptoms (i.e., manic shift or worsening of the clinical phenotype) [3, 4, 125–129, 131, 150–152, 185].

Despite the very limited number of studies applying tACS in psychiatry, its efficiency seems promising in the psychiatric field keeping in mind the following considerations: (1) some studies have recruited treatment-resistant patients, and managed to diminish their symptoms [3, 127]; (2) the relatively good safety profile of tACS may advocate twice-daily stimulations, use in pregnancy, or large stimulation doses without fear of clinical worsening [128, 131, 150–152]; (3) the novelty of its treatment approach targeting specific alterations of brain functions at specific locations makes it significantly differ from conventional treatment strategies, such as pharmacotherapy. Although psychotropic drugs are widely accepted and approved in psychiatry, they still pose substantial problems with resistance, compliance and safety profile [195–197]; (4) tACS could help to target baseline oscillations, as well as event-related potentials [185]; (5) utilization of tACS should not be restricted to therapeutic purposes. The reactivity of the brain circuits to the stimulation protocol could serve as a possible tool to determine the diagnosis, classification or prognosis of psychiatric disorders, for instance, in patients with MCI [194]. However, tACS in psychiatric research is still far from being approved as a reliable tool for the management of psychiatric conditions. Further research is necessary to replicate these findings and to answer important questions.

An intriguing problem might be whether disturbed brain oscillations are causally related to the disorder or represent just an association. Moreover, it is not yet clear whether tACS can be investigated as a stand-alone therapeutic tool or rather an add-on option to target specific residual symptoms. The concomitant use of drugs while applying tACS could complicate future research. Drug-naïve and drug-non-compliant patients could be recruited to rule out effects of the drugs or to prove a synergistic or antagonistic effect between both tACS and pharmacotherapy. Along with this, the therapeutic role of tACS should be precisely defined with respect to whether it can improve the whole clinical picture of psychiatric illness [150] or is confined to targeting a specific modality of symptoms [185] that did not respond to other therapeutic options. Referring to the phenomenon of Arnold tongues, the weak tACS current could entrain the brain activity associated with a certain brain state when the stimulation targets these brain oscillations at their frequency. Hence, a certain brain state may be induced in participants to maximize these oscillations, so they can easily be entrained by tACS (i.e., state-dependent stimulation) [198]. In that sense, tACS could be initially used to target a pattern of brain oscillations driven by a single modality or symptom of psychiatric disorders. This was shown to be possible in targeting P300 amplitude driven by WM in ADHD and gamma oscillations induced by WM in MCI [185, 194].

The discrepancy of brain dynamics and response to tACS between healthy participants and patients constitutes an enigma that should be considered during replication of similar stimulation protocols. Healthy participants may be more susceptible to specific tACS stimulation protocols than patients with psychiatric disorders [129, 130] or vice versa [185, 186]. Similarly, acute and chronic patients may show distinct tACS responses, especially tACS after-effects, which

necessitates long-term plasticity that might be affected in chronic patients [199]. Future research may try to determine potential responders to tACS based on their electrophysiological markers or clinical phenotype.

In light of these future research questions, several points could be highlighted. The more individualized the stimulation protocol is designed, the more effectively it normalizes the disturbed oscillations, for example, in the schizophrenic case reports and the ADHD study [125, 126, 185]. tACS effects do not depend on the direct application of a specific frequency per se but on modulation of the pre-existing endogenous oscillations that are coupled with the specific brain state. Accordingly, it might be helpful to personalize future stimulation paradigms, by individually defining disturbed EEG patterns regarding frequency and localization of interest prior to stimulation and then tailoring the stimulation parameters (frequency and location of stimulation) accordingly [200, 201]. Such personalisation of the stimulation protocols stands in accordance with previous findings of the heritable electrophysiological endophenotypes associated with some psychiatric disorders [202, 203]. For this, tACS modelling techniques might be recommended to optimize stimulation parameters and obtain better results [13]. Overall, in the same context, electrophysiological recording via EEG or MEG could be valuable to observe achievement of the desired change in brain electrical activity and to individualize the stimulation protocol [204]. Finally, multicentre double-blind clinic trials could be fostered to investigate larger sample sizes. This may also facilitate the utility of different stimulation protocols in different patients or within the same individuals to rule out a stimulation effect per se [4, 125, 131, 150] and to question the potential synergism of different stimulation parameters, respectively (for more technical guidance: [12, 205–207]).

