Transcranial Alternating Current Stimulation as an Alternative Treatment for Patients with Attention-Deficit Hyperactivity Disorder (ADHD)

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List of Abbreviations

ANOVA	Analysis of variance
ADHD	Attention-Deficit/Hyperactivity Disorder
CPT	Continuous Performance Task
ERP	Event-related-potential
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
NiBS	Non-invasive brain stimulation
NICE	National Institute for Health and Care Excellence
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
TES	Transcranial electric stimulation
VSR	Virtual Seminar Room
VR	Virtual Reality

1. Abstract

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by persistent inattention, hyperactivity, and impulsivity, with massive psychosocial and health-economical burdens. To improve ADHD symptoms, patients often receive long-lasting psychopharmacological treatment. Despite the high success of psychopharmacology, a significant minority of patients experience undesirable side effects or do not respond to the therapy. Since ADHD is associated with altered brain oscillations, a promising alternative treatment approach with less side effects is the application of non-invasive brain stimulation (NiBS). The potential of NiBS to modulate brain oscillations makes it a promising technique for the treatment of mental disorders that are characterized by pathologically altered brain oscillations compared to healthy controls. Thus, the main aim of this dissertation was to explore transcranial alternating current stimulation (tACS), a novel NiBS technique, as an alternative therapy intervention for adult ADHD.

To examine its clinical effectiveness, within the scope of this research, adults with ADHD received active tACS and a placebo stimulation on distinct days. Recorded subjective, behavioral, and neurophysiological data were analyzed before and after each intervention. While in the first tACS study conventional attention tasks were used to assess attentional performance, the second study was conducted in a developed reality-close, multi-modal, and standardized virtual reality (VR) test environment.

Electrophysiological analyses did not confirm that tACS significantly modulated the targeted brain oscillations. Consequently, no stimulation-related improvement of attentional ability was determined. Although we were not able to confirm a benefit of tACS for ADHD patients so far, the developed realistic and multi-modal VR test environment provides a comprehensive and ecologically valid assessment tool, capturing the complexity of ADHD symptomatology. Overall, our research emphasizes the need for further fundamental research to develop ADHD-tailored tACS therapies. In addition, our findings demonstrated that VR test settings advance the assessment of ADHD symptoms and are suitable for testing the efficiency of potential ADHD treatment interventions.

2. Introduction and Aims with References

2.1 Symptoms and Therapy of Attention-Deficit Hyperactivity Disorder (ADHD)

ADHD is a childhood-onset developmental disorder that manifests as the core symptoms of inattention, impulsivity, and/or hyperactivity (American Psychiatric Association, 2013). Traditionally, ADHD was viewed as a childhood disorder that grows out of with age. By the end of the 20th century, there was convincing evidence for the existence of ADHD in adults and its continuity from childhood to adulthood (Wood et al., 1976). Patients diagnosed with ADHD show various neuropsychological characteristics, including impairments in attention and executive functions such as information processing, working memory, and inhibitory control (Woods et al., 2010; Kofler et al., 2020). But ADHD is also often associated with high creativity (see, for example, Abraham et al., 2006; Hoogman et al., 2020). In general, the clinical presentation of ADHD is heterogeneous, with a wide spectrum of severities and symptoms. The clinical presentation of adult ADHD is more diverse than that observed in pediatric populations, extending beyond typical motor symptoms. This presentation includes a wider range of emotional dysregulation and functional impairment (for a detailed overview, see Barkley et al., 2010). Lifespan research on consequences for patients with ADHD has revealed various individual burdens, such as difficulties in academic careers (Barbaresi et al., 2007; Birchwood and Daley, 2012), occupational burdens (Halmøy et al., 2009), difficulties in social interactions and relationships (Eakin et al., 2004; Gardner and Gerdes, 2015), higher accident rates (Brunkhorst-Kanaan et al., 2021), the development of comorbid mental disorders such as anxiety and affective disorders (Sobanski et al., 2007; Torgersen et al., 2009), and high societal burdens expressed by massive global economic costs (Chhibber et al., 2021; Matza et al., 2005).

Stimulant medication is usually considered the first-choice treatment with good therapeutic effects (Bolea-Alamañac et al., 2014; Cortese, 2020). Although pharmacological interventions have been proven effective, the management of ADHD symptoms remains an ongoing challenge. One challenge is the suboptimal medication adherence which may result in more severe symptoms (Safren et al., 2007; Perwien et al., 2004; Semerci et al., 2016). For a review of factors that influence medication adherence in adults with ADHD, see the study by Khan and Aslani (2021). In addition, stimulants may cause adverse events in some patients, such as sleep disturbances (Wynchank et al., 2017), decreased

appetite and weight (Kis et al., 2020), as well as cardiovascular effects (Cortese et al., 2018; Hennissen et al., 2017). Moreover, current clinical guidelines emphasize the evaluation of potential long-term risks associated with pharmacological treatments for adult patients with ADHD. These guidelines recommend regular health examinations, suggesting that at least an annual assessment is necessary to determine the ongoing appropriateness of medication use (see, for example, NICE Guideline, 2018). Psychosocial treatment, cognitive training, and neurofeedback are additional treatment options that may improve symptoms but require significant effort and time (Cortese et al., 2015; Daley et al., 2014; Evans et al., 2018; Moreno-García et al., 2022; Nimmo-Smith et al., 2020).

Another increasingly researched and clinically applied therapeutic option for ADHD is transcranial direct current stimulation (tDCS), a NiBS technique that involves the continuous depolarization or hyperpolarization of neurons in a targeted brain area (Nitsche and Paulus, 2000). TDCS has been the focus of many studies and is proposed as a promising alternative therapeutic approach for ADHD (Salehinejad et al., 2022), providing potential long-term benefits through neuroplasticity, which offers a significant advantage over the transient efficacy of pharmacological treatment (Rubia, 2018). This treatment approach aims to modulate underactive frontal brain regions in patients with ADHD (Hart et al., 2012). However, to fully comprehend its clinical utility, larger sample sizes are required for further systematic investigations (Salehinejad et al., 2020). In contrast, the potential benefits of a new NiBS technique, transcranial alternating current stimulation (tACS), for treating ADHD are still largely unexplored (Westwood et al., 2019).

2.2 Neurophysiological Correlates of Attention Deficits in ADHD

Research has consistently demonstrated differences in the neuromechanisms between adults with ADHD and healthy controls. These differences are primarily characterized by the dysregulation of brain regions associated with attention, emotion, and executive functions, such as the prefrontal cortex, anterior cingulate cortex, basal ganglia, and cerebellum (Bayard et al., 2020). Research using functional magnetic resonance imaging (fMRI) has demonstrated, for instance, reduced activity in these brain regions for adults with ADHD during tasks that require attention and cognitive control, compared to healthy controls (Hart et al., 2013). Moreover, electroencephalography (EEG) studies have reported altered brain activity, including reduced frontal theta oscillations (Adamou et al., 2020;

Snyder and Hall, 2006) and a reduced event-related P300 amplitude in adults with ADHD (Peisch et al., 2021; Szuromi et al., 2011).

As previously noted, ADHD is a highly heterogeneous neurodevelopmental disorder, encompassing a range of comorbid psychiatric conditions, diverse clinical presentations, varying neurocognitive impairments, and developmental trajectories (Luo et al., 2019). Therefore, various medical and (neuro-)psychological assessments must be undertaken to diagnose ADHD (Kooij et al., 2019). While clinical interviews and rating scales are reliable methods to assess ADHD (Faraone et al., 2021), the diagnostic value of traditional neuropsychological assessments is limited, likely due to their low ecological validity and the diverse clinical presentation of ADHD (Baggio et al., 2020). To address this problem, virtual reality (VR) technique can help to enhance the ecological validity by capturing the complexity of everyday life situations in a standardized test environment (Wiebe et al., 2022).

Taken together, capturing ADHD with a single neurophysiological variable is unlikely due to its heterogeneity (Lenartowicz and Loo, 2014). In addition, different ADHD subtypes appear to be associated with distinct neural markers (see, e.g., Qian et al., 2019; Sanefuji et al., 2017). The heterogeneity of ADHD complicates its diagnosis and treatment, emphasizing the need to identify specific neuromarkers, such as altered brain oscillations, for the development of individualized, effective treatments.

2.3. Brain Oscillations and Transcranial Alternating Current Stimulation (tACS) as an Alternative Treatment Approach for ADHD

TACS is a novel NiBS technique that modulates intrinsic brain activity, specifically brain oscillations (Helfrich et al., 2014). Brain oscillations, which occur in distinct frequency bands (delta: less than 4 Hz, theta: 4-7 Hz, alpha: 8-12 Hz, beta: 13-30 Hz, gamma: higher than 30 Hz) play a crucial role in the transmission of information within and between different brain regions (Ward, 2003). Thereby, different frequency bands are associated with specific cognitive functions (Beste et al., 2023; Kahana, 2006). The theta band is related to various cognitive functions, such as attentional processing, navigation, memory processes, and sensory motor integration (for review, see Karakaş, 2020), while alpha oscillations are involved in attention processing, working memory, sensory processing, and the suppression of irrelevant information (Alamia et al., 2023; Klimesch, 2012; van

Ede, 2018; Wianda and Ross, 2019). A modulation of oscillations via tACS is achieved by applying a sinusoidal waveform with gradually alternate voltage between an anode and cathode electrode on the scalp (Ruffini et al., 2013). The exact physiological mechanisms underlying tACS effects are still under debate. Generally, tACS entails administrating electric currents to the scalp, penetrating the skull to primarily impact cortical neurons, with the voltage transitioning from positive to negative every half cycle (Elyamany et al., 2021). The main proposed mechanisms of action are entrainment, the modulation of cortical excitability, and the induction of long-term synaptic plasticity. Entrainment describes the adaptation of an intrinsic brain oscillation to a frequency-specific extrinsic driving force (Helfrich et al., 2014; Zaehle et al., 2010). To entrain brain oscillations successfully by tACS, it is important to consider the following principle: when an intrinsic oscillator is weakly stimulated, only a narrow range of frequencies, typically within 1 Hz of the stimulation frequency, can synchronize the oscillator with the external force. However, as stimulation intensity increases, the frequency range over which synchronization occurs becomes wider, typically within a stimulation frequency of 2 Hz (Herrmann et al., 2016; Huang et al., 2021; Kurmann et al., 2018). This synchronization region, which resembles a triangular shape, is referred to as the *Arnold's tongue* (Strogatz, 2003). While entrainment effects occur online, during the ongoing stimulation, offline effects persist beyond the stimulation period (see, e.g., Heise et al., 2019; Pozdniakov et al., 2021). The mechanisms underlying these offline effects involve neuroplasticity, which refers to the brain's ability to adapt to changes in the environment by increasing or decreasing neuronal synchronization (for a detailed overview, see Elyamany et al., 2021). Several EEG studies have demonstrated that the modulation of brain oscillations via entrainment can lead to improvements in cognitive performance (for a systematic review, see Klink et al., 2020). For instance, it was shown that it is possible to enhance cognitive performance parameters by stimulating theta-tACS (Lang et al., 2019; Mosbacher et al., 2021; Pahor and Jaušovec, 2018). Other researchers have found improved visuospatial attentional performance after applying alpha-tACS (Coldea et al., 2021; Hilla et al., 2023; Kasten and Herrmann, 2017; Kemmerer et al., 2022). A recent systematic review and meta-analysis has endorsed tACS for enhancing specific cognitive function, further supporting its therapeutic effectiveness (Grover et al., 2023). Due to its ability to enhance attentional processing, tACS is a promising therapeutic approach for addressing various cognitive

disorders, particularly those associated with altered brain oscillations compared to healthy controls (Elyamany et al., 2021). Research has identified potential ADHD-related neuromarkers for tACS targeting, such as decreased alpha frequency band power (e.g., Kiiski et al. 2020) and reduced P300 amplitude (e.g., Hasler et al., 2016). Recently, it has been suggested that tACS can have a positive impact on ADHD symptoms by increasing the P300 amplitude (Boetzel and Herrmann, 2021; Dallmer-Zerbe et al., 2020). Another study compared tACS to the ADHD medication *Ritalin*. Results reported an advantage of tACS, demonstrating a higher reduction in attention deficit, hyperactivity, and impulsivity compared to *Ritalin* (Farokhzadi et al., 2021). However, as noted above, tACS has been largely neglected in ADHD research, so its utility in the therapy of ADHD remains unclear and needs further investigation (Westwood et al., 2019).

2.4 Aims of the Dissertation

The main objectives of this dissertation were to investigate the feasibility of a multi-modal, realistic, and standardized test-environment for assessing ADHD symptoms and to explore tACS as a treatment for adult ADHD. To address these objectives, first a virtual reality seminar room (VSR) was developed that is capable of characterizing ADHD symptoms (Publication 1). The VSR simulates a real-life seminar room with various distractions and offers multiple data measurement options (e.g., EEG, eye tracking, and actigraphy), creating a more realistic, complex, and yet standardized testing environment. In addition, two different tACS application techniques were tested for their efficacy in modulating brain oscillations and improving ADHD symptoms: the first tACS intervention aimed to modulate the P300 amplitude in adults with ADHD conducting a standard neuropsychological test. During the second tACS intervention, participants were immersed into the VSR while receiving tACS stimulation with the aim of increasing the alpha band power (Publication 2 and 3). This dissertation includes a comprehensive discussion of the potential utility of tACS as a treatment for ADHD, including detailed information on its implications for clinical application, as well as a comparison between tDCS and tACS. Finally, a roadmap is presented for investigating the potential of tACS in future ADHD treatment studies.

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3. Publications

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Multimodal Virtual Reality-Based Assessment of Adult ADHD: A Feasibility Study in Healthy Subjects

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Abstract

Neuropsychological assessments are often surprisingly inaccurate in mapping clinically-reported attention-deficit hyperactivity disorder (ADHD) symptoms, presumably due to their low ecological validity. Virtual reality (VR) might offer a potential solution for this problem, given its capability to generate standardized and yet highly realistic virtual environments. As the first adaptation of existing virtual classroom scenarios to an adult population, we developed a Virtual Seminar Room (VSR) for multimodal characterization of ADHD symptoms. To test its feasibility, $N = 35$ healthy participants were immersed into the VSR via a head-mounted display and carried out a VR-embedded continuous performance task (CPT) under varying levels of distractions in two experimental blocks (24 min each). CPT performance, electroencephalography (EEG) measures, and head movements (actigraphy) were simultaneously recorded and analyzed offline. Although CPT performance remained constant throughout the task, head movements increased significantly from Block 1 to Block 2. In addition, EEG theta (4–7 Hz) and beta (13–30 Hz) power was higher during Block 1 than Block 2, and during distractor-present than distractor-absent phases. Moreover, P300 amplitudes were higher during Block 1 than Block 2, and P300 latencies were prolonged in distractor-absent compared with distractor-present phases. Although the paradigm awaits further improvements, this study confirms the general feasibility of the VSR and provides a first step toward a multimodal, ecologically valid, and reliable VR-based adult ADHD assessment.

Keywords

Virtual Seminar Room, ADHD, VR, multimodal assessment, EEG, inattention, continuous performance task

Attention-deficit hyperactivity disorder (ADHD) is a childhood-onset developmental disorder that manifests in symptoms of inattention, impulsivity, and/or hyperactivity (American Psychiatric Association, 2013). While symptoms of impulsivity and hyperactivity often diminish with age, inattention symptoms frequently persist across the whole lifespan (Francx et al., 2015; Franke et al., 2018; Willcutt et al., 2012). Therefore, ADHD is not only a disease of childhood and adolescence but often also of adulthood. On a neuropsychological level, adults with ADHD show deficits in a variety of cognitive domains, including sustained attention, interference control, behavioral inhibition, and perceptual speed (Chamorro et al., 2021; Hervey et al., 2004; Woods et al., 2002). Among the neuropsychological tests most commonly employed, is the continuous performance task (CPT; Rosvold et al., 1956). In this task, participants are presented with a series of stimuli and instructed to press a response key as soon as a certain, infrequent target stimulus appears and to suppress responses to any other, nontarget stimuli. For reaching optimal task performance, participants, thus, need to concomitantly sustain their attention and control their impulsive behavior throughout the task, which is why the CPT theoretically appears well-suited for assessing inattention and impulsivity.

Although the CPT is often employed in the assessment of ADHD, it has been of surprisingly limited diagnostic utility so far. In fact, although numerous variants of the CPT have been developed, with modifications in form, number, and frequency of stimuli, correlations between clinically reported ADHD symptoms and CPT performance are typically only low to moderate (Barkley, 1991; Lange et al.,

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2014). Likewise, although at group level some CPT differences between ADHD patients and healthy controls have been observed, a precise, CPT-based single-subject classification between ADHD patients and healthy controls is not yet possible (Barkley, 2019; Lange et al., 2014).

So far, the reasons for the CPT's low diagnostic utility are not sufficiently understood. However, several causes are conceivable. First, ADHD is a highly heterogeneous disorder. The pattern and severity of cognitive deficits differ greatly between patients, with some individuals even scoring in the normal range on neuropsychological tasks, therefore not showing any impairment at all (Mostert et al., 2015; Nigg et al., 2005; Willcutt et al., 2005). Second, most CPT evaluations focus on markers of inattention (e.g., omission errors) and impulsivity (e.g., commission errors), while markers of hyperactivity are usually not evaluated. A CPT-based evaluation of this ADHD core symptom, however, appears possible by acquiring additional levels of analysis, for example, recording the participant's motor activity during the CPT. Hall et al. (2016), for instance, demonstrated that by combining CPT performances with actigraphy, classification rates can be improved. And third, ecological validity of most CPT implementations appears to be rather low. Given the need for a highly standardized and reproducible test environment, most existing CPT implementations confine themselves to the presentation of simple, two-dimensional stimuli (e.g., letters or numbers) via computer screens. Such test implementations, however, raise the question, as to how far such a stimulus presentation may reliably mimic everyday life challenges, where environments are substantially more complex and the individual is surrounded by various distracting external stimuli (Varao-Sousa et al., 2018).