Despite the relative safety profile of tACS, several side effects could coincide with the stimulation period: phosphenes, dizziness, headache and skin sensations, such as tingling, itching, etc.[205]. Phosphenes tend to be more frequent upon frontal montages due to retinal stimulation. On the other hand, dizziness is more common in posterior montages due to vestibular stimulation. Skin adverse events, as well as phosphenes, frequently co-occur with higher frequencies and/or intensities [208–210]. Headache could outlast the stimulation phase, especially with longer stimulation duration [211, 212]. In contrast to tDCS, tACS induces less serious (e.g., epilepsy) and less persistent (e.g., burn and dermatitis) adverse events [208, 213].

To display a balanced overview of the current insufficient knowledge on tACS, two major limitations should be presented: (1) some studies failed to show an effect in both healthy participants and patients, and (2) entrainment of brain oscillations is confounded by other proposed mechanisms of action. The individual functional as well as the structural variability of the brain, the wide range of stimulation parameters and technical difficulties could explain why tACS failed to alter the behavioural outcomes [67, 129, 186, 214, 215]. In this regard, strict modelling techniques and peri-stimulation EEG recordings could decipher the inability of tACS to induce electrophysiological or behavioural outcomes. Consistently, this limitation is complicated by the obstacle of stimulation artefact rejection in EEG or MEG [216, 217]. Future research may be needed to identify optimal tACS parameters to ensure a consecutive effect.

A second major drawback of tACS is the indirect mechanisms of action rather than direct entrainment of endogenous brain oscillations. Stimulation of peripheral nerves and the retina could account for the entrainment of brain oscillations [213, 218–222]. Similarly, cranial electrotherapy stimulation, a close alternating current stimulation tool applied on the forehead and mastoids, induces electrical brain changes via direct stimulation of cranial nerves [223, 224]. Although this hypothesis of the retina and peripheral somatosensory stimulation cannot be fully excluded, evidence supports the direct causality of tACS to entrain brain oscillations [20, 222, 225]. Consistent with this conclusion, tACS revealed frequency-, phase- and montage- and state-specific effects [67, 198, 222, 226]. Further research could try to estimate the contribution of these indirect mechanisms to the whole tACS using modelling techniques, as well as active control groups [222].

## Conclusions

tACS, a unique form of NIBS, results in both online and offline brain changes by entraining brain oscillations and inducing neuroplasticity, respectively. It has been extensively used to alter electrophysiological brain activity, and thus cognitive functions in healthy participants. Similarly, disturbed brain oscillations in psychiatric conditions may constitute a potential target for modulation by tACS without major adverse events. Its first few applications in psychiatry seem promising and encouraging for more research to discover its full potential with respect to therapeutic and diagnostic roles. Given its safety profile, these first studies may support tACS feasibility in altering disturbed brain oscillations, thus improving behavioural outcomes. However, further well-structured double-blind controlled trials with larger sample sizes and longer follow-up durations are still needed to replicate the current findings. They may help to detect response predictors and control for various confounding factors. In this regard, electrophysiological recordings, as well as modelling techniques, are encouraged to optimize stimulation protocols and to detect possible factors contributing to the effects of tACS.

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## Compliance with ethical standards

**Conflicts of interest** CSH holds a patent on brain stimulation. The other authors declare no competing interests.



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# 4. General Discussion:

## 4.1. Summary of our results:

In our current project, we aimed to advance a recent line of schizophrenia research by fostering a symptom-based approach, by investigating the symptom-related brain oscillations and the feasibility of their modulation. The first two publications present successful examples of such modulation using either cognitive or electrical methods. The target oscillations were shown to carry functional relevance to the respective tasks, and their modulation resulted in changes in corresponding behavioural outcomes.

In the first publication, we employed top-down modulation of dichotic listening to influence gamma-band interhemispheric connectivity, which is known to be enhanced during auditory hallucinations. Participants were instructed to either neutrally report the presented sounds in the dichotic listening task or deliberately shift their attentional control to the left or right ear. As hypothesized, we observed the expected behavioural changes, with increased reports from the ear to which participants directed their attention. Consistently, interhemispheric communication was enhanced as a result of this top-down modulation, particularly during deliberate attention to the right ear. This may be attributed to increased right-to-left hemispheric information transfer, reflecting augmented reciprocal inhibition to overcome left ear input.

In the second publication, theta-tACS applied to the dorsolateral prefrontal cortex effectively improved reaction times in working memory tasks among healthy participants, especially during high-load trials. At the oscillatory level, our stimulation protocol increased frontal theta oscillations implicated in working memory. More interestingly, the increase in theta oscillations was indicative of tACS after-effects, supporting its role in the long-term augmentation of the target theta waves.

These two examples highlight the significance of brain oscillations and their causal role in generating behavioural outcomes. They also demonstrate the feasibility of modulating these oscillations using different methods. Such modulation could help identify potential targets for future clinical research aimed at addressing schizophrenia symptoms, such as auditory hallucinations and working memory deficits, which are dependent on these brain oscillations.

In our third publication, we emphasized the relevance of tACS in psychiatric research and its promising potential to support this symptom-based approach. Our systematic search of the literature revealed successful and meaningful results from modulating brain oscillations to mitigate symptoms of various psychiatric disorders, including schizophrenia. In summary, the initial results of tACS in psychiatric populations support further investigation, although critical optimization of its settings is still required to achieve reproducible and clinically meaningful outcomes.

## 4.2. Contrast with previous literature:

Our results from the modulation of brain oscillations align with previous findings in the literature. Regarding the dichotic listening task, our top-down modulation managed to shift the typical ear advantage in the neutral condition to a left ear advantage during the left attention conditions and enhanced the default right ear advantage in the right attention condition (Hugdahl and Westerhausen 2016; Hiscock and Kinsbourne 2011). The left ear reports were associated with increased interhemispheric connectivity (Steinmann et al. 2014a; Steinmann et al. 2018b; Steinmann et al. 2018a). Interestingly, the top-down modulation resulted in alterations in interhemispheric oscillatory communication, particularly in the right attention condition, which resonates with previous findings of frontal attentional influence on auditory perception in the auditory cortices (Grady et al. 1997; Gootjes et al. 2006; Payne et al. 2017). Taken together, our results highlight the functional relevance of the measured brain oscillations, and their potential modulation based on task needs.

In the second publication, we found that theta-tACS applied to the dorsolateral prefrontal cortex was capable of behaviourally improving reaction times, but not accuracy rates. This inconsistency has been reported in many previous tACS experiments (Al Qasem et al. 2022; Antal et al. 2022), where different stimulation protocols yielded diverse results. This phenomenon could be explained by the fine specificity of the targeted brain oscillations, where different spatial and temporal parameters of brain oscillations contribute to various working memory properties (Abubaker et al. 2021; Nakamura-Palacios et al. 2023; Booth et al. 2022; Zhang et al. 2024). Moreover, the working memory improvement we reported coincided with a parallel enhancement of the targeted task-relevant theta oscillations, aligning with previous findings on the pivotal role of frontal theta brain oscillations in working memory (Pomper and Ansorge 2021). To fully understand the oscillatory dynamics

in working memory, it is essential to fine-tune the stimulation parameters to correlate with the specific characteristics of the brain oscillations of interest.