A solution for creating more reality-close test situations may be offered by virtual reality (VR) technology. Through creating three-dimensional (3D), immersive, and interactive virtual environments which allow to reliably mimic everyday life demands, ecological validity can be increased while still maintaining a high level of standardization (Parsons, 2015).

Regarding ADHD assessment during childhood and adolescence, two similar, but independently-developed virtual test environments have been investigated over the last years: the Virtual Classroom by Rizzo et al. (2006) and the AULA Nesplora by Iriarte et al. (2016). In the Virtual Classroom, children with ADHD are immersed into a virtual environment that resembles an ordinary classroom. Sitting at a desk surrounded by virtual classmates, the children are instructed to follow a classical visual CPT that is presented on the blackboard. To enhance reality closeness and incorporate a measure of distractibility and external interference control, different visual, auditory, and audio-visual distractors inside the virtual environment (e.g., a paper-plane flying through the room) can be presented during the task (Parsons & Rizzo, 2019). The design of the AULA Nesplora is similar, except that it contains both visual and auditory CPT stimuli (Iriarte et al., 2016). Both virtual test environments have been shown to differentiate between ADHD children/adolescents and healthy controls, with ADHD patients committing more overall errors in the CPT (Areces et al., 2018; Mühlberger et al., 2016; Neguț et al., 2017; Parsons et al., 2007; Rizzo et al., 2006) and displaying a larger amount of head- and overall body-movements during task completion (Areces et al., 2018; Parsons et al., 2007; Rizzo et al., 2006). In the Virtual Classroom, ADHD patients were additionally more affected by the insertion of distractors than healthy controls (Neguț et al., 2017; Parsons et al., 2007; Rizzo et al., 2006). Moreover, Adams et al. (2009) found a higher classification rate for discriminating ADHD patients from healthy controls if the classifier was trained on a VR-based CPT compared with a traditional CPT.

Although the two virtual test environments have demonstrated their potential utility in assessing ADHD during childhood and adolescence, no similar VR scenarios have yet been developed for adult ADHD patients. Moreover, besides behavioral assessments and actigraphy analyses, no other variables of interest have been investigated yet. To gain further insights into possible neuromarkers of ADHD, it would, however, be beneficial to additionally examine task-dependent brain activity.

Regarding electroencephalography (EEG), one oscillation of interest might, for instance, be the theta rhythm (4–8 Hz), which has been reported to be abnormally elevated in ADHD patients (see, for example, Adamou et al., 2020). More specifically, it has been suggested that the increased theta power in ADHD children and adolescents declines with age but remains enhanced during adulthood (Bresnahan & Barry, 2002; Koehler et al., 2009; Picken et al., 2020).

Another interesting EEG parameter is the theta–beta ratio (TBR), which reflects the ratio between absolute theta power and absolute beta power (12–40 Hz) and has been associated with attentional control (e.g., Angelidis et al., 2016). Although for several years the TBR was considered a robust neuromarker for ADHD (see, for example, Arns et al., 2013; Barry et al., 2003), more recent studies found only low diagnostic utility (e.g., Loo & Makeig, 2012) and qualified the TBR-hypotheses: Although TBR differences between children with ADHD and healthy controls appear to exist (Monastra et al., 2001; Snyder & Hall, 2006; Zhang et al., 2017), a significant TBR difference between adult ADHD patients and healthy controls could not be consistently found (Kiiski et al., 2020; Saad et al., 2015; van Dijk et al., 2020).

A third EEG parameter of interest relating to event-related potential (ERP) analyses is the P300 component, a positive voltage deflection ~300 ms after the target stimulus, which has been associated with stimulus evaluation

(Sutton et al., 1965). Evidence from numerous studies suggests reduced amplitude (Grane et al., 2016; Hasler et al., 2016; Marquardt et al., 2018; Prox et al., 2007; Szuromi et al., 2011; Wiersema et al., 2006; Woltering et al., 2013) and prolonged latency (Idiazábal et al., 2002; Lazzaro et al., 2001; Tsai et al., 2012; Yamamuro et al., 2016) of this ERP component in ADHD patients compared with healthy controls.

The aim of the present, preregistered feasibility study was to complement existing VR research by undertaking a first step toward a VR-assisted, ecologically valid, and multimodal assessment procedure for adult ADHD patients. As a first step, we developed a new Virtual Seminar Room (VSR) scenario that resembles the already existing virtual classroom paradigms but is specifically tailored to adults. Moreover, our VSR not only enables CPT performance and actigraphy analyses but also ecological momentary assessment and EEG analyses. To demonstrate the general feasibility of our newly developed scenario, we applied our VSR to a sample of $N = 35$ healthy adults. Our main objectives were, first, to ensure that the VR scenario is feasible and does not induce discomfort in participants (see, for example, Barrett, 2004), and second, to test whether the simultaneous assessment of the different measures in VR is possible. Here, our main focus was on the combination of VR and mobile EEG, considering that EEG signals are easily distorted by head movements or pressure on the electrodes (Tauscher et al., 2019). In the VSR, both of those confounders are difficult to avoid. On one hand, a head-mounted display (HMD) on top of an EEG cap may induce strain on the electrodes, which might cause artifacts interfering with EEG signals. On the other hand, an immersive VR experience can only be created if participants can freely move their heads and look around, which may lead to an increased amount of motion artifacts.

Therefore, to test whether our setup allows us to derive plausible data, we analyzed participants' CPT performance, EEG data, and head actigraphy over time and during distractor-present and distractor-absent task phases. Regarding CPT performance over time, previous VR classroom studies did not find a performance drop in healthy participants (see, for example, Bioulac et al., 2012). However, in the current VSR paradigm, the CPT blocks are substantially longer, and therefore we expect to observe a similar increase in error rates over time, as observed in traditional computer-based CPTs (Ballard, 1996a; Grier et al., 2003). Regarding the influence of distractions on CPT performance, previous VR classroom studies yielded mixed results. Although Parsons et al. (2007) found distractor-induced increases in error rates in healthy controls, Neguț et al. (2017) did not. Therefore, considering the length of our task and the comparatively high number of distractor-present and distractor-absent phases, we expect to see a distractor-induced performance decline in our present sample. Regarding ERP analyses, we expect to see a target P300 as in previous CPT studies (Fallgatter et al., 2000; Kirmizi-Alsan et al., 2006). Moreover, regarding TBR analyses, we expect an increased TBR over time which has been attributed to mind-wandering in the past (van Son et al., 2018). With regards to head actigraphy, we hypothesize that, similar to previous VR classroom studies, head movements will increase over time (Mühlberger et al., 2016) and in distractor phases (DP) compared with non-distractor phases (NDP; Parsons et al., 2007).

Method

Participants

Thirty-five healthy volunteers ($M_{age} = 23.43$; $SD = 2.87$; 14 males) were recruited for the study via mailing lists, direct advertisements, and social media. Eligibility criteria were normal or corrected-to-normal vision, no history of severe psychiatric or neurological disease and sufficient knowledge of the German language. Participants filled in a demographic questionnaire in which they had to inform the experimenter about current medication and whether they received any neurological, psychiatric or psychotherapeutic treatment. All participants gave written informed consent and received an expense allowance of 20 € for their participation. The study was approved by the University of Bonn's medical ethics committee (protocol number: 011/20) and preregistered at the German Clinical Trials Register (https://www.drks.de/, Trial-ID: DRKS00021495).

General Procedure

The experiment lasted approximately 2 hr and was conducted in the VR laboratory of the University Hospital of Bonn. Upon arrival, participants were first informed about the study procedure and then signed the consent sheet. Next, they filled in three digital questionnaires via a computer, using the online survey tool SoSci-Survey (https://www.soscisurvey.de/). The three questionnaires administered were a demographical questionnaire, the Scale for the Evaluation of Attention Deficits (revised version, SEA-R, Volz-Sidiropoulou et al., 2007) and the Scale of Impulsive Behavior 8 (I-8, Kovaleva et al., 2012). After these questionnaires were filled in, the participants were prepared for the EEG measurement. Next, they became equipped with a HMD and immersed into the VSR, in which they first underwent a 60 s familiarization phase and then the actual CPT. In total, the CPT lasted ~48 min and took place directly within the VSR (details in "Continuous Performance Task" section). After the CPT was finished, the participants remained in the VSR to document their momentary level of cybersickness. To this end, they completed a subset of the Virtual Reality Sickness Questionnaire (VRSQ, Kim et al., 2018) by means of a VR-embedded gesture-based user

Figure 1. The Virtual Seminar Room.
(A) Real-world third-person perspective and (B) first person perspective in the virtual environment. Participants were immersed into the Virtual Seminar Room (VSR), in which the continuous performance task (CPT) was presented at the canvas in front of the room.

interface (UI, see "Experience Sampling" section). Finally, the participants left the virtual environment and completed a recognition test (see "Recognition test" section) and an expense allowance sheet.

Apparatus and Virtual Environment Implementation

The experimental apparatus and VSR are displayed in Figure 1. Participants sat at a 1 m × 1 m table (cf. Figure 1A) within a 3.70 m × 2.65 m VR-play area (cf. Figure 1B). The VSR was presented via the HMD HTC VIVE Pro (HTC Corporation, Taoyuan City, Taiwan). This HMD has a 110-degree field of view, 90 Hz screen refresh rate and 1,440 × 1,600 per eye image resolution. The VSR was self-assembled under Unity 3D 2019.1.10f1 (Unity Technologies, San Francisco, CA, USA) and C#. When immersed into the VSR, participants found themselves sitting at a 1 m × 1 m virtual table, whose position matched the position of the 1 m × 1 m table in the real world. The virtual table was located in the back of the VSR, so that the participants had a good overview over the entire VSR. The VSR contained the typical furniture found in a seminar room, including a canvas right at the front wall of the VSR. Moreover, the VSR contained virtual classmates that performed unobtrusive idle movements during NDP and, if applicable, more complex actions during DP (details in "Continuous Performance Task" section). The 3D objects, sounds, and animations used for implementing the VSR were obtained from different commercial and non-commercial asset sources (i.e. Mixamo, Unity Asset Store, Renderpeople).

Both the physical and virtual environments were spatially mapped by positional tracking, such that whenever the participants changed their head position in the real world, the HMD position in the virtual world adjusted accordingly. Using the Leap Motion system (Leap Motion Incorporation, San Francisco, CA, USA) together with a Unity SDK (https://developer.leapmotion.com/unity; accessed 07.01.21), the participants' biological hand movements were real-time tracked and translated to two virtual hands shown in the VSR. The 3D hand models used for that were obtained from the "Leap Motion Realistic Hands" collection (downloadable over Unity's asset store) and represented white-colored, average-sized human hands. The virtual hands were animated in such a way, that whenever the participants moved one of their biological hands, the

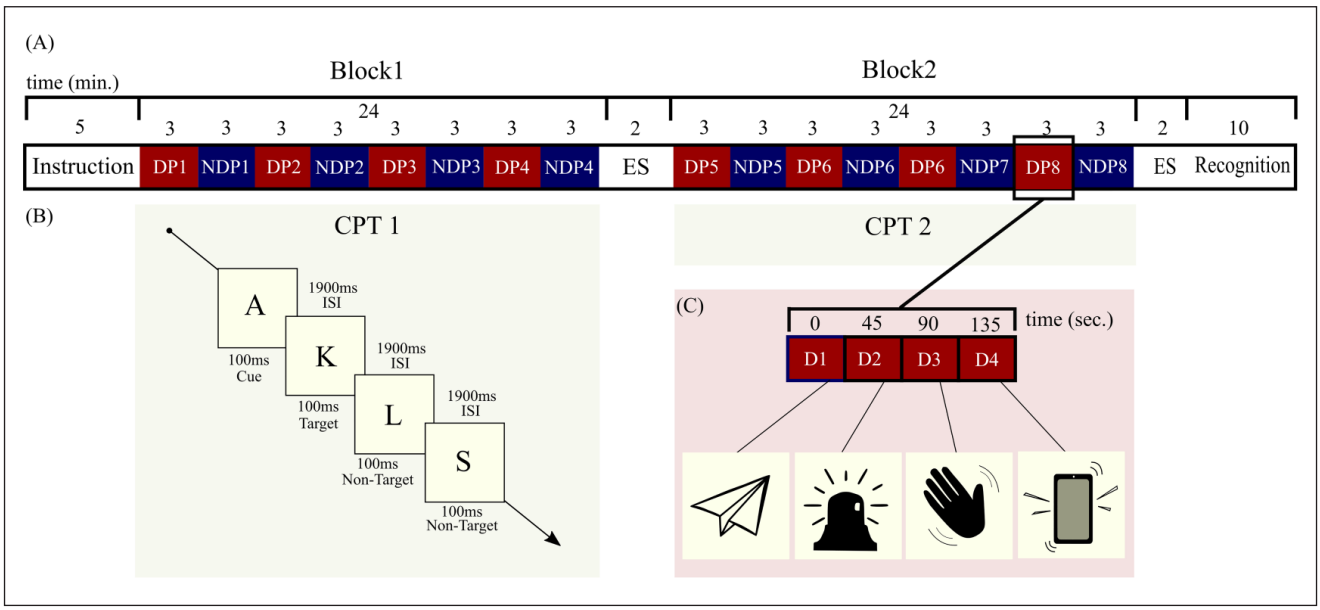

Figure 2. Experimental Design.
(A) Time course of the experiment. After being acquainted with the general procedure of the experiment and continuous performance test (CPT), the participants had to perform two CPT blocks (24 min each) and to undergo an experience sampling (ES) after each block. While the two CPT blocks were running, distracting events were concomitantly happening in the Virtual Seminar Room (VSR) during distractor phases (DP), but not during non-distractor phases (NDP). Within each CPT block, four DP and four NDP were alternatingly run, whereby each of these phases lasted 3 min. (B) Implementation of the CPT. Participants performed the CPT with an interstimulus interval of 1900 ms and a stimulus interval of 100 ms. Upon each target letter sequence ("A—K" or "H—F"), participants had to react with a spacebar press, while for any other letter sequence they had to withhold any button presses. (C) DP and NDP. During DP, distracting events were presented every 45 s in the VSR. 15 of these distractors were solely visual (e.g., a paper plane), 15 solely auditory (e.g., phone ringing) and 15 audiovisual mixed (e.g., an ambulance driving by).

respecting virtual hand moved correspondingly and without noticeable delay at the respecting position in virtual space. The virtual hands were used to amplify the level of embodiment and to enable gesture-based experience sampling (see "Experience Sampling" section).

Continuous Performance Task

The implementation of the CPT is illustrated in Figure 2. Directly implemented into the VSR, the CPT was realized by a series of single letters that were iteratively presented at the middle of the virtual canvas. As soon as a target letter sequence appeared, participants had to press the spacebar on a keyboard in front of them, following the second of the two letters in the sequence, while for any other letter sequence they had to withhold any button presses. The two target letter sequences defined were "A—K" and "H—F." Whereas the sequence "A—K" was derived from other VR CPT studies (Mühlberger et al., 2016; Neguț et al., 2017), the sequence "H—F" was added to further increase task difficulty. Each letter was shown for 100 ms, with an interstimulus interval of 1900 ms (Mühlberger et al., 2016). After a practice run of 20 trials, the actual CPT began, which was split into two blocks (Block 1, Block 2) with a duration of 24 min each. In each block, 360 letter pairs were presented, out of which 108 (~30%) letter pairs represented a target sequence and 252 a non-target sequence (~70%), a ratio similar to the one used by Neguț et al. (2017). To increase task difficulty, the non-target pairs entailed 126 pseudo-target sequences, in which the first letter was either an "A" or "H," but the second was not "K" or "F," or the second letter was a "K" or "F," but the first was not "A" or "H."

While the two CPT blocks were running, intermittently distracting events were played in the VSR (cf. Figure 2). More specifically, within each CPT block, four DP and four NDP were alternatingly run, whereby each of these phases lasted 3 min. Whereas in a DP, different distracting events occurred every 45 s, no distractors were played during an NDP. Among the 32 distractors presented in total, 10 were solely visual (e.g., a classmate waving), 11 solely auditory (e.g., a dog barking), and 11 audiovisual (e.g., an ambulance driving by; for a complete list of all distracting events presented, see SM1). Although the distractor order was completely randomized, the phase order was counterbalanced across participants, in that for even participant numbers, the experiment started with a DP and for odd numbers, it started with an NDP.

For assessing CPT performance, three parameters of interest were extracted for each participant: the rate of

Figure 3. Experience Sampling.
(A) For an immediate assessment of the participants' experiences during continuous performance task (CPT) performances, a virtual user interface showed up after each CPT block and surveyed the participants about their momentary subjective levels of inattention, impulsivity and hyperactivity, (B) real-world third-person perspective, and (C) real-world first person view.

omission errors (i.e., the percentage of nonresponses to target stimuli), the rate of commission errors (i.e., the percentage of responses to nontarget stimuli) and reaction time variability (RTV), which was defined as the standard deviation of reaction times toward correct hit trials divided by the mean reaction time (Kofler et al., 2013; Levy et al., 2018). Omission error rates are considered a measure of inattention, whereas commission error rates are thought to reflect impulsivity (Nichols & Waschbusch, 2004). RTV is considered a measure of vigilance, as lapses in attention lead to temporary slowing of responses, resulting in overall more variable reaction times (Levy et al., 2018).