## 4.3. Brain oscillations in schizophrenia:

Previous literature has exhaustively examined the changes in brain oscillations and their associations with the clinical features of schizophrenia (Uhlhaas and Singer 2010; Moran and Hong 2011). Although this association might not always imply a causal relationship, they exhibit a unique tool to probe the pathophysiological alterations in the disease and may help find new treatment modalities (Hirano and Uhlhaas 2021). In this regard, not only have aberrant local brain oscillations been reported in schizophrenia, but also interregional synchronization and desynchronization, leading to the concept of brain dysconnectivity in schizophrenia (Li et al. 2019; Stephan et al. 2009). In that sense, a particular interest was allocated to the gamma-band oscillations, which play a significant role in interregional connectivity. Additionally, gamma-band oscillations present a proxy for the excitation/inhibition balance of the brain's cellular microarchitecture, providing a target for new treatment options (Lisman 2012; Uliana et al. 2024). This clinical relevance of brain oscillation in the case of schizophrenia suggests comprehensive research to entangle its complexity and pave the way for more precise circuit-based modulation.

Consequently, it is not surprising to observe a huge number of research trials aiming at discovering possible treatments based on these oscillations via their electrical or pharmacological modulations. Given its uniqueness to specifically target precise brain networks, tACS has been extensively employed in clinical research including patients with schizophrenia (Wei et al. 2023; Zhang et al. 2023; Pathak et al. 2023). The results showed promising role in alleviating the cognitive, negative, and positive symptoms of schizophrenia. However, there is still an intriguing need to further investigate the optimisation of the stimulation protocols and identify subgroups of patients with a prognostic response to tACS modulation. Additionally, pharmacological interventions targeting brain oscillations have been studied in the context of schizophrenia (Koch et al. 2016; Xu and Wong 2018; Uhlhaas and Singer 2015). Many substances, such as iclepertin and bitopertin, have been suggested to affect the disturbed brain oscillations, where NMDA-based applications showed sufficient promise (Jarab et al. 2025; McNally and McCarley 2016). For this, various compounds were investigated to directly or indirectly enhance glycine function on NMDA receptors and

showed as a result clinical improvement (Pei et al. 2021). This pharmacological modulation affects the gamma brain oscillations via resetting the excitation/inhibition balance (Harvey and Yee 2013).

## 4.4. Impacts of our results:

Our results may not only help understand the basic neurobiological mechanisms of cognitive brain functions but pave also the way to further translation in research with clinical populations. The results from the dichotic listening tasks confirm the previous findings of enhanced interhemispheric connectivity and its necessity for speech lateralisation and the perception of sounds from the non-advantaged ear (Steinmann et al. 2014a). Moreover, it highlights one of the physiological effects of attentional control at the lower perceptual level, where this top-down influence increases the interhemispheric communication to overcome the upcoming auditory inputs (Hugdahl and Westerhausen 2016). In this regard, the reciprocal inhibition between the two hemispheres upon the reception of competitive sounds was indicated in the dichotic listening paradigm (Brancucci et al. 2004). Based on brain oscillatory patterns, these findings contribute to the understanding of auditory processing via objective measurable correlates regarding attentional control of auditory stimuli.

At the clinical research level, these discoveries can be exploited for two purposes in the context of auditory hallucinations. First, since auditory hallucinatory experiences are associated with increased interhemispheric communication, their pathophysiology could be further deciphered with respect to attention control as a manifestation of top-down modulation. Attention control impairment is predominantly observed in schizophrenia (Luck and Gold 2008), patients might not be able to better allocate their attentional resources to focus on a specific stimulus, especially in the auditory modality (Luck et al. 2019). This might explain why these patients may not be able to shift their attention upon exposure to different competing stimuli such as in dichotic listening (Bozikas et al. 2014). This might be explained by the dysconnectivity patterns between frontal and temporal regions underlying top-down control (Ćurčić-Blake et al. 2017). Given the current results, it might be expected that the higher interhemispheric communication and interaction between both auditory cortices might be affected in patients with schizophrenia compared to healthy participants. Interestingly, both domains (attention impairment and auditory hallucinations) are somehow connected, since auditory hallucinations can be considered as an impairment of the top-down

control of bottom-up processes (Hugdahl 2009; Zheng et al. 2021). However, more research is needed to disentangle this complex picture of auditory hallucinations and top-down modulation. The second line of clinical research could focus on modulating interhemispheric connectivity to mitigate auditory hallucinations based on the interhemispheric miscommunication theory (Steinmann et al. 2019). New potential treatments could target these oscillations either pharmacologically or electrically. Glycine modulators, for instance, could help restore NMDA receptor hypofunction in schizophrenia, thereby regaining the excitation/inhibition balance, as suggested by the ketamine model of schizophrenia (Thiebes et al. 2018; Haaf et al. 2018). This model, which involves NMDA receptor blockade, has shown to induce imbalance, trigger auditory hallucinations, and increase interhemispheric connectivity. Additionally, electrical stimulation can be employed via dual-site tACS to decouple two stimulated brain regions (Saturnino et al. 2017). Similarly, both auditory cortices may be simultaneously stimulated to decrease their synchrony in an attempt to mitigate the accompanying auditory hallucinations (Meier et al. 2019).

Concerning the second publication of theta-tACS, which exhibited improvement in the behavioural aspects of working memory. The study further underscores the relevance of theta oscillations for working memory functioning and their possible causal link (Brzezicka et al. 2019; Itthipuripat et al. 2013; Pomper and Ansorge 2021; Riddle et al. 2020; Wal et al. 2021). This may help investigate the physiological correlates of working memory and the spatial specificity of the frontal lobe in this regard. Despite the association between theta oscillations and this cognitive function, other key players have been identified such as gamma oscillations, the interregional synchrony and the merging of these factors in the form of cross-frequency theta-gamma coupling (Sauseng et al. 2004; Alekseichuk et al. 2016; Lisman 2010; Riddle et al. 2020). Our results highlight the importance of theta waves with respect to the temporal factor at specific working memory load, where we should improvement in the reaction times only at high demands. In the light of our findings, future research might try to disentangle this complexity to precisely allocate the involvement of each frequency band (Abubaker et al. 2021). On the other hand, the spatial specificity of the brain could partially explain some aspects working memory. In our case, we focused on the frontal lobe and linked its function to reaction velocity, while other research findings attributed other aspects to other brain regions such as the hippocampus (Wal et al. 2021). This would trigger more research to identify the specific roles of different brain regions in working memory probably with the help of tACS modulation.

Clinically, schizophrenia research has indicated disturbances in theta oscillations, particularly in the frontal regions and in relation to working memory impairments (Tauscher et al. 1998; Schmiedt et al. 2005; Haenschel et al. 2009). Such reproducible findings should encourage future research to address these disturbances, for example, using tACS. Having demonstrated successful improvement in working memory, our study could be translated to patients with schizophrenia in an attempt to improve working memory impairments, especially since we observed tACS aftereffects on task-related theta oscillations. In this regard, some trials have already been conducted in clinical populations, showing promising results despite the lack of strong efficacy evidence. For example, frontoparietal theta tACS improved working memory in low-performing patients (Wang et al. 2024; Chang et al. 2021; Zhang et al. 2023; Shanbhag et al. 2019; Kallel et al. 2016). If these translations demonstrate further success and reproducibility, longitudinal randomized controlled trials could be implemented to assess the clinical benefits of tACS.

## 4.5. Challenges and limitations of brain oscillations:

Despite the promising results regarding the implications of brain oscillations in brain functions and their possible modulation, several aspects pose obstacles for upcoming research. First, the relationship between brain oscillations and brain functions is often associative rather than causal (Ricci et al. 2021). Although the anatomical relevance of certain brain regions or connectivity has been established through various approaches, such as neurological lesion studies (Vaidya et al. 2019), the functional link cannot always be proven with current methods. In this context, direct functional readouts like EEG oscillations may not inherently imply a causal relation to the associated brain function but rather an epiphenomenon that requires further testing for its mechanistic role (Herrmann et al. 2016). Our results from the dichotic listening task are not an exception to this rule. Interhemispheric connectivity plays a causal and mechanistic role in the perception of the non-advantaged ear, as evidenced in patients with corpus callosum lesions or agenesis (Hugdahl and Westerhausen 2016; Westerhausen and Hugdahl 2008). However, measured EEG readouts, such as interregional connectivity at a specific frequency band, might not causally correlate with perceptual readouts (Greaves et al. 2025). This necessitates more causation-oriented research for each specific case of brain oscillations. On the other hand, the role of theta oscillations appears to signify a causal relationship, even for particular aspects of working

memory, such as its capacity, based on previous findings on their predictability of behavioural outcomes (Lisman 2010). Consequently, tACS could be exploited to prove the possible causal link of brain oscillation to specific brain functions (Tavakoli and Yun 2017).