Experience Sampling

Assessment of the participants' subjective performances was carried out by a gesture-controlled UI (cf. Figure 3). After each block, this UI appeared as a VR-embedded, semi-transparent overlay in front of the participants. The UI iteratively surveyed the participants about three typical ADHD symptoms: inattention ("I had difficulty concentrating during this block."), impulsivity ("I often had to stop myself from giving a wrong answer."), and hyperactivity ("I moved a lot during this block."). For each statement, the participants had to indicate their momentary level of agreement on a 7-point Likert-type scale, ranging from −3 ("totally disagree") to +3 ("totally agree"). The VRSQ, which was assessed at the end of the VR experiment, was also presented via this UI.

Recognition Test

To assess the extent to which the participants noticed the presented distractors during the CPT, a recognition test was administered at the end of the experiment. The recognition test surveyed the participants about 64 distracting events that might potentially have happened during the CPT. For each of these potential events at issue, participants were presented a "reminder" picture and/or sound file of the respective event and were asked whether they recognized the event or not (e.g., "Did you notice that this person yawned?"). To control for false-positive answers, only 32 of the 64 suggested events represented an event that actually happened. For the statistical analysis, recognition sensitivity (d') was separately calculated for each participant. To adjust for extreme values (i.e., hit or false alarm rate of 0 or 1), the loglinear approach was used (Hautus, 1995; Stanislaw & Todorov, 1999).

EEG Recording and Analyses

EEG was acquired via a wireless EEG system (Smarting®, mBrainTrain®, Belgrade, Serbia). The electrode montage represented a subset of the 10–20 system and consisted of 24 Ag/AgCl sintered ring electrodes: Fp1, Fp2, AFz, F3, Fz, F4, T7, C3, Cz, C4, T8, CPz, P7, P3, Pz, P4, P8, POz, O1, O2, M1 and M2. The ground electrode (DRL) was placed at FPz, while FCz served as reference (CMS). The amplifier was attached to the back of the EEG cap (EASYCAP, Herrsching, Germany) and communicated wirelessly with the computer via Bluetooth. All impedances were kept below 10 kΩ. The EEG signal was recorded via Lab Streaming Layer (https://github.com/sccn/labstreaminglayer) with a 500 Hz sampling rate and 24-bit step-size resolution. Data analysis was performed using Matlab 2018b (The MathWorks Inc., Natick, MA, USA) and EEGLAB 2019 (Delorme & Makeig, 2004).

Pre-Processing and Data Cleaning. For offline analyses, EEG data were first low-pass filtered with a cut-off frequency of 40 Hz and high-pass filtered with a cut-off frequency of 1 Hz (Hamming windowed finite impulse response filter of order 1,650, transition bandwidth 1 Hz) and then detrended. No rereferencing was applied. Next, data were screened for noisy EEG channels. In four datasets, channel Fz had to be replaced via spherical interpolation using EEGLAB's inbuilt function *pop_interp* (Perrin et al., 1989). Moreover, all datasets were screened for missing data segments due to Bluetooth connection losses. In three datasets, missing data segments ranging from 48 to 132 s were found. In these cases, the entire DP or NPD in which the respecting corrupted sequence occurred, was removed, before all further EEG analyses were performed. As a next step, all EEG datasets were cleaned from artifacts. To this end, the continuous EEG data were first epoched into 2-second time windows and nonstereotypic artifacts were removed by the built-in EEGLAB function *pop_jointprob* with a threshold of 1.7 standard deviations. Next, an independent component analysis (ICA) using *pop_runica* (extended version) was computed on the epoched EEG data and components containing stereotypical artifacts, like for example ocular, cardiac or muscle activity, were identified by visual inspection. The ICA demixing matrix was then applied to the original continuous dataset (1–40 Hz filtered) and the previously identified artifactual components were rejected before back-projecting them onto the source space.

Frequency Analyses. Time-frequency analyses focused on TBR differences between phases (DP vs. NDP) and blocks (Block 1 vs. Block 2). Therefore, the ICA-corrected continuous EEG data were first cut into four separate epoched subsets (one for each condition): One subset for DP segments from Block 1, another subset for NDP segments from Block 1, a third subset for DP segments from Block 2, and a fourth subset for NDP segments from Block 2. To investigate stimulus-independent changes in the frequency bands, epochs for each subset were obtained by cutting all belonging DP or NDP into as many non-overlapping 5 s segments as possible. Next, the following identical preprocessing and analysis steps were undertaken on every subset: First, all segments of the respecting subset were baseline corrected (0–5 s). Second, using EEGLAB functions, all segments containing obvious, nonstereotyped artifacts exceeding 2 standard deviations were rejected. On average, $M = 83.75$ segments ($SD = 2.33$) remained within each subset. Third, a time-frequency analysis on channel Fz was performed on each remaining segment using Matlab's *pspectrum* function. Frequencies ranged between 0 and 35 Hz, while the frequency resolution amounted to 0.034 Hz. Fourth, all derived power spectra were averaged to obtain one mean power spectrum. Fifth, the mean theta (4–7 Hz) and beta (13–30 Hz) power of the respecting subset (condition) was derived by taking the average power across all frequency bins that fell into the respecting frequency range and laid within 0.5 to 4.5 s. Finally, TBR values for the statistical analyses were calculated by dividing the theta power values by the beta power values.

ERP Analyses. ERP analyses focused on differences in the target P300 between phases and blocks. Therefore, the ICA-corrected continuous EEG data were first low-pass filtered at 15 Hz (Hamming windowed FIR filter of order 440, transition bandwidth 3.75 Hz) and separated into DP and NDP. Here, each subset was derived by aggregating all available segments within each pertaining phase from −2,200 to +2,000 ms (4.2 s), relative to each available correctly identified target stimuli (i.e., each detected "K" that followed an "A," respectively, each detected "F" that followed an "H"). Next, for each segmented subset, the same preprocessing and analysis steps were carried out: First, using EEGLAB functions, all derived segments were baseline corrected from −2,200 to −2,000 ms relative to target onset. Second, segments containing residual artifacts were identified and rejected using the *pop_jointprob* function with a threshold of 3 SDs. On average, this resulted in $M = 5.81$ ($SD = 0.72$) segments for each subset. Third, ERPs were computed by averaging the segments for channel CPz, since P300 activity regarding target detection is expected to be mainly elicited in centro-parietal regions (Duncan et al., 2009; Polich, 2007). Finally, for statistical analyses, the maximum P300 peak and its corresponding latency were identified for each participant within the time range of +200 to +500 ms relative to target onset (automatic detection). To compare blocks, all DP and NDP were allocated to the first or second block. For creating topographic maps, a grand average over all conditions was calculated.

Actigraphy Recording and Analyses

Actigraphy analyses focused on differences in head position shifts and head rotations between phase types and blocks. Both actigraphy parameters were inferred from the built-in positional tracking of the Vive system, by means of which the HMDs momentary positions and rotations during the experiment were each recorded with a ~90 Hz sampling rate and in 3D Euclidean space coordinates.

For later offline analyses, the actigraphy data were first down-sampled to ~10 Hz and then the Euclidean distance between each sample point (3D position or rotation vector) and its preceding sample point was separately calculated for the HMD position data and HMD rotation data. Next, to statistically compare the amount of head position shifts and rotations between conditions, the mean Euclidean distance in respect to head position shifts and head rotations was derived for each type of phase and each block.

Statistical Analyses

Eleven main dependent variables were in the focus of this study: commission error rates, omission error rates, RTVs, TBRs, P300 latencies and amplitudes, head position shifts, head rotations, self-rated inattention, self-rated impulsivity, and self-rated hyperactivity. Using graphical inspection and skewness values, all main dependent variables were first checked for normality before any further statistical analyses were conducted. If a variable was highly skewed, data transformation was applied. That is, commission error rates, omission error rates, and RTV were square-root transformed and head position shift and head rotation were log-transformed. After transformation, skewness of these variables was acceptable (between −1 and 1). Since analyses of variance (ANOVAs) are, however, considered to be sufficiently robust against normality violations (Blanca-Mena et al., 2017; Schmider et al., 2010), ANOVAs were applied also for these variables.

For each variable of interest, except for the self-rating variables, a separate 2 × 2 repeated-measures ANOVA with the within-factors "Block" (Block 1 vs. Block 2) and "Phase" (DP vs. NDP) was conducted. For reporting ANOVA effect sizes, partial eta squared (η_p^2) was used. According to Cohen (1988), $\eta_p^2 = .01$ indicates a small effect, $\eta_p^2 = .06$ a medium effect and $\eta_p^2 = .14$ a large effect. For *t*-test effect sizes, Cohen's *d* was used, whereby $d = .20$ indicates a small effect, $d = .50$ a medium effect and $d = .80$ a large effect (Cohen, 1988).

Moreover, to identify potential interrelations between objective and subjective measures of inattention, impulsivity, and activity, exploratory correlation analyses were conducted: First, all three CPT variables were correlated with recognition *d*'. Second, omission error rates were correlated with self-rated inattention, commission error rates with self-rated impulsivity, and head position shifts/head rotations with self-rated activity. Third, the inattention and impulsivity measures were correlated with each other. All correlations were tested for significance and Bonferroni–Holm correction was applied to correct for multiple comparisons.

Three participants were not included in the statistical analyses, two due to technical failures and one, because after the experiment they admitted having taken antidepressant medication which led to meeting an exclusion criterion for our healthy sample. Therefore, the final sample analyzed comprised $n = 32$ individuals (11 male, 21 female), aged between 19 and 29 years ($M = 23.03$, $SD = 2.52$). For all statistical analyses, Matlab R2018b was used and the α-level was set to .05.

Results

CPT Performance

On average, the total commission error rate amounted to $M = 0.53\%$ ($SD = 0.58\%$) and the omission error rate to $M = 2.89\%$ ($SD = 3.74\%$). The average reaction time (RT) amounted to $M = 0.41$ s ($SD = 0.05$ s), whereas the average RTV, in turn, was $M = 0.23$ ($SD = 0.08$). Pearson correlations between Block 1 and 2 performances yielded internal consistencies of $r = .744$ ($p < .001$) for omission errors, $r = .733$ ($p < .001$) for commission errors, $r = .814$ ($p < .001$) for RT and $r = .507$ ($p = .003$) for RTV. CPT descriptive statistics for each experimental condition can be found in Supplemental Table S2. ANOVAs did not yield any significant effects for any of the three CPT outcome parameters (cf. Figure 4, for statistical details, see Table 1).

Electrophysiological Analyses

Frequency Analyses. Results of the time-frequency analyses are shown in Figure 5. In line with the literature (Ishihara & Yoshii, 1972) and across conditions, theta power prominently showed up over frontal-midline and occipital electrodes, whereas beta power was more broadly distributed over the whole scalp (cf. Figure 5B). Regarding TBRs (cf. Figure 5C), the ANOVA neither revealed a significant main effect of "Block", $F(1, 31) = 0.00$, $p = .960$, $\eta_p^2 = .00$, nor of "Phase", $F(1, 31) = 0.47$, $p = .500$, $\eta_p^2 = .01$, nor an interaction effect, $F(1, 31) = 0.04$, $p = .850$, $\eta_p^2 = .00$.

As an exploratory follow-up analysis, theta and beta power at electrode Fz were also evaluated individually, using the same 2 × 2 repeated-measures ANOVA design. Beforehand, both variables were square-root transformed to reduce skewness to an acceptable level ($\leq \pm 1$). Regarding theta power (cf. Figure 5D), the ANOVA revealed significant main effects of "Block", $F(1, 31) = 22.51$, $p \leq .001$, $\eta_p^2 = .42$, and "Phase", $F(1, 31) = 9.89$, $p = .004$, $\eta_p^2 = .24$. Whereas the

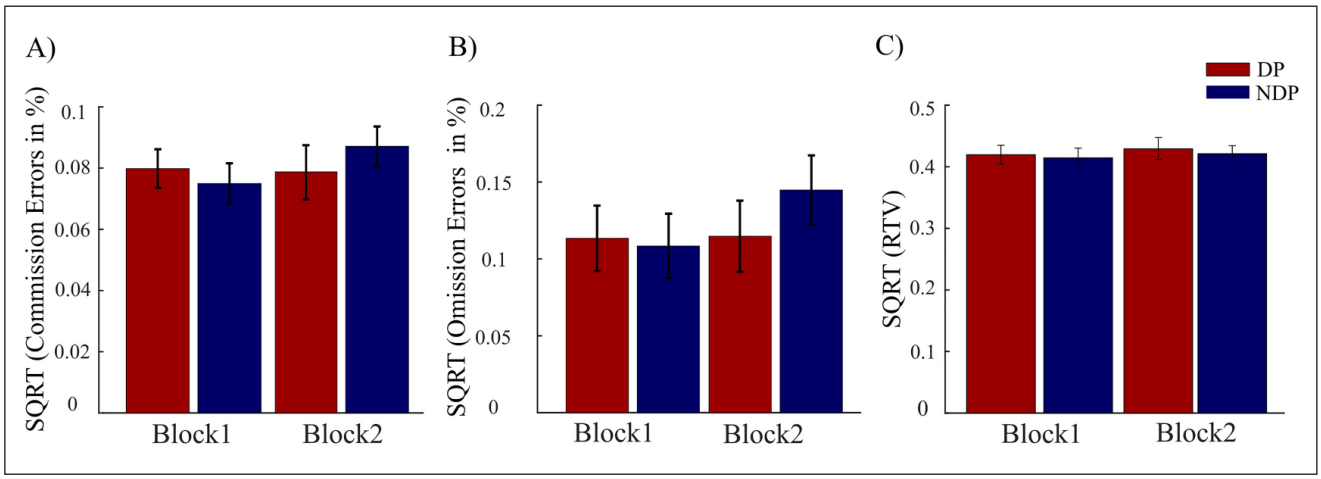

Figure 4. Continuous Performance Task (CPT) Results.
Note. (A) Percentage of commission errors, (B) percentage of omission errors, and (C) reaction time variability (RTV) in distractor phases (DP) and non-distractor phases (NDP) of Blocks 1 and 2. All barplots depict square root transformed data. Analyses of variance (ANOVAs) did not yield significant effects for any of the three parameters.

Table 1. ANOVA Results of CPT Performances.

CPT parameter	Predictor	*df*	*F*	*p*	η_p^2
Omission error rate	Block	1, 31	1.33	.257	.04
	Phase	1, 31	0.61	.441	.02
	Block × Phase	1, 31	1.39	.247	.04
Commission error rate	Block	1, 31	0.60	.446	.02
	Phase	1, 31	0.12	.735	.00
	Block × Phase	1, 31	2.06	.161	.06
RTV	Block	1, 31	0.41	.529	.01
	Phase	1, 31	0.51	.480	.02
	Block × Phase	1, 31	0.03	.871	.00

Note. CPT = continuous performance task; RTV = reaction time variability.

effect of "Block" was due to a higher theta power in Block 2 than Block 1, the effect of "Phase" was due to a higher theta power under NDP than DP. No interaction effect was found by the ANOVA, $F(1, 31) = 0.02$, $p = .885$, $\eta_p^2 = .00$.

Concerning beta power (cf. Figure 5E), the ANOVA revealed the same pattern: Also here significant main effects of "Block", $F(1, 31) = 20.17$, $p \leq .001$, $\eta_p^2 = .39$, and of "Phase", $F(1, 31) = 13.28$, $p \leq .001$, $\eta_p^2 = .30$, were found, but no interaction effect, $F(1, 31) = 0.73$, $p = .398$, $\eta_p^2 = .02$. And again, the "Block" effect was due to a higher beta power in Block 2 than 1, whereas the "Phase" effect consisted in a higher beta power under NDP than DP. Frequency descriptive statistics for each experimental condition can be found in Supplemental Table S2.

ERP Analyses. One dataset was identified as an outlier and therefore excluded from further ERP analyses. Waveforms and topographies of the analyzed ERPs are depicted in Figure 6A. In line with the literature, the extracted ERPs showed the typical waveform and topography of a target P300 (e.g., Polich, 2007), with a maximum peak at around 330 to 347 ms over centro-parietal electrodes. The ANOVA on the target P300 amplitudes (Figure 6B, left panel) revealed a significant block effect, $F(1, 30) = 4.71$, $p = .038$, $\eta^2 = .14$, indicating that amplitudes were higher in the first compared with the second block. The ANOVA on the target P300 latencies (Figure 6B, right panel), in turn, revealed a significant phase effect, $F(1, 30) = 5.15$, $p = .031$, $\eta^2 = .15$, indicating prolonged latencies in NDP compared with DP. There were no other significant effects (for statistical details, see Table 2). P300 descriptive statistics for each experimental condition can be found in Supplemental Table S2.