A second important aspect is the descriptive parameters of signal analysis, where EEG brain oscillations cannot be simplified to one parameter but must be considered in terms of temporality, locality, frequency composition, amplitude, and interregional relationships in multi-regional analysis (Jensen et al. 2019). This complex picture is often reduced to one or two parameters for simplicity, but the intricate nature of brain functioning requires consideration of all these aspects to comprehensively and precisely describe the roles of brain components. As a result of this reduction, it might be challenging to reproduce the expected modulatory effects on brain oscillations. In our case of interhemispheric communication, only gamma-band synchronization between the auditory cortices was found to be task-relevant (Steinmann et al. 2014a). This has neurobiological correlates, considering the excitation/inhibition model and its linkage to the microarchitecture of the cerebral cortex firing at gamma frequencies (Bartos et al. 2007). In the case of working memory, although frontal theta oscillations play a significant causal, they represent only a part of the larger picture for this cognitive function when considering the relevance of the gamma band and the spatial specificity of the hippocampus and parietal regions (Lisman 2010; Alekseichuk et al. 2016).

A third challenge for brain oscillations research is the feasibility of targeted modulation. Although various pharmacological and electrical interventions are currently available to alter brain oscillations, these interventions require further optimization and fine-tuning of their parameters (Stone 2011; Egerton et al. 2020; Zhand et al. 2019; Zhang et al. 2023). Pharmacological compounds do not selectively act on target binding sites but rather involve actions on other receptors. For example, glycine modulators bind unselectively to all possible glycine binding sites, potentially leading to various side effects or non-specificity (Bartolomeis et al. 2020; Zakowicz and Pawlak 2022). In the case of tACS, the stimulation protocols include a wide range of parameters that need to be set for optimal targeting of specific brain oscillations. This complexity can complicate the reproducibility and efficacy of tACS (Pathak et al. 2023). Future multicentre research and subsequent meta-analyses should be conducted to reach a consensus on promising stimulation protocols. These protocols should be tuned to the endogenous brain oscillations to ensure their efficacy. In our case, the

constellation of parameters used for tACS has proven to work only momentarily (online effects) on reaction times. However, future research could be employed to further optimize our protocol while maintaining and even improving the behavioural effects to cover other aspects of working memory.

Last but not least is the individual variability of brain oscillations, which are often linked with generalizable and reproducible patterns of brain waves. However, this is not always the case, as these oscillations seem to depend on the endogenous dynamics of individuals and their brain states (Dimitriadis et al. 2023; Wansbrough et al. 2024; Suetani and Kitajo 2020), which becomes more complicated with the heterogeneity of psychiatric symptomatology (Uhlhaas and Singer 2010). This complex oscillatory picture poses challenges for pharmacological interventions, which are not often personalized easily. Future research may aim to identify certain subclasses of patients who would benefit from such medications, especially based on their oscillatory fingerprints (Leucht et al. 2022). In this regard, tACS stands out as an exceptional tool for individualizing stimulatory interventions (Wansbrough et al. 2024). Not only can the frequency be customized, but also the location of the injected current can be tailored for each participant to ensure the targeting of specific brain regions, assisted by advanced simulation techniques (Kasten et al. 2019). Moreover, closed-loop tACS has shown promise in precisely targeting ongoing brain oscillations while individualizing the stimulation settings (Frohlich and Townsend 2021). Future research may leverage these advantages to assess the feasibility of this personalization and precision.

# 5. Summary:

Schizophrenia is a complex neuropsychiatric disorder characterized by disruptions in cognition, perception, and behaviour. Traditional approaches to understanding and treating schizophrenia have primarily focused on categorical diagnostic criteria, often overlooking the underlying neurophysiological mechanisms. In our current research project entitled "Pharmacological and Electrical Modulation of Disturbed Networks in Schizophrenia and the Clinical High-Risk State for Psychosis," we aimed to identify potential treatment targets for specific symptoms of psychosis and schizophrenia, particularly auditory hallucinations and working memory impairment. Our goal was to advance a symptom-based approach by investigating the role of brain circuits relevant in schizophrenia symptoms and exploring their modulation as a potential therapeutic avenue.

To achieve these goals, we carried out a preliminary work to initially investigate these brain networks in healthy participants to assess the feasibility of our approach, with the aim of future translation to patients with psychosis. The current thesis comprises three published studies. The first two studies demonstrate the feasibility of modulating task- and symptom-relevant brain oscillations through cognitive modulation and electrical stimulation techniques in healthy individuals. The third study presents a review on the potential role of transcranial alternating current stimulation (tACS) in psychiatric research.

In the first study, we employed a dichotic listening paradigm to examine interhemispheric connectivity in the gamma-band, a frequency known to be altered in individuals experiencing auditory hallucinations. By manipulating attentional control, we successfully induced changes in interhemispheric oscillatory communication, reinforcing the functional role of gamma oscillations in auditory perception and attention.

The second study investigated the effects of tACS applied to the dorsolateral prefrontal cortex during a working memory task. Our findings demonstrated that theta-tACS improved reaction times in high-load trials and increased frontal theta power, supporting the notion that non-invasive brain stimulation can enhance cognitive performance through oscillatory entrainment.

In the third study, we conducted a systematic search of the literature to assess the broader implications of tACS in psychiatric research. Our analysis highlighted the potential of tACS to modulate pathological brain rhythms associated with psychiatric disorders, including schizophrenia. However, we also emphasized the need for optimized stimulation protocols to achieve consistent and clinically meaningful outcomes.

Our findings may contribute to the growing evidence that brain oscillations play a crucial role in cognition and psychopathology. Specifically, we highlight the significance of interhemispheric gamma synchronization in auditory processing and frontal theta oscillations in working memory. These insights may provide promising targets for neuromodulation interventions. Clinically, our results suggest that modulating gamma connectivity could be relevant for treating auditory hallucinations, while theta-tACS may offer a non-invasive approach to improving cognitive deficits in schizophrenia.

In conclusion, these results may contribute to the ongoing effort to develop a symptom-based framework for schizophrenia research by demonstrating the functional relevance of brain oscillations and their susceptibility to modulation. Our findings could provide a foundation for future research aimed at refining neuromodulation techniques and translating these insights into clinical applications. While further research is needed to refine stimulation protocols and tailor interventions to patient subgroups, our findings might support the potential of oscillation-based treatments as a promising avenue for mitigating cognitive and perceptual disturbances in schizophrenia.

# 6. Zusammenfassung:

Schizophrenie ist eine komplexe neuropsychiatrische Störung, die durch Beeinträchtigungen der Kognition, Wahrnehmung und des Verhaltens gekennzeichnet ist. Traditionelle Ansätze zum Verständnis und zur Behandlung der Schizophrenie haben sich überwiegend auf kategoriale Diagnosekriterien konzentriert und dabei oft die zugrunde liegenden neurophysiologischen Mechanismen vernachlässigt. In unserem aktuellen Forschungsprojekt mit dem Titel „Pharmakologische und elektrische Modulation gestörter Hirn-Netzwerke in der Schizophrenie und im klinischen Hochrisiko-Stadium für die Entwicklung einer Psychose“ hatten wir das Ziel, potenzielle Behandlungsziele für spezifische Symptome der Psychose und Schizophrenie zu identifizieren, insbesondere für akustische Halluzinationen und Arbeitsgedächtnisstörungen. Unser Ziel war es, einen symptomorientierten Ansatz voranzutreiben, indem wir die Rolle von Gehirnnetzwerken, die für die Symptome der Schizophrenie relevant sind, untersuchten und ihre Modulation als potenziellen therapeutischen Ansatz erforschten.