Actigraphy Analyses

The ANOVA for head position shifts (Figure 7A) yielded a significant main effect of "Block", $F(1, 31) = 24.34$,

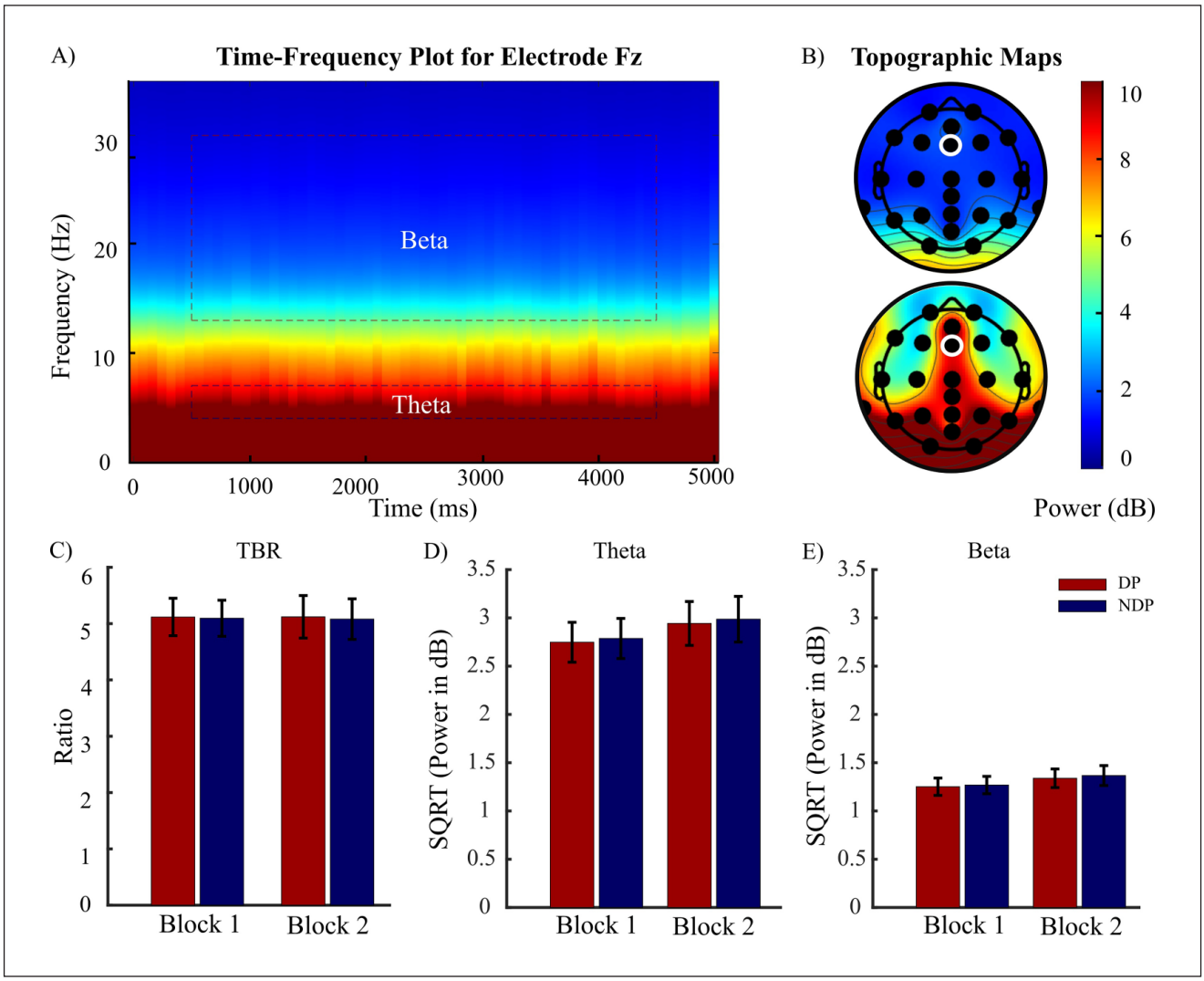

Figure 5. Results of the Time-Frequency Analyses.
Note. (A) Time-frequency spectrum across conditions between 0 and 30 Hz at electrode Fz (grand average of 5 s segments). (B) Corresponding topographic maps for analyzed theta power (4–7 Hz, lower plot) and beta power (13–30 Hz, upper plot). Electrode Fz is white circled. (C) Theta-beta-ratio (TBR), (D) theta power, and (E) beta power distributions during the different continuous performance task blocks (Block 1 vs. Block 2) and phases (distractor phases (DP) versus non-distractor phases (NDP)). Barplots for theta and beta power depict square root transformed data.

$p < .001$, $\eta_p^2 = .44$, but no main effect of "Phase", $F(1, 31) = 1.41$, $p = .244$, $\eta_p^2 = .04$, and no significant interaction, $F(1, 31) = 0.43$, $p = .518$, $\eta_p^2 = .01$. The effect of "Block" revealed that stronger head position shifts were conducted during Block 2 than Block 1.

Head rotation findings were in line with these findings (cf. Figure 7B). The ANOVA yielded a significant main effect of "Block", $F(1, 31) = 9.14$, $p = .005$, $\eta_p^2 = .23$, in that stronger head rotations were executed under Block 2 than Block 1. Likewise, the ANOVA did not reveal a main effect of "Phase", $F(1, 31) = 0.06$, $p = .813$, $\eta_p^2 = .00$, nor a significant interaction, $F(1, 31) = 0.07$, $p = .798$, $\eta_p^2 = .00$. Actigraphy descriptive statistics for each experimental condition can be found in Supplemental Table S2.

Experience Sampling and Recognition Test

Self-rated levels of inattention, hyperactivity, and impulsivity during the two blocks are depicted in Figure 8. Self-reported inattention and hyperactivity were significantly higher in the second experimental block compared with the first experimental block, inattention: $t(31) = -5.17$, $p < .001$, $d = -.91$, hyperactivity: $t(31) = -3.73$, $p < .001$, $d = -.66$. There was no significant difference in self-reported impulsivity between the two experimental blocks, $t(31) = -1.36$, $p = .184$, $d = -.24$. Across participants, the mean cybersickness score was $M = -0.37$ ($SD = 0.93$), indicating that participants experienced little or no symptoms of discomfort in the VR environment. In the recognition test, d' was on average $M = 1.32$ ($SD = 0.58$).

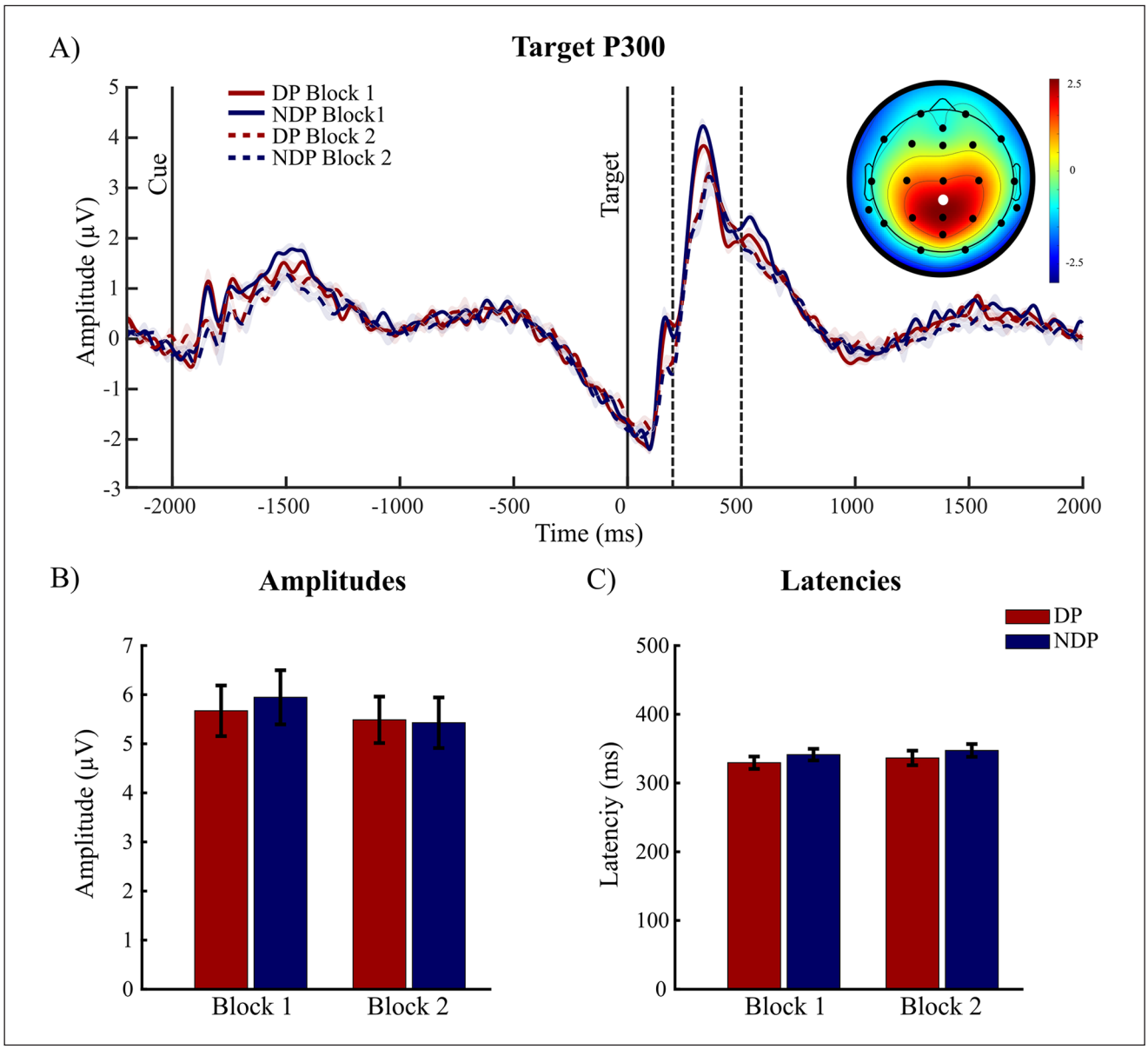

Figure 6. Results of the Target P300 Analyses.
(A) Waveform and topography of the target P300 at channel CPz (white marked electrode) across distractor phases (DP) and non-distractor phases (NDP) for each block. The red waveforms depict the target P300 DP and the blue waveforms the target P300 during NDP. Black dotted lines indicate the interval used for the statistical analyses and topography compilations. (B) Target P300 peak amplitudes and (C) corresponding latencies for both blocks and phases.

Table 2. ANOVA Results of P300 Amplitudes and Latencies.

Parameter	Predictor	*df*	*F*	*p*	η_p^2
P300 amplitude	Block	1, 30	4.71	.038	.14
	Phase	1, 30	1.04	.316	.03
	Block × Phase	1, 30	2.15	.153	.07
P300 latency	Block	1, 30	1.10	.303	.04
	Phase	1, 30	5.15	.031	.15
	Block × Phase	1, 30	0.01	.920	.00

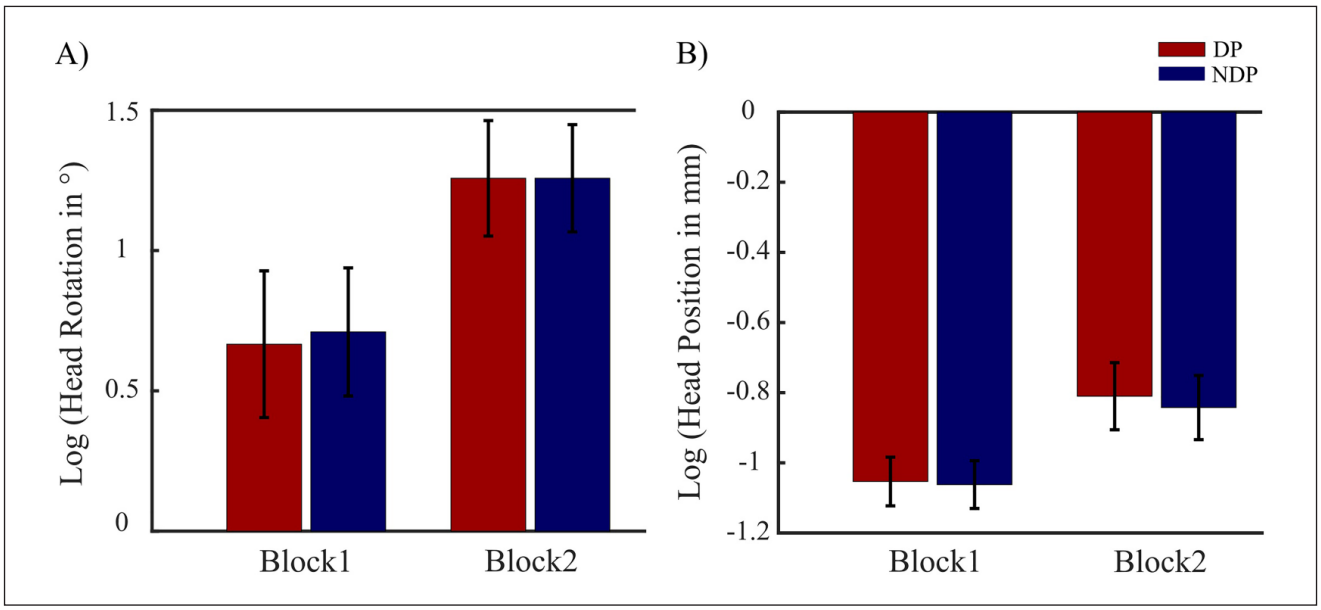

Figure 7. Results of the Actigraphy Analyses.
(A) Head rotations and (B) head position shifts in distractor phases (DP) and non-distractor phases (NDP) of Blocks 1 and 2. Barplots depict log-transformed data. Analyses of variance (ANOVAs) for head position shifts and rotation yielded that participants conducted stronger head position shifts and head rotations during Block 2 than Block 1.

Correlation Analyses

The correlation analyses revealed a significant positive correlation between head position shifts and subjective hyperactivity, $r(30) = .63$, $p < .001$. Moreover, an additional moderate negative correlation was found between recognition test score and RTV, $r(30) = -.38$, $p = .032$, which, however, did not remain significant after Bonferroni–Holm correction (adjusted $p = .310$). All other correlations were between $r = \pm.40$ and nonsignificant, even without correction. For the exact correlation results with both uncorrected and Bonferroni–Holm corrected p values, see Supplemental Table S3.

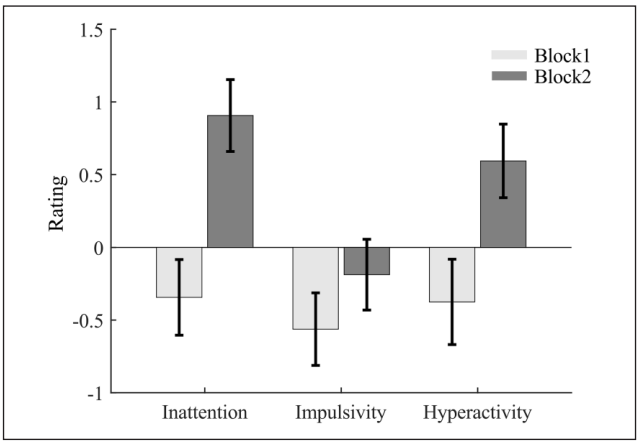

Figure 8. Self-Ratings of Inattention, Impulsivity, and Hyperactivity.
Subjective inattention, impulsivity, and hyperactivity ratings for Blocks 1 and 2. *T*-tests yielded significantly higher subjective inattention and hyperactivity during Block 2 than Block 1.

Discussion

In this feasibility study, we examined the viability of a VSR as a potential assessment tool for identifying and multimodally characterizing inattention, impulsivity, and hyperactivity symptoms in adult ADHD patients. As a first step toward such a tool, we immersed $N = 35$ healthy adults into our VSR and let them perform a CPT under varying levels of distractions. Although during distractor phases (DP), distracting events regularly occurred every 45 s, no distracting events occurred during non-distractor phases (NDP).

With regards to the general feasibility of the VSR, our study yielded promising results in terms of both tolerability and data plausibility. All included participants were able to undergo the whole experiment from start to finish, and no session had to be paused due to physical discomfort or any other reason. In fact, self-reported cybersickness scores indicated little to no discomfort during immersion. Furthermore, we succeeded to simultaneously record both behavioral and neurophysiological data. Our concerns about artifacts due to participants' movements or due to the HMD were justified, but we were able to sufficiently clean up the EEG signal, in order to enable physiologically plausible ERP and frequency analyses.

For CPT outcome measures, we neither found differences between Block 1 and Block 2 nor between DP and NDP. That is, CPT performance neither declined over the course of the experiment nor was it significantly influenced by the occurrence of distracting events. Although the first null finding complies with Bioulac et al.'s (2012) virtual classroom study, which found that CPT performance deteriorated over time in children with ADHD, but not in healthy controls, the latter null finding converges with the two Virtual Classroom studies by Rizzo et al. (2006) and Neguț et al. (2017), which revealed that, unlike children with ADHD, healthy controls did not show performance differences between DP and NDP. Given that all these previous studies were conducted with children and varying task designs, such comparisons should, however, be made with caution. Although Bioulac et al.'s (2012) CPT, for instance, only lasted 14 min, our own CPT endured 48 min. Consequently, we expected fatigue-induced performance deteriorations in our healthy participants, too. A better explanation for the present null findings, therefore, might be that our CPT was not sufficiently sensitive for detecting small performance drops, possibly due to a ceiling effect: On average, participants committed only 6.24 omission errors ($SD = 8.08$) and 6.53 commission errors ($SD = 7.03$) over the whole 48 min of the task, and in at least one of the two blocks, 50% of participants made fewer than two commission errors and over two thirds (69%) made fewer than two omission errors. In sum, based on these results, we cannot unambiguously conclude that our CPT maps change in attention better than traditional, computer-based CPTs.

Regarding our TBR evaluations, we neither found any Block 1 versus Block 2 nor DP versus NDP differences. Thus, contrary to our expectations, we did not find evidence for attention-related TBR changes. One possible explanation could be that the TBR is not a sensitive marker of attentional control. In fact, the TBR has so far almost exclusively been studied as a potential discriminating feature between ADHD populations and healthy populations (for a review, see Arns et al., 2013), but only little as a general EEG measure of attention per se. Hence, although the few studies conducted indicate an association between TBR and attention (Angelidis et al., 2016; Putman et al., 2014; van Son et al., 2018), further confirmatory studies are necessary. An alternative explanation could be that participants' attention levels simply stayed stable throughout the task. It is to be noted, however, that our relatively small sample of $N = 35$ might not have been sufficient to detect intra-individual TBR differences. Still, it can be observed that although the TBR itself remained stable, both beta power and theta power significantly increased from Block 1 to Block 2 and were also higher during NDP than DP. Both the long CPT duration and variation of distractor levels thus clearly induced oscillatory changes in the EEG.

Furthermore, it could be reasoned that the theta power increase from Block 1 to Block 2 was due to a drop in sustained attention over time. Given previous evidence for a positive association between frontal theta power and higher mental effort (Sauseng et al., 2006), this line of reasoning conflicts with our result of lower theta power during DP than NDP as we expected distractions to increase cognitive demands. Hence, if theta power increased as a function of mental effort, we would have expected higher theta power during DP than NDP instead. However, there is also evidence suggesting that in repetitive tasks with low difficulty, task-irrelevant stimuli can facilitate attention performance by increasing arousal and therefore counteracting task-induced fatigue (Olivers & Nieuwenhuis, 2005; Smucny et al., 2013; Zentall & Zentall, 1983). Considering that participants' performance was overall very high in our study, thus indicating low task difficulty, it could be assumed that arousal levels were higher during DP than NDP, leading to the observed decline in theta power.

The increase in beta power from Block 1 to Block 2, in turn, complies with a study by Boksem et al. (2005), who also reported an increase over time in theta and beta power in a visual attention task. Although an increase in theta power is considered to reflect mental fatigue due to attentional demands, increasing beta power might reflect compensatory attentional efforts to counteract time-on task-related fatigue and maintain cognitive control (Boksem et al., 2005; see also Stoll et al., 2016). This interpretation also appears applicable to the present EEG results, especially if one also considers the present behavioral and subjective results: Although subjectively, participants clearly reported an attention decrease from Block 1 to Block 2, their CPT performance remained unaffected by this subjective attention decrease. That is, they were still able to compensate for their increasing mental fatigue. The effect of higher beta power during NDP than DP, in turn, could potentially reflect distraction-induced lapses in task engagement, since previous literature has associated task-related beta power increases with increasing task engagement and alertness (Coelli et al., 2015; Kamiński et al., 2012). Hence, it might be speculated that the distractors played during the DP temporarily interrupted the participants' task engagement in the CPT.

As regards ERP analyses, we successfully extracted the expected topography and waveform of a target P300 with an averaged peak from 330 to 347 ms for phases and blocks. This confirms that not only frequency analyses but also ERP analyses can be reliably conducted with our VSR. As pertains statistics, we found a reduced P300 amplitude in Block 2 as compared with Block 1 and a prolonged latency in NDP as compared with DP. Previous studies have associated a reduced P300 amplitude and prolonged latency with mental fatigue and higher cognitive workload, for example,

during driving simulation paradigms (Coleman et al., 2015; Zhao et al., 2012). Although our result of a reduced P300 amplitude over time is in line with these findings, indicating an increase in mental fatigue over time, the prolonged latency in NDP compared with DP is surprising, as we would have expected DP to be more cognitively demanding than NDP. Perhaps, however, this finding can be explained in a similar way as our finding of reduced theta power in DP: Due to the distracting events, arousal levels may have increased in DP, leading to a reduction in fatigue, which then resulted in shorter P300 latencies.

Regarding actigraphy and self-rating measures, we found three indications that participants increased their body activity from Block 1 to Block 2. Not only did participants self-report higher activity levels in Block 2 but they also conducted more head position shifts and head rotations during Block 2. Our assumption is that this increase in body activity can be attributed to increasing fatigue and impatience over the course of the CPT and, therefore, an increasing difficulty in sitting still. The current VSR scenario thus appears capable of inducing hyperactivity, and this effect should become even more pronounced, if the scenario will be applied to ADHD patients. Regarding the comparison between DP and NDP, no significant actigraphy differences were found. This corresponds to the Virtual Classroom study by Rizzo et al. (2006), who also did not find differences in head, arm, and leg activity between distractor and non-distractor conditions in healthy children. Parsons et al. (2007), on the other hand, reported higher means of body movement in distractor than in non-distractor conditions in healthy children, but this difference was not inference-statistically analyzed.

There were no correlations between SEA-R attention score and omission error rate, nor between I8 impulsivity score and commission error rate. A possible explanation for this repeatedly observed lack of convergent validity (Aichert et al., 2012; Cyders & Coskunpinar, 2011; Gomide Vasconcelos et al., 2014; Solanto et al., 2004; but see Asbjørnsen et al., 2010; Epstein et al., 2003) is that computerized tasks and self-report scales reflect different facets of behavior. Although the CPT objectively measures attention performances during a single experimental session in a specific, laboratory setting, self-report scales typically summarize subjective experiences over much longer periods of time and across a variety of situations (Barkley, 1991; Meyer et al., 2001; Slobodin & Davidovitch, 2019). Another reason might be that in the present study the CPT was not sensitive enough to detect small differences in inattention and impulsivity between participants, and therefore CPT parameters did not correlate with subjective scores. However, due to this lack of correlation, the results of the current study provide no evidence that the VSR can map individual attention differences in everyday life and is more ecologically valid than traditional CPTs.

Limitations and Future Directions

One important limitation of the present study is that the CPT was not particularly difficult for healthy participants. Consequently, ceiling effects may have resulted in an insufficient depiction of the true variance between participants' individual attention and impulsivity capacities. That we did not find influences of time and varying distraction levels on CPT performances, as well as no correlations between CPT performances and subjective levels of inattention and impulsivity, should therefore not be over-interpreted. Instead, these null results might potentially just be attributable to variance restrictions, due to a too low task difficulty.

Low CPT error rates are also suboptimal for EEG analyses. Besides analyzing the target P300, it would be, for instance, also interesting to analyze error-related potentials, like the error-related negativity (ERN). The ERN negatively peaks between 50 and 100 ms following an error response and has repeatedly been found to be attenuated in amplitude and shortened in latency in ADHD patients compared with healthy controls (for a meta-analysis, see Geburek et al., 2013). For analyzing the ERN, the EEG signal, must, however, be aggregated across several trials, which is not possible, if the error rate is as low as in the present study.

Consequently, to ensure sufficiently high error rates and performance variance in both ADHD patients and healthy controls, it is crucial to increase the CPT's difficulty for future studies. One way to achieve a higher difficulty would be to modify the CPT parameters, for instance, by increasing the task speed, lowering the ratio of targets to non-targets, or reducing stimulus salience (Ballard, 1996a, 1996b). Another possibility would be to increase the level of distraction. In the present study, the number of distractors per DP was relatively low, since distracting events were played only every 45 s. This led to long periods in which no distraction occurred. In addition, some distracting events turned out to be not salient enough. As revealed by our recognition task, 12 of the distractors (1 auditory, 6 visual, 5 audio-visual distractors) were not noticed by over 50% of our participants. Thus, for further studies, both distraction frequency and the salience of distractors might also be increased.

Another possibility for improvement of the present VSR implementation is to complement the existing measurement methods with additional ones. Further insights into the participant's distractibility could, for instance, be gained by eye-tracking recordings, which would allow to track at which distractors participants look closely and which they ignore, especially given the observation of impaired oculomotor inhibition in ADHD (Chamorro et al., 2021).

Conclusion

This study set out to test the feasibility of a VR paradigm to investigate attention, impulsivity, and hyperactivity in a multi-modal assessment procedure. Our results confirm that

it is possible to simultaneously analyze these symptoms by several neuropsychological, phenomenological, electrophysiological, and actigraphic measures. Although in our healthy participants, no CPT performance differences were observed, presumably due to ceiling effects, we found various time on tasks effects in respect to electrophysiological, phenomenological, and actigraphical measures. In the next step, to further prove the validity of our multimodal VSR, a sample of adult ADHD patients will be investigated.

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Author Contributions

AW, KK, DA, and ML designed the experiment under the supervision of NB. ML collected the data. AW, KK, and NB analyzed the data. AW, KK, and NB wrote major parts of the manuscript. AP, SL, BS, BA, and UE contributed to, reviewed, and edited the manuscript. All authors contributed to the article and approved the submitted version.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

Data Availability Statement

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

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3.2 Publication 2: P300 Modulation via Transcranial Alternating Current Stimulation in Adult Attention-Deficit/Hyperactivity Disorder: A Crossover Study

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P300 Modulation *via* Transcranial Alternating Current Stimulation in Adult Attention-Deficit/Hyperactivity Disorder: A Crossover Study

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Objective: A repeated finding regarding event-related potentials (ERPs) is that patients with ADHD show a reduced P300 amplitude. This raises the question of whether the attention of ADHD patients can be increased by stabilizing the P300. Assuming that the P300 is generated by event-related oscillations (EROs) in the low frequency range (0–8 Hz), one approach to increase the P300 could be to stimulate the patient's P300 underlying ERO by means of transcranial alternating current stimulation (tACS). The aim of this follow-up study was to investigate this hypothesized mechanism of action in adult ADHD patients.

Materials and Methods: Undergoing a crossover design, 20 adult ADHD patients (10 female) received an actual stimulation *via* tACS on one day and a sham stimulation on another day. Before and after each intervention, EEG characteristics (P300 amplitudes, low frequency power) and attention performances (d2 attention test, visual oddball task (VOT)) were recorded.

Results: Electrophysiological analyses revealed no evidence for an enhanced P300 amplitude or low frequency power increase after actual stimulation compared to sham stimulation. Instead, a significant effect was found for a stronger N700 amplitude increase after actual stimulation compared to sham stimulation. Consistent with the P300 null results, none of the examined neuropsychological performance measures indicated a tACS-induced improvement in attentional ability.

Conclusion: Contrary to a previous study using tACS to modulate the P300 in adult ADHD patients, the current study yields no evidence that tACS can increase the P300 amplitude in adult ADHD patients and that such P300 enhancement can directly improve neuropsychological parameters of attention.

Keywords: P300, attention deficit/hyperactivity disorder, ADHD, transcranial alternating current stimulation, tACS, therapy

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common developmental disorder that persists into adulthood, and is associated with core symptoms of inattention, hyperactivity, and impulsivity (1). With an estimated global lifetime prevalence of 2.58% (2), ADHD causes not only severe individual suffering such as difficulties in academic career (3, 4), occupational burdens (5–11) and difficulties in social interactions and relationships (12–19), but also a high burden for society and economy. Considering not only direct diagnostic and treatment costs, but also secondary follow-up costs (e.g., productivity losses due to inability to work or early retirement, justice system costs), the global total annual costs of ADHD are estimated to be at least 831 million [for a systematic review, see (20)]. Therefore, the treatment of ADHD is not only important to reduce individual suffering, but also to avert economic damage.

So far, ADHD is primarily treated by psychostimulants, cognitive behavioral therapy, or a combination of both (21). Although stimulant medication is thereby usually considered as first-choice treatment (22–24), it often leads to undesirable side effects such as sleep disturbances (25), decreased appetite and weight decrease (26) or cardiovascular effects (27). Moreover, in a significant subgroup of ADHD patients, psychostimulants have no, or no sufficient treatment effect (28–30). Also, some patients develop tolerances to psychostimulants (31) and often interrupt or discontinue their medication (32), particularly due to adverse events (33). Consequently, the development of further, effective ADHD therapy approaches with fewer side effects is urgently required.

One explanatory factor for individual differences in response to psychostimulants may be the high pathophysiological heterogeneity within the ADHD population [for a critical discussion, see (34)]. Various combinations of environmental and genetic factors, for instance, lead to diverse neuropsychological impairments and thus to different ADHD symptom profiles (35). Consequently, great research effort is currently being undertaken to identify ADHD biomarkers that are of predictive value for ADHD treatments and could guide practitioners in deciding which treatment options hold most promise in each individual case [for a systematic review, see (36)]. Similarly, there is hope that the discovery of reliable biomarkers helps to develop new treatment approaches that directly target the pathomechanisms revealed by the biomarkers and are not merely symptom-driven.

One such biomarker that might prove useful as a target site in ADHD treatment is the P300 component in electroencephalographic event-related potentials (ERPs) (37). The P300 is a positive voltage deflection around 300 ms after a target stimulus over centro-parietal regions and associated with attentional allocation and stimulus processing (38, 39). Reliable elicitation of the P300 can be achieved, for example, by oddball paradigms, in which subjects are required to respond to infrequent target stimuli and to ignore frequent distractor stimuli (40). Probing such oddball paradigms in ADHD, several studies have found a reduced P300 amplitude (41–48) and prolonged latency (44, 49–53) in adult ADHD patients compared to typically developed individuals. In addition, several research groups report increased P300 amplitudes along with attention improvements after administration of ADHD medication (54–57) or mindfulness-based cognitive behavior therapy (MBT) (58). Hence, the P300 appears to be a reasonable target site for the exploration and development of further therapeutic methods.

If the P300 is abnormally altered in ADHD patients but normalizes after psychostimulant administration or MBT, the question arises whether an attention improvement is also achievable by a direct modulation of the P300, e.g., by applying transcranial alternating current stimulation (tACS). tACS is a non-invasive technique in which the brain is stimulated *via* an alternating current of a beforehand determined frequency. As certain can be considered that tACS can modulate endogenous brain oscillations and, more importantly, cognitive processing [for review, see (59)]. Regarding attentional processing, for instance, an improved accuracy in conjunction search after alpha tACS (i.e., a stimulation frequency around 8 to 12 Hz) (60) and an improved voluntary top-down attention after gamma tACS (i.e., a stimulation frequency >30 Hz) (61) has been reported.

During tACS, the presumed mechanism of action is mainly attributed to the entrainment of intrinsic brain oscillations to the external stimulation signal (59, 62, 63). Entraining oscillations is observed to be most efficient when the frequency of the applied current is close to the intrinsic brain frequency (64). The administered current alters internal neuronal excitability by causing changes in the resting potential (65). Whether neuronal excitability is thereby enhanced or weakened, and consequently increases or decreases the probability of neural firing, is determined either by depolarization or hyperpolarization (66). Taken together, when tACS is applied, the external sinusoidal force and the internal neural firing patterns are synchronized. Moreover, tACS is thought to induce changes in synaptic plasticity (67–69). Whether the synaptic activity between neurons is intensified or attenuated is thereby determined by the timing of the neurons' input and output activity (pre- and post-synaptic events). TACS can affect this spike probability of neurons and it is believed that these synaptic changes persist after cessation of stimulation, leading to increased power at the chosen stimulation frequency (70–72). This phenomenon is called spike-timing-dependent plasticity [for further details, see e.g., (73)].

Whether tACS can also modulate ERPs is less validated. While the few existing empirical studies on this issue (74–78) yielded mixed results, at least from a theoretical perspective such modulability appears expectable, given that ERPs can be regarded as event-related oscillations (ERO) (79). The P300 component at issue here, for instance, has been closely linked with an ERO in the delta (0–4 Hz) to theta (4–8 Hz) range (80–84). Therefore, at least theoretically, tACS appears to offer a promising therapeutic approach to modulate not only oscillations but also ERPs in ADHD patients.

Despite this high potential tACS may have for the treatment of ADHD, the use of tACS in ADHD has so far little been studied. In fact, consistent with the findings of a recent review of neurostimulation in ADHD (85) that found 30 studies, but none of which applied tACS, our own literature search only yielded one study recently published Dallmer-Zerbe et al. (75) and another study recently published by Farokhzadi et al. (86).

In the study by Farokhzadi et al. (86), treatment with 10 Hz alpha tACS was compared to psychostimulant treatment in 62 ADHD children. Over the course of 8 weeks, one group received alpha tACS thrice a week for 10–15 min at pre-frontal electrode sides, while another group received psychostimulant treatment over the same course of time. The reported result is that tACS was more effective than psychostimulant treatment in improving attention and impulsivity, as assessed by the "integrated visual and auditory test." Although promising, one methodological problem with this result is that it is only based on behavioral, but not on neurophysiological investigations (i.p. an investigation of the EEG alpha spectrum). Therefore, it cannot be ruled out that the group differences found are due to some other mechanisms (e.g., more social devotion during the tACS than psychostimulant intervention) rather than being due to the assumed electrostimulative mechanism of action.

In the study by Dallmer-Zerbe et al. (75), in turn, 18 adult ADHD patients either underwent tACS or placebo stimulation for approximately 20 min. TACS was thereby applied at the participant's individual ERO, and the presentation of the target stimuli was timed in such a way that the participant's induced P300 always coincided with the positive voltage peaks of the ongoing tACS. Results showed a significant enhancement of the P300 amplitude in the stimulation group and a tACS-induced decrease in omission errors (75). Also this study had, however, some methodological flaws. In particular, the implemented oddball task turned out to be too easy, so that hardly any errors were committed. Moreover, a between-subjects design was used with only 8 patients per group. Hence, the study might have been underpowered.