Um diese Ziele zu erreichen, führten wir eine Vorarbeit durch, um diese Gehirnnetzwerke zunächst bei gesunden Teilnehmern zu untersuchen und die Machbarkeit unseres Ansatzes zu bewerten, mit dem Ziel einer späteren Übersetzung auf Patienten mit Psychose. Die vorliegende Dissertation umfasst drei veröffentlichte Studien. Die ersten beiden Studien zeigen die Machbarkeit der Modulation von aufgaben- und symptomrelevanten Gehirnwellen durch kognitive Modulation und elektrische Stimulationstechniken bei gesunden Individuen. Die dritte Studie ist eine Übersichtsarbeit über die potenzielle Rolle der transkraniellen Wechselstromstimulation (tACS) in der psychiatrischen Forschung.

In der ersten Studie verwendeten wir ein dichotisches Hörparadigma, um die interhemisphärische Konnektivität im Gamma-Bereich zu untersuchen, einer Frequenz, die bei Personen mit akustischen Halluzinationen verändert ist. Durch die Manipulation der Aufmerksamkeitskontrolle induzierten wir erfolgreich Veränderungen in der interhemisphärischen oszillatorischen Kommunikation, was die funktionelle Rolle von Gamma-Oszillationen in der auditiven Wahrnehmung und Aufmerksamkeit verstärkte.

Die zweite Studie untersuchte die Auswirkungen von tACS, die auf den dorsolateralen präfrontalen Kortex, während einer Arbeitsgedächtnisaufgabe angewendet wurde. Unsere

Ergebnisse zeigten, dass Theta-tACS die Reaktionszeiten bei Aufgaben mit hoher Belastung verbesserte und die frontale Theta-Power erhöhte, was die Vorstellung unterstützte, dass nicht-invasive Gehirnstimulation die kognitive Leistung durch oszillatorische Entrainment verstärken kann.

In der dritten Studie führten wir eine systematische Literaturrecherche durch, um die breiteren Implikationen von tACS in der psychiatrischen Forschung zu bewerten. Unsere Analyse hob das Potenzial von tACS hervor, pathologische Gehirnrhythmen zu modulieren, die mit psychiatrischen Störungen, einschließlich Schizophrenie, in Verbindung stehen. Wir betonten jedoch auch die Notwendigkeit, die Stimulationsprotokolle zu optimieren, um konsistente und klinisch bedeutsame Ergebnisse zu erzielen.

Unsere Ergebnisse könnten zu den wachsenden Belegen beitragen, dass Gehirn-Oszillationen eine entscheidende Rolle in der Kognition und Psychopathologie spielen. Insbesondere heben wir die Bedeutung der interhemisphärischen Gamma-Synchronisation in der auditiven Verarbeitung und der frontalen Theta-Oszillationen im Arbeitsgedächtnis hervor. Diese Erkenntnisse könnten vielversprechende Ziele für Neuromodulationsinterventionen bieten. Klinisch deuten unsere Ergebnisse darauf hin, dass die Modulation der Gamma-Konnektivität relevant für die Behandlung von akustischen Halluzinationen sein könnte, während Theta-tACS einen nicht-invasiven Ansatz zur Verbesserung kognitiver Defizite bei Schizophrenie bieten könnte.

Abschließend können diese Ergebnisse einen Beitrag zum laufenden Bemühen leisten, ein symptomorientiertes Framework für die Schizophrenieforschung zu entwickeln, indem die funktionelle Relevanz von Gehirn-Oszillationen und ihre Modulierbarkeit aufgezeigt werden. Unsere Ergebnisse könnten eine Grundlage für zukünftige Forschungen bieten, die darauf abzielen, Neuromodulationstechniken zu verfeinern und diese Erkenntnisse in klinische Anwendungen zu überführen. Obwohl weitere Forschung notwendig ist, um Stimulationsprotokolle zu verfeinern und Interventionen auf Patientengruppen abzustimmen, unterstützen unsere Ergebnisse das Potenzial von oszillationsbasierten Behandlungen als vielversprechenden Ansatz zur Minderung kognitiver und wahrnehmungsbezogener Störungen bei Schizophrenie.

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