Therefore, the aim of the current study was to replicate overall study findings by the previous study by Dallmer-Zerbe et al. (75), and consequently to investigate to what extent tACS can modulate the target P300, the low frequency range, and neuropsychological test performances in adult ADHD patients. To this end, we carried out a crossover study with two separate measurement days in which our 20 adult ADHD patients received a placebo stimulation (sham) in one case and an actual tACS in the other, while conducting an optimized visual oddball task (VOT). Using a mobile EEG system, individual stimulation parameters were determined and individually adjusted on site, using a time-frequency decomposition of the P300. We revised several aspects of the former study by Dallmer-Zerbe et al. (75) like, for example, we used a crossover study design instead of between-subjects design or adjusted the VOT to increase task difficulty (a detailed list comparing both experiments can be found in the **Supplementary Table 1**).

MATERIALS AND METHODS

Participants

A total of 22 ADHD patients (11 female, M_{age} = 28.55, SD = 8.77, age range: 19–48) volunteered in this study, out of which 20 underwent the entire experiment. All participants were recruited *via* the specialized outpatient clinic for adult ADHD of the Clinic for Psychiatry and Psychotherapy of the University Hospital Bonn. Participants were either personally invited to the study during medical consultations or contacted *via* a study applicant pool in which they had previously registered. A brief telephone screening was then conducted with each study prospect, and if there were no reasons for exclusion, the patient was allowed to participate in the study. Written informed consent was obtained from all participants and they all received an expense allowance of 30 € for their participation. Moreover, the study was approved by the medical ethics committee of the University of Bonn (protocol number: 357–19) and pre-registered at the German Clinical Trials Register (Trial-ID: DRKS00020828).[1]

Study Design and General Procedure

The study was carried out on three measurement days and as a crossover study with two interventions. The two interventions compared "actual stimulation" and "sham stimulation." On Day 1, a comprehensive clinical examination was performed, during which the ADHD diagnosis was validated, and the patient's mental state was evaluated. On Days 2 and 3 in turn, the actual experiment took place, with one of the two conditions being run on each measurement day. While fifty percent of the participants underwent the actual stimulation first on Day 2 and the sham stimulation on Day 3, the remaining fifty percent underwent the sham stimulation first on Day 2 and the actual stimulation on Day 3.

Eligibility Assessment and Clinical Characterization

All participants were already diagnosed with ADHD or were in the process of diagnosis at our specialized outpatient clinic for adult ADHD. To confirm the ADHD diagnoses and further characterize their individual ADHD symptom profiles, all participants underwent the structured clinical "Interview of Integrated Diagnosis of ADHD in Adulthood" [IDA-R; (87)]. Moreover, to clarify potential comorbidities and exclusion criteria, the German version of the "diagnostic short interview for mental disorders" [Mini-Dips-OA; (88)] was carried out. Likewise, participants filled in four further self-rating questionnaires:

- *Demographic questionnaire*: A lab-internal, self-designed questionnaire that gathered some biographical data (birth, gender, education, family status) relevant for the study.
- *ADHD Self-Report-Scale* [*ADHS-SB*; (89)]: The ADHS-SB is a 22-item questionnaire that surveys key symptoms of ADHD and allows to derive three domain-specific scores (inattention, hyperactivity, impulsivity) and one overall ADHD score.
- *Depression-anxiety-stress-scales* [*DASS-21*; (90)]: A short 21-item questionnaire that assesses indications of depression, anxiety, and stress. For each symptom area, a separate score from 0 (no burden at all) to 21 (maximum burden) may be calculated.
- *WHO quality of life scale questionnaire–short version* [*WHOQOL-Bref*; (91)]: A 26-item questionnaire assessing quality of life in the past 4 weeks in four main domains

[1] https://www.drks.de/

(physical health, psychological health, social relationships, and environment). To be eligible for the study, participants needed to be right-handed [according to the Edinburgh Handedness Inventory; (92)], to be between 18 and 50 years old, and to have corrected-to-normal or normal vision. In addition, any of the following exclusion criteria had to be absent: Presence of a severe comorbid affective disorder (mild to moderate was included), any psychosis or substance dependence, current use of any psychotropic medication other than ADHD medication, presence of a serious neurological disorder (especially epilepsy), presence of a dermatological disorder of the head, or pregnancy.

Experimental Procedure

Except for the stimulation method applied (actual stimulation vs. sham stimulation) and a short familiarization with the VOT at the first experimental session, the experimental procedure on Day 2 and 3 was identical (cf. **Figure 1**). Whether participants first received the actual or sham stimulation was counterbalanced across all participants. While participants knew that on one session, they would receive a placebo stimulation and on the other session an actual stimulation, they were kept uninformed about the order of stimulation procedures. On both days of measurement, ADHD medication had to be discontinued 24 h beforehand. For both measurement days, the experiment took place in the Virtual Reality laboratory of the University Hospital of Bonn and the experimental procedure was as follows: First, to record their momentary attention level, participants performed the d2 attention test (d2; cf. section "d2 Attention Test"). Next, the participants were prepared for the actual stimulation or sham stimulation and concomitant EEG measurement. In both experimental sessions, the preparation procedure was thereby identical. After that, the actual experiment started, which consisted of three experimental blocks: a *pre-intervention block*, an *intervention block*, and a *post-intervention block*. The three experimental blocks were each separated by 5- to 10-min breaks (depending on the duration of the online EEG analysis). EEG was recorded throughout blocks and a VOT (cf. section "Visual Oddball Task") had to be performed in each of the three blocks. The only difference between the three blocks was that during the intervention block, actual stimulation or sham stimulation was applied. To customize the electrical stimulation, the participants' individual frequency of ERO and P300 peak latency was determined (cf. section "Online Analysis") in the first short break immediately before the intervention block. As soon as the stimulation parameters were determined, the intervention block with either actual stimulation or sham stimulation started (for details, see section "Synchronization Between Stimulus Presentation and Transcranial Alternating Current Stimulation"). From here on, the experimenter could no longer be blinded to intervention since the stimulator had to be operated manually according to either the sham stimulation or actual stimulation. After the intervention block and a further short break, the last post-intervention block started. Finally, after finishing all three experimental blocks, participants again completed the d2 and filled in a questionnaire assessing adverse effects of tACS (93). In total, the experimental procedure took approximately 2.5 to 3 h, including preparation time for attaching tACS and EEG electrodes.

d2 Attention Test

As stated, the d2 (94) was applied before and after the three experimental blocks to compare the participant's individual attention and concentration performances before and after intervention. In accordance with the test manual, the d2 was thereby administered as a paper-pencil test. That is, participants had to cross out target symbols (letter "d" with two strokes) between distracting non-target stimuli (letter "d" with one, three, or four strokes and letter "p" with one, two, three, or four strokes) through 14 consecutive lines of 47 characters each. They were instructed to cross out as many target symbols as possible within a time limit of 20 s per line. Between these 20 s phases, there was no pause, so that the total test time was less than 5 min. To evaluate d2 test performances, the following performance metrics were calculated: the total number of characters processed (as a measure of processing speed), the d2 concentration performance (i.e., the number of correctly identified characters minus all conducted errors), commission errors (i.e., deleted non-target characters), and omission errors (i.e., missed target characters).

Visual Oddball Task

In all three blocks, the VOT was conducted for about 20 min. Participants sat on a chair 70 cm away from a computer screen on which the oddball task was presented. Stimuli were displayed *via* NBS Presentation (Version 21.0 build 06.06.19, Neurobehavioral Systems Inc., Albany, CA, United States) and logged together with keyboard inputs *via* Lab Streaming Layer (LSL)[2].

On the center of a gray computer screen, 2° to the left or right tilted gabor stimuli ($\sim$ 4 cm $\times$ 4 cm) were iteratively displayed, each with a duration of 500 ms. In total, 400 gabor stimuli were presented, out of which 300 (75%) represented standard stimuli and 100 (25%) target stimuli. Whether the left-tilted or right-tilted gabor stimuli represented the standard stimuli, and thus were presented thrice as often, was counterbalanced across all subjects. That is, in 50% of participants, the left-rotated gabor stimuli represented the frequent standard stimuli throughout measurement days, while in the remaining 50%, they represented the infrequent target stimuli. The ISI between the gabor stimuli was jittered between 1,000 and 2,500 ms. During the intervention block, the target stimulus onset was adjusted so that the peak of the individual mean P300 amplitude coincided with the positive peak of the tACS signal (details below). The participants' task was to press a key with their left index finger upon each left-rotated stimulus and a key with their right index finger upon each right-rotated stimulus. Thereby, they were requested to execute their keyboard presses as quickly as possible and as accurately as possible and to fixate onto a fixation circle displayed on the computer screen throughout the task. For assessing VOT performances, four main parameters of interest were extracted for each participant: omission error rate (i.e., the percentage of non-target button responses to target stimuli), commission

[2]https://github.com/sccn/labstreaminglayer

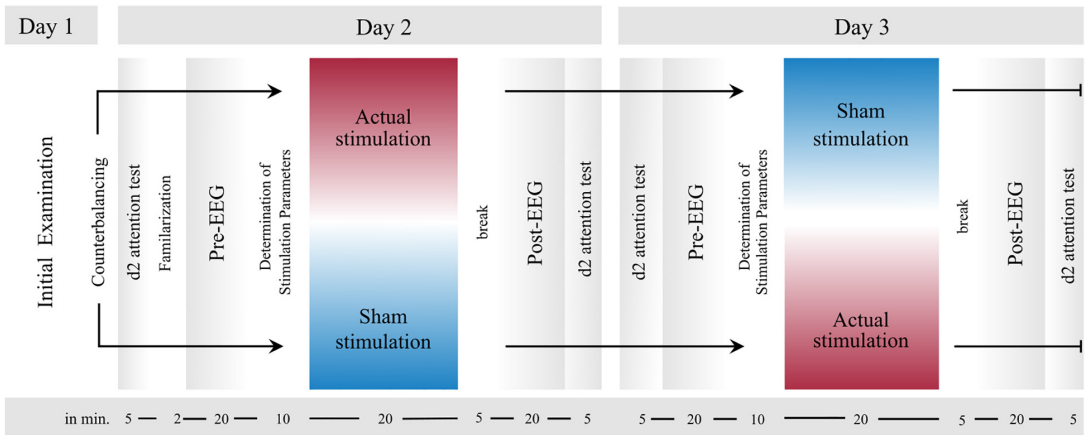

FIGURE 1 | Experimental Design. After an initial examination (Day 1), the two experimental sessions (Day 2 and Day 3) proceeded in the same order, except for a brief familiarization with the visual oddball task (VOT, cf. section "Visual Oddball Task") in the first experimental session. First, the d2 attention test was performed before all electrodes were attached to the participants' head. Next, the first block (pre-intervention) started, in which participants accomplished the VOT. Immediately thereafter, there was a short break, during which the tACS parameters were computed from the EEG data of the first block. As soon as these parameters were collected, the second block (intervention) started, during which actual stimulation or sham stimulation was applied. Finally, the third block (post-intervention) started after a short break. During all three blocks EEG was measured. Last, the d2 was conducted again.

error rate (i.e., the percentage of target button responses to standard stimuli), d-Prime [i.e., a sensitivity measure, calculated by d' = z(Hit Rate)−z(False alarm rate)] and mean reaction time (RT, mean reaction time of the correct target responses). While the omission error rate is considered as a measure of inattention, the commission error rate is thought to reflect impulsivity (95).

Electrical Brain Stimulation and Electrode Montage

Electrical stimulation was only administered during the intervention block using a battery-operated stimulator system (DC-stimulator plus, Neuroconn, Ilmenau, Germany). In total, four 7 cm × 3.5 cm rubber electrodes were placed on the participant's head, whereby two of them were placed above C1/C2 and the other two above C5/C6 (for orientation of the electrodes, see **Supplementary Figure 1**). The electrode montage was selected based on a simulated finite-element model of current flow. More specifically, using the ROAST Toolbox (96) and the MNI standard brain as template, different electrode montages were simulated in respect to their predicted intracranial electrical field in parietal and temporal regions (i.e., the region, where the P300 is most prominent) (97). The selected electrode montage thereby offered the best compromise between the requirement to generate a high intracranial current flow in the target region and the requirement to avoid blocking any EEG electrodes relevant for the EEG analyses. A graphical illustration of the conducted electrode montage simulation may be found in the **Supplementary Figure 1**. The four tACS electrodes were applied using conductive paste (Ten20 conductive paste, Weaver and Co, Aurora, CO, United States), and for all participants, impedances were kept below 10 kΩ .

For the actual stimulation condition, tACS was applied for about 20 min, with an intensity of 1 mA (peak-to-peak). The previously conducted electric field simulation with an injected current of 1 mA peak-to-peak per electrode pair yielded to an electric field strength of ∼ 0.1 V/m (**Supplementary Figure 1**). Previous studies showed [c.f. e.g., (98)] that similar electric field strengths in the target area produced aftereffects. The stimulation frequency was individually adjusted for each participant and reflected the participants' individual frequency peak between 1 and 8 Hz during target trials (details below). To minimize discomfort, the stimulation was faded in and out for about 10 s. For the sham stimulation, in turn, tACS was again faded in for about 10 s, but then only lasted for another 10 s, before it was again faded out for 10 s. Hence, in total, the "tACS" during the sham stimulation conditions only lasted for 30 s including fade-in and fade-out phases and served the purpose of realistically mimicking the phenomenological experience of actual stimulation. This procedure is one of the commonly used placebo stimulation techniques [e.g., (99)]. To identify potential differences in the perception of both conditions, at the end of each session participants were asked whether they received actual or sham stimulation, and whether they perceived any tACS side effects (93).

Synchronization Between Stimulus Presentation and Transcranial Alternating Current Stimulation

To always coincide each participant's individual target P300 during the intervention block with a positive voltage peak of the running tACS, a similar synchronization approach was used as in the previous study (75) (cf. **Figure 2A**). As the internal oscillation is believed to synchronize with the external tACS

force and to thereby enhance its power, in-phase tACS (internal oscillation frequency matches with external force) is reported to synchronize EROs, while anti-phase tACS (internal oscillation frequency does not match with external force) is reported to desynchronize EROs [for a discussion, see (100)]. That is, the presentation of the next stimulus was paused by a waiting period until a pulse of the stimulator signaled that the tACS waveform was at a certain position that its next positive peak would coincide with the next P300 peak triggered by the stimulus (cf. **Figure 2**). During this wait period, a fixation point was shown. Technically, this was realized by transmitting the pulse from the stimulator to NBS Presentation at the beginning of each new sinusoidal wave (i.e., upon each zero crossing in the sinusoidal's ascending flank). Based on this, it was possible to define when the next positive tACS peak would occur and thereby adapt the delay for showing the stimuli (cf. **Figure 2B**). This calculation thereby considered both, the fixed P300 latency and individual stimulation frequency, which were already determined during the VOT pre-intervention block (cf. see section "Online Analysis").

Electroencephalography Recording and Analysis

Electroencephalography (EEG) was acquired *via* a wireless EEG system (Smarting®, mBrainTrain®, Belgrade, Serbia) from 22 Ag/AgCl sintered ring electrodes (Fp1, Fp2, AFz, F3, Fz, F4, T7, C3, Cz, C4, T8, CPz, P7, P3, Pz, P4, P8, POz, O1, O2, M1, M2 according to the international 10/20 system). FPz served as ground (DRL) and FCz as reference electrode (CMS). The amplifier was attached to the EEG cap (Easycap, Herrsching, Germany) and communicated wirelessly with the recording computer *via* Bluetooth. Keeping all impedances below 15 kΩ, the EEG was digitized at 500 Hz (one data set was unintentionally recorded at 250 Hz) and with a 24-bit step-size resolution *via* (LSL). The marker stream originating from NBS Presentation was thereby also acquired *via* LSL, such that the EEG recording files entailed all event information of the conducted VOTs. Data analysis was performed using Matlab 2021b (The MathWorks Inc., Natick, MA, United States) and eeglab 2021.0 (101).

Online Analysis

For the on-site EEG analysis during the experiment, the participant's EEG data from the pre-intervention block was filtered with a 40 Hz low-pass filter and a 0.1 Hz high pass filter, and then detrended. Next, before the computation of an independent-component-analysis (ICA) the continuous EEG data was epoched into 2 s time windows. After that, a fast ICA was computed using pop_runica (ica type "fastica") on the epoched EEG data and its components were visually inspected. ICA components reflecting obvious artifacts (e.g., horizontal or vertical eye movements, heartbeats, muscle activity or electrode artifacts) were identified, backprojected to the filtered continuous EEG data, and then rejected. Next, for the calculation of the P300 peak latency, the ICA-corrected continuous EEG data was first epoched from −2 to + 5 s relative to each target stimulus, and then baseline-corrected beginning from −2 s until target onset. Remaining non-stereotypic artifacts were removed by built-in EEGLAB functions (kurtosis thresholding and joint probability test with ± 3-SD single-channel and global-channel thresholds). Then, the participant's P300 latency was derived by averaging all epochs for electrode Pz and identifying the maximum P300 amplitude peak between 250 and 450 ms after target stimulus onset.

The participant's most dominant event-related oscillation during the P300 time window, in turn, was determined by a frequency analysis. First, using Matlab's pspectrum function, the power spectrum at electrode Pz was calculated for each epoch and then all derived power spectra were averaged to obtain one mean power spectrum. The obtained frequency resolution was 0.1 Hz and the obtained time resolution 0.124 ms. Next, the highest frequency power within the time frame of ± 200 ms around the previously determined P300 latency and within the frequency range of 1 and 8 Hz was determined and used as the individual stimulation frequency.

Pre-processing and Data Cleaning

For the EEG offline analyses, the EEG datasets from the pre-intervention and post-intervention block were first merged, down-sampled to 250 Hz, temporally filtered between 0.5 and 40 Hz, and detrended.

In three datasets, noisy EEG channels (max. 3) were identified and replaced *via* spherical interpolation using the pop_interp function. For one dataset, a 1.1 s long highly artifactual data segment was removed. Next, for the computation of an ICA, the continuous EEG data was segmented in 2 s time windows and non-stereotypic artifacts were removed using built-in EEGLAB functions (joint probability test, ± 2-SD single-channel and global-channel thresholds). After that, an ICA ("extended" version) was computed and components reflecting horizontal or vertical eye movements, heartbeat, muscle activity or electrode artifacts, were visually identified, backprojected to the continuous EEG data and then rejected. Hence, at the end of this cleaning process, continuous EEG data sets were obtained that were already filtered between 0.5 and 40 Hz and cleaned from stereotypic artifacts by means of the conducted ICA.

Event-Related Potentials Analyses

Event-related potentials analyses focused on differences in the target P300 between interventions (actual stimulation vs. sham stimulation) and blocks (pre-intervention vs. post-intervention block). To this end, the merged and ICA-corrected continuous EEG datasets for each intervention were first rereferenced to the common average, low-pass filtered below 6 Hz (to exclude alpha activity), epoched from −0.5 to 1.5 s relative to each target stimuli, and then cut into two separate subsets: One subset containing the epochs of the pre-intervention block before actual stimulation or sham stimulation, another subset containing the epochs of the post-intervention block after actual stimulation or sham stimulation. Next, the same following pre-processing and analysis steps were performed on each subset: First, a baseline correction was applied on each epoch by subtracting the mean voltage of the −0.5 s epoch prior to stimulus onset from all data points. Second, within each epoch, channels that exceeded a differential average amplitude of 150 μV were marked for rejection. Channels that were marked as bad on more than

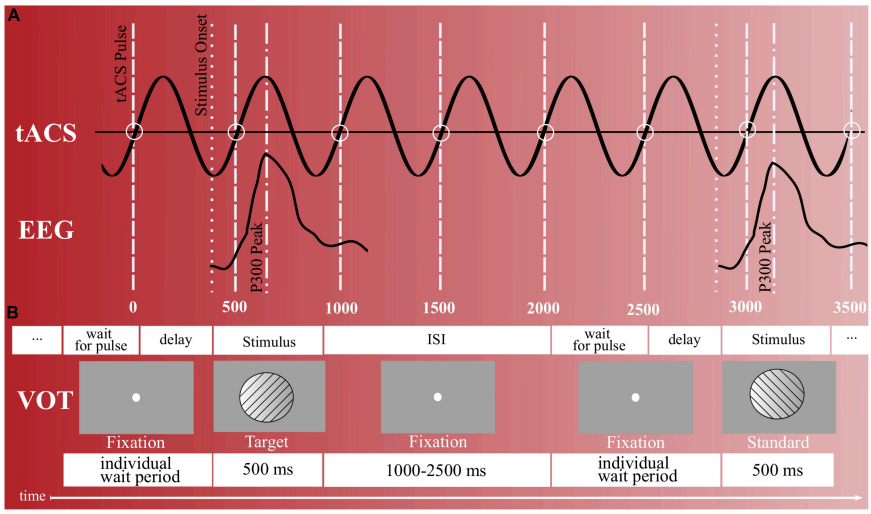

FIGURE 2 | Stimulus presentation and timing. **(A)** Synchronization between target trials and tACS peaks during the intervention block (actual stimulation). To coincide the participant's elicited P300s with the tACS's positive voltage peaks, NBS presentation waited for a pulse of the stimulator (wait for pulse). In addition, an individual delay existed that delayed until the tACS waveform was at the specific position so that its next positive peak would coincide with the next P300 peak triggered by a target stimulus. **(B)** Visual oddball task with right- and left-tilted gabor stimuli. Upon each left-rotated stimulus, participants were to respond with a left-hand button press and upon each right-rotated stimulus with a right-hand button press. In total, 400 gabor stimuli were presented, out of which 25% represented target stimuli and 75% standard stimuli. ISI = inter stimulus interval.

15% of all epochs were excluded. Epochs having more than 10 bad channels were excluded, while epochs with less than 10 bad channels were included. The bad-channel data was replaced with spherical interpolation of the neighboring channel values [TBT, (102)]. Third, the ERP of the respecting condition was calculated by taking the average across epochs. Finally, for the statistical analyses, for each dataset, the mean P300 amplitude was calculated for electrode Pz within the time range from + 200 to + 550 ms. In addition, the maximum P300 peak between 250 and 550 ms was extracted for each dataset. The same processing procedure was implemented for inspecting the standard P300.

Frequency Analysis

The frequency analyses focused on spectral differences in the delta to theta range between interventions and blocks. To this end, the ICA-corrected continuous EEG datasets for each condition were again rereferenced to the common average, epoched from −0.5 to + 1.6 s relative to each target stimulus, and then cut into two subsets for pre- and post-block measurements. Next, the identical following pre-processing and analysis steps were performed on each subset: First, a baseline correction was applied from −0.5 to 0 s, before the same non-stereotypic artifact removal was implemented as described for the P300 analysis. Next, a continuous wavelet transformation (CWT) was conducted on each retained epoch for channel Pz. The frequency range obtained reached from 0.25 to 6 Hz in 47 steps on a log scale and the time resolution amounted to 0.004 ms. After that, the derived power spectra were logarithmized and a mean power spectrum was derived by averaging across all derived power spectra. Finally, for the statistical analyses, the mean delta and theta (0.5–5.5 Hz) power of the respecting subset (condition) was derived by taking the average power across all frequency bins falling into the respecting frequency range and time range between 250 and 550 ms.

Statistical Analyses

Two participants had to be excluded after the first diagnostic appointment, one because of meeting the exclusion criteria and another one due to health problems. Additionally, out of the 20 participants who completed the entire experiment, one participant had to be excluded from the analyses due to incorrect task execution. Hence, 19 participants remained for further analyses from which the following outcome variables were extracted: Omission error rate, commission error rate, mean RT and reaction time variabilities (RTV) for the VOT analyses; processing speed, omission errors, commission errors and concentration performance for the d2; target P300 mean amplitudes for the ERP analyses; and low frequency power values for the wavelet analysis.

For each main dependent variable, a two-way repeated measures ANOVA with the two within-factors "Block" (pre-intervention vs. post-intervention) and "Intervention" (actual stimulation vs. sham stimulation) was conducted. For specifying ANOVA effect sizes, partial eta squared (η_p^2) was used, where $\eta_p^2 = 0.01$ indicates a small effect, $\eta_p^2 = 0.06$ a medium effect, and $\eta_p^2 = 0.14$ a large effect (103). For indicating effect sizes of *t*-tests, on the other hand, Cohen's d was used, where $d = 0.20$ indicates a small effect, $d = 0.50$ a medium effect, and $d = 0.80$ a large effect (103). The α-level was set to 0.05.

In addition, to identify potential associations between the different outcome parameters, exploratory Pearson correlation analyses between each possible variable pair were conducted on the absolute change (difference from pre-to-post) across both intervention types. Correlation analyses were tested for significance and Bonferroni-Holm correction was applied to correct for multiple comparisons. All statistical analyses were carried out using Matlab (The MathWorks Inc., Natick, MA, United States, Version 2021b).

RESULTS

Sample Characteristics

Sociodemographic and clinical characteristics of the finally analyzed sample are reported in **Table 1**. 57.89% of participants were diagnosed with the combined ADHD type, 5.26% with the predominantly hyperactive-impulsive subtype and 36.84% with the predominantly inattentive ADHD subtype. The most common current comorbidities found were anxiety disorders (36.84%) and affective disorders (21.05%). According to the DASS-21 (90), participants revealed, on average, only mild scores for depression (M = 10.26; SD = 3.48), anxiety (M = 9.11; SD = 2.45) and stress (M = 12.53; SD = 5.65). On average, participants were 27.95 years (SD = 8.57) and most participants had a higher education entrance qualification (78,95%). After each experimental session, participants were asked to judge if they were actually stimulated with tACS or if they received the sham stimulation. 47,37% of the sample correctly judged that they received actual stimulation at the actual stimulation session, while 52,63% thought they were actually stimulated at the sham stimulation session. Since it was a 50% chance to correctly identify the actual stimulation, participants seemed to be blinded.

Visual Oddball Task

Results of the VOT analyses are shown in **Figure 3**. Regarding omission error rate (**Figure 3A**), the ANOVA revealed a significant main effect of "Block" [$F_{(1,18)}$ = 20.13, $p < 0.001$, η_p^2 = 0.53], but no main effect of "Intervention" [$F_{(1,18)}$ = 0.08, p = 0.781, η_p^2 = 0.00] and no interaction effect [$F_{(1,18)}$ = 0.16, p = 0.693, η_p^2 = 0.01]. The block effect consisted of more omission errors being committed during the post-intervention (M = 26.63; SD = 17.49) than pre-intervention (M = 17.55; SD = 13.01) block.

Regarding d-Prime (**Figure 3C**), the ANOVA revealed a significant main effect of "Block" [$F_{(1,18)}$ = 17.85, $p < 0.001$, η_p^2 = 0.50], but no main effect of "Intervention" [$F_{(1,18)}$ = 0.47, p = 0.501, η_p^2 = 0.03] and no interaction effect [$F_{(1,18)}$ = 0.32, p = 0.576, η_p^2 = 0.02]. The "Block" effect consisted of a smaller d-Prime sensitivity score during the post-intervention (M = 1.88; SD = 0.94) than pre-intervention (M = 2.25; SD = 0.87) block.

For commission error rate (**Figure 3B**), RT (**Figure 3C**) and reaction time variability (**Figure 3D**), the ANOVA yielded neither a main effect of "Block" or "Intervention," nor an interaction effect (detailed ANOVA tables are shown in the **Supplementary Table 2**).

d2 Task

Overall performances of the d2 task are depicted in **Figure 4**. Two datasets had to be excluded due to complications in the execution of the task. For processing speed and concentration performance, there were 2 outliers (>3 SD), and for errors of omission and commission, there was 1 outlier (>3 SD), so that a total of only 16 and 17 datasets, respectively, were included in the respective statistical analyses.

For all d2 performance parameter, the ANOVA revealed a significant block effect. Regarding processing speed (**Figure 4A**), the effect of "Block" revealed higher processing speed during the post-intervention block (M = 570.19; SD = 60.48) as compared to the pre-intervention block (M = 538.06; SD = 59.66). For concentration performances (**Figure 4B**) the "Block" effect consisted of a higher concentration performance during the post-intervention (M = 235.97; SD = 36.44) than pre-intervention (M = 216.75; SD = 34.61) block. For omission errors (**Figure 4C**) results revealed that less target stimuli were missed during the post-intervention (M = 10.03; SD = 6.91) than pre-intervention (M = 14.71; SD = 8.31) block. Results for commission errors (**Figure 4D**) yielded that more stimuli were wrongly identified as a target during the post-intervention (M = 3.85; SD = 3.08) than pre-intervention (M = 2.44; SD = 1.69) block.

There was neither a significant effect for "Intervention," nor an interaction effect for all four d2 performance parameter (detailed ANOVA tables are shown in the **Supplementary Table 3**).

Analyses of Event-Related Potentials

Planned Analysis of the Event-Related Potential P300

The topographies and waveforms of the examined ERPs are depicted in **Figure 5**. Consistent with the literature, extracted ERPs showed the typical waveform and topography of a P300 during an oddball task [for review see e.g., Polich (38)], with a maximum peak at around 250 to 550 ms over centro-parietal electrodes. Moreover, also in agreement with the literature (104, 105), the P300 mean amplitude across conditions turned out to be significantly [$t(18) = -4.25$, $p \leq 0.001$]) higher for target ERPs than standard ERPs (cf. **Figure 5A**).

Regarding experimental conditions, the ANOVA on target P300 mean amplitudes revealed a trend for the main effect "Block" [$F_{(1,18)}$ = 3.40, p = 0.082, η_p^2 = 0.16] but neither an effect of "Condition" [$F_{(1,18)}$ = 0.27, p = 0.609, η_p^2 = 0.01], nor an interaction [$F_{(1,18)}$ = 0.03, p = 0.870, η_p^2 = 0.00]. The trend for "Block" consisted of an amplitude decrease during the post-intervention (M = 2.72; SD = 1.30) compared to the pre-intervention (M = 3.00; SD = 1.48) block. Individual mean amplitude plots are included in the **Supplementary Figure 2**. The ANOVA for maximum P300 peak amplitude revealed no significant effects (cf. **Supplementary Table 4**).

Exploratory Analysis of a Late Event-Related Potential

On visual inspection of the ERP waveforms, there appears to be a difference in a late negative ERP component that peaks around 800 ms after target onset (cf. **Figure 5B**). Therefore, to examine whether this difference is not merely descriptive, we performed

an exploratory ERP analysis using the same analysis procedure and the same preprocessed datasets than before, but with a time window of interest slightly shifted backward (700 to 1000 ms). The ANOVA on this late ERP mean amplitudes revealed no main effect of "Intervention" [$F_{(18,1)} = 0.24$, $p = 0.240$, $\eta_p^2 = 0.08$], but a trend for "Block" [$F_{(1,18)} = 4.03$, $p = 0.060$, $\eta_p^2 = 0.18$] that consisted of higher ERP mean amplitudes during the post-intervention ($M = 0.69$; $SD = 1.29$) than pre-intervention ($M = 0.16$; $SD = 1.48$) block. Moreover, the ANOVA revealed a significant interaction [$F_{(1,18)} = 6.56$, $p = 0.020$, $\eta_p^2 = 0.27$]. Following up this effect, paired t-tests revealed that the late ERP mean amplitudes significantly increased from pre-intervention ($M = -0.09$; $SD = 1.14$) to post-intervention ($M = 0.71$; $SD = 1.31$) under actual stimulation [$t(18) = -2.70$, $p = 0.015$], but not under sham stimulation [$t(18) = -0.98$, $p = 0.339$].

Frequency Analyses

Time-frequency power spectra of the wavelet analyses are depicted in **Figure 6**. In line with previous research (74, 75), our wavelet analysis revealed strongest activity in the P300 time window for the ERO in the delta to theta (0–8 Hz) frequency spectrum. The ANOVA on the

TABLE 1 | Sociodemographic and clinical sample characteristics.

Total sample (*n*):		19*	
Female [*n* (%)]:		10 (52.63)	
Age [*M* (*SD*)]:		27.95 (8.57)	
Interview data:			
IDA-R			Maximum reachable scores:
ADHD presentations [*n* (%)]			
Combined type		11 (57.89)	
Predominantly hyperactive-impulsive type		1 (5.26)	
Predominantly inattentive type		7 (36.84)	
ADHD scores [*M* (*SD*)]			
Total		36.42 (9.14)	54
Inattention		21.58 (3.04)	27
Hyperactivity		7.32 (5.08)	15
Impulsivity		7.53 (3.99)	12
Mini-DIPS			
n (%)	Current diagnosis	Previous diagnosis	
Affective disorder	4 (21.05)	5 (26.32)	
Anxiety disorder	7 (36.84)	1 (5.26)	
Post-traumatic stress disorder	0	2 (10.53)	
Obsessive-compulsive disorder	3 (15.79)	0	
Sleep disorder	3 (15.79)	1 (5.26)	
Impulsivity Screening	1 (5.26)	4 (21.05)	
Questionnaire data: *M* (*SD*)			
ADHS-SB			Maximum reachable scores:
Total		23.53 (11.78)	54
Inattention		12.95 (5.52)	27
Hyperactivity		5.79 (4.95)	15
Impulsivity		4.79 (3.44)	12
WHOQOL			Maximum reachable scores:
Total		70.97 (10.46)	100
Physical health		73.12 (10.67)	100
Psychological health		63.16 (15.67)	100
Social relationships		69.30 (16.45)	100
Environment		78.29 (12.61)	100
DASS-21			Maximum reachable scores:
Total		10.63 (3.41)	21
Depression		10.26 (3.48)	21
Anxiety		9.11 (2.45)	21
Stress		12.53 (5.65)	21

*ADHS-SB, ADHD self-assessment scale; DASS, depression-anxiety-stress-scales; IDA-R, integrated diagnosis of ADHD in adulthood; Mini-DIPS, diagnostic short interview for mental disorders; WHOQOL, world health Organization quality of life questionnaire. *Out of 20 participants who completed the entire experiment, one participant had to be excluded from the analyses due to incorrect task execution. Hence, 19 participants remained for analyses.*

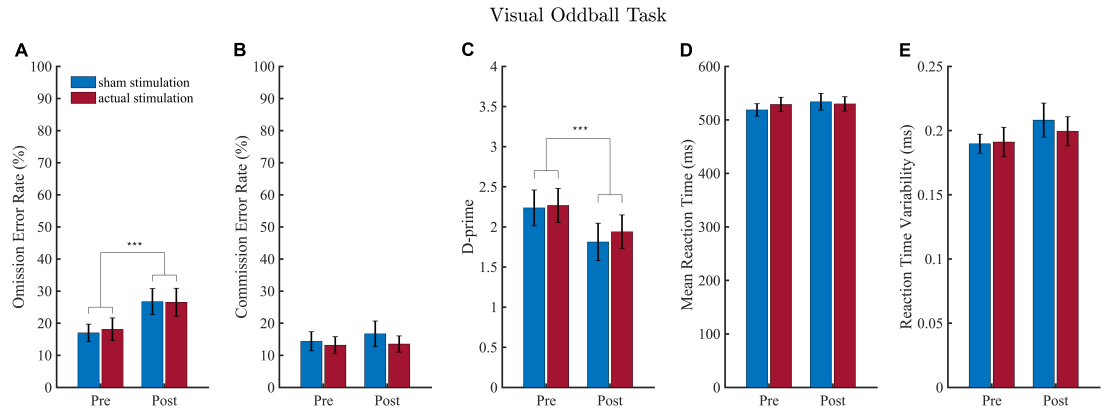

FIGURE 3 | Results of the visual oddball task (VOT). Error rates are depicted in **(A,B)** and the sensitivity measure D-prime in **(C)**. Results of the mean reaction time (RT) and reaction time variability (RTV) are illustrated in **(D,E)**. Values depict means and SEMs for the sham stimulation (blue bars) and actual stimulation (red bars) before and after actual or sham stimulation. ***$p < 0.001$.

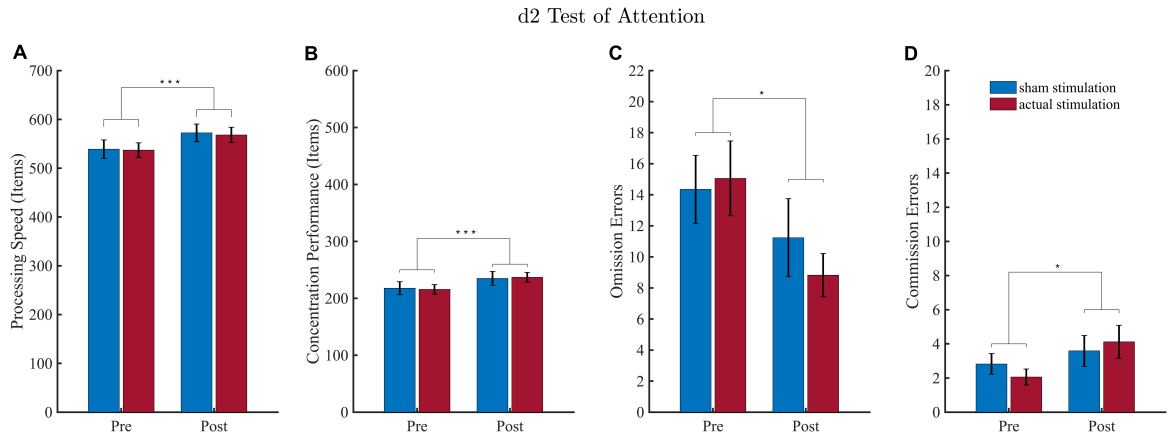

FIGURE 4 | Results of the d2 attention test (d2). Values depict means and SEMs for the sham stimulation (blue bars) and actual stimulation (red bars) before and after intervention. **(A)** Processing speed depicts the total number of characters processed on average for each condition. **(B)** Concentration performance depicts the number of correctly identified characters minus all conducted errors averaged for each condition. **(C,D)** Number of omission and commission errors averaged for each condition. *$p < 0.05$, ***$p < 0.001$.

ERO power values revealed a significant main effect of "Block" [$F_{(1,18)} = 8.26$, $p = 0.010$, $\eta_p^2 = 0.31$], but no main effect of "Intervention" [$F_{(1,18)} = 0.01$, $p = 0.934$, $\eta_p^2 = 0.00$] and no significant interaction [$F_{(1,18)} = 0.21$, $p = 0.653$, $\eta_p^2 = 0.01$]. The "Block" effect consisted of less activity in the ERO band during the post-intervention ($M = 0.58$; $SD = 0.30$) than pre-intervention ($M = 0.63$; $SD = 0.31$) block. Topography plots are shown in the **Supplementary Figure 3**.

Explorative Correlation Analyses

Results of the correlation analysis are shown in **Table 2**. There was a significant positive correlation between the late ERP mean amplitude and VOT RT [$r(18) = 0.70$, Bonferroni-Holm adjusted $p = 0.045$] as well as between the VOT omission error rate and the d prime scores [$r(18) = -0.89$, Bonferroni-Holm adjusted $p < 0.001$]). In addition, there was a significant positive correlation between maximum and mean P300 amplitude [$r(18) = 0.70$, Bonferroni-Holm adjusted $p < 0.05$]. All remaining correlations did not remain significant after Bonferroni-Holm adjustment.

DISCUSSION

In this study, we aimed to increase the P300 amplitude in ADHD patients *via* tACS and to demonstrate an attentional improvement induced by this P300 elevation.

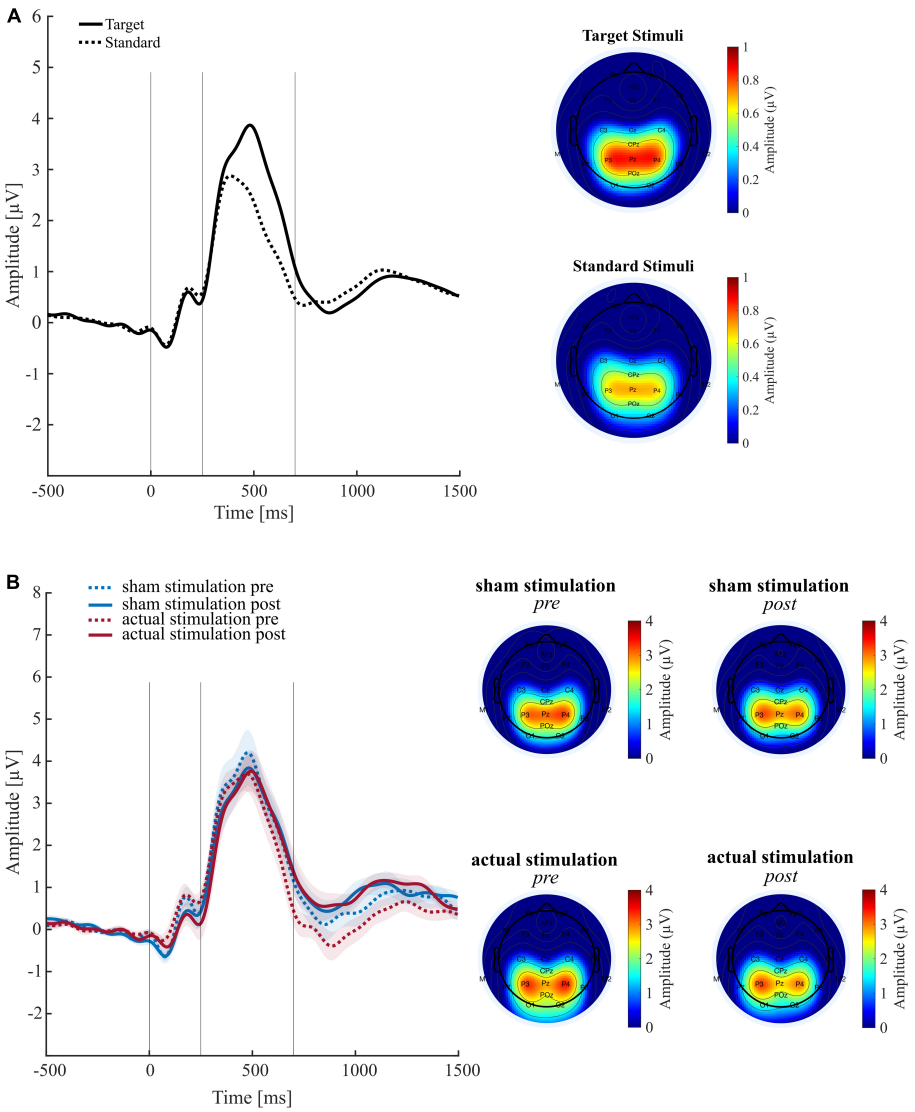

FIGURE 5 | Results of the event related potential (ERP) analyses. **(A)** Grand average ERP waveforms (left panel) and associated topographies (right panel) across all conditions for target and standard stimuli. **(B)** Target P300 ERPs (left panel) and associated topographies (right panel) for each main experimental condition. Shaded curves reflect the standard error of the mean. Time windows for statistical analysis are depicted in the entire 250–550 ms time window.

Specifically, our hypotheses were (1) that by applying tACS at the participant's individual ERO, it would be possible to enhance the P300 amplitude in ADHD patients, and (2), that this induced P300 elevation would lead to immediate improvements in neuropsychological attention measures. To test our hypotheses, we subjected our ADHD patients to both, an actual stimulation, and a sham stimulation, and evaluated their EEG characteristics (P300 amplitudes, low frequency power) and attention performances (d2 attention test, VOT) before and after the two interventions.

No Evidence for a Stimulation-Induced P300 Increase

Contrary to our expectations, we were not able to demonstrate a stronger increase in P300 amplitude under actual stimulation than sham stimulation. Instead, we only found some indication for a tACS-induced amplitude increase in a late ERP component (discussion below). Hence, limited to our analyses and in contrast to the previous study with ADHD patients (75), but in line with another study conducted in healthy participants (74), we currently cannot provide evidence that our methodological

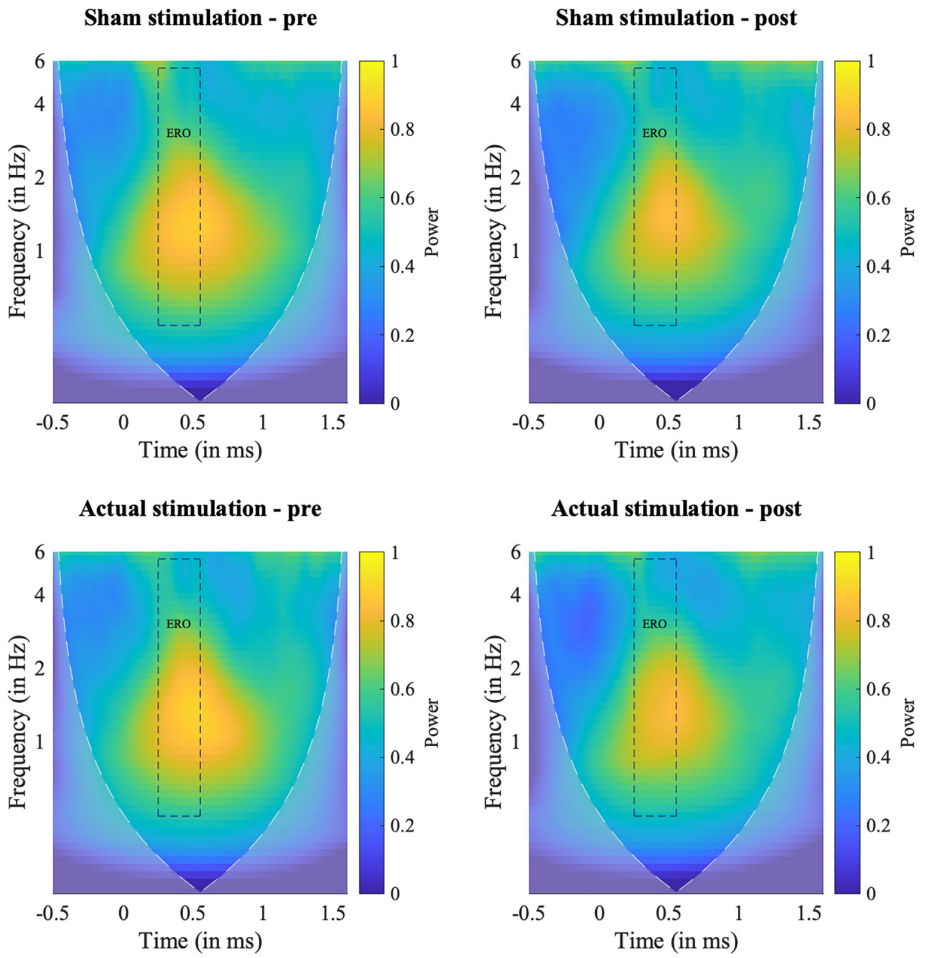

FIGURE 6 | Results of the frequency analyses. Time-Frequency spectra of the wavelet analyses for target hits for the ERO between 0 and 6 Hz at electrode Pz (Grand average). Squares indicate the temporal (0.25–0.5 s) and spectral (0.5–5.5 Hz) region of interest used for the statistical evaluation. Shaded areas outline the area where the calculated wavelet power might be distorted due to edge artifacts.

approach of aligning the participant's generated P300 peaks with positive deflections of the tACS signal is able to amplify the P300.

Why we did not succeed in increasing the participants' P300 through our tACS application cannot be conclusively determined, but some possible reasons can be suggested. First, it should be noted that the effect of tACS may vary due to individual differences in the neuroanatomy, which result in varying electric fields inside the brain (98). Therefore, one explanation might be that despite our careful simulation attempts to find the right electrode montage, we failed to stimulate the correct target region by assuming an inaccurate P300 source location. In the future, it should therefore be considered whether individualized electrode assemblies can be employed, with the help of which individual neuroanatomical peculiarities can be better accounted for.

Likewise, inter- and intraindividual variability in brain activity may have influenced the success of brain stimulation, for example, by an unfavorable brain state during stimulation (106). If this has been the case, a closed loop system that measures brain activity during stimulation *via* EEG and adjusts the applied stimulation accordingly, could potentially provide mitigation here. However, research studies targeting closed loop systems aiming to adapt fluctuating stimulation parameters to momentary brain activity are currently rare and require further investigation (107–110).

TABLE 2 | Results of correlations analyses.

	P300 mean amplitude	P300 maximum amplitude	Late ERP mean amplitude	Low frequency Power	VOT omission error rate	VOT commission error rate	VOT dprime	VOT RT	VOT RTV	d2 omission errors	d2 commission errors
Pre-to-Post											
P300 mean amplitude		0.70*	0.13	0.14	0.19	−0.28	−0.15	−0.04	−0.17	0.07	−0.21
P300 max. amplitude			0.36	0.39	0.14	−0.20	−0.14	−0.06	−0.37	0.07	−0.13
Late ERP mean amplitude				0.23	0.20	−0.14	−0.18	0.69*	0.14	0.31	0.01
Low frequency Power					0.17	0.25	−0.37	0.09	0.14	0.23	0.02
VOT omission error rate						0.35	−0.89***	0.33	0.29	−0.12	0.23
VOT comission error rate							−0.56	0.02	0.36	−0.13	−0.23
VOT dprime								−0.34	−0.39	0.12	0.07
VOT RT									0.63	0.07	−0.02
VOT RTV										0.06	−0.24
d2 omission errors											−0.12
d2 commission errors											

*Pearson correlations (r) between the absolute change (i.e., the difference from pre to post intervention) for all main behavioral and neurophysiological measures across intervention conditions. Correlations including d2 outcome parameter are calculated with 16, while all others with 19 datasets. *p < 0.05, ***p < 0.001. Bonferroni-Holm correction was applied to correct for multiple comparisons. RT, reaction time; RTV, reaction time variability; VOT, visual oddball task.*

Moreover, we find that not only the participant's P300, but also their event-related low frequency power (0–6 Hz) remained unaffected by our two stimulation interventions. Hence, the reason for failing to increase the P300 could be that the participant's ERO, which is assumed to be causative of the P300 (80, 81, 83, 84), could not sufficiently be increased. Thus, the question arises why the participant's ERO has not been changed by tACS. One finding to consider here is that brain oscillations only seem to be increasable by tACS if their power is rather low before stimulation (111, 112). Hence, one possible reason might be that the EROs of our adult ADHD sample were already elevated before the tACS intervention, and therefore could not be further increased. This would be in line with some evidence for an elevated delta and theta power in adult ADHD (113–118), although other studies did not find this effect (119–121). If an elevated delta to theta power in ADHD patients would explain our null finding, the question, however, arises why this effect did not also show up in the previous ADHD study by Dallmer-Zerbe et al. (75) and why the low-frequency power even decreased from pre- to post.

Another reason why we might have failed to enhance the participant's ERO might be some mismatch between the externally applied tACS frequency and actual ERO. Time constraints during experimental sessions with patients demand a quick EEG data analysis, which may have prevented us from being sufficiently accurate in identifying the participant's exact ERO. If the external stimulation frequency matches the endogenous frequency, already low stimulation intensities lead to entrainment. However, the larger the variance between internal and external frequency is, the stronger the force of tACS must be to entrain these oscillation (122).

Finally, evaluations of an experiment by Wischnewski et al. (76, 123) indicate that frontal theta tACS (and perhaps this effect also applies to our tACS electrode montage) may induce a P300 drop at least in healthy participants. That is, contrary to their intention of enhancing the participant's P300 by theta tACS, the participant's P300 decreased by this intervention. Surprisingly, however, this P300 decrease (76) does not seem to have been caused by modulating the participant's internal theta power, since it was not affected by the application of tACS (123). One possible implication of this is that there is another indirect mechanism by which an externally applied theta tACS may reduce the P300 amplitude, and perhaps a similar mechanism may potentially also have occurred in our experiment, but further research is required to explore underlying mechanisms.

Preliminary Evidence for a Stimulation-Induced Late Component Increase

While we found no evidence for a tACS-induced P300 increase, we interestingly found a significant ($p = 0.020$) interaction effect for a late negative ERP component (700–1,000 ms), in that this ERP component was significantly increased after actual stimulation [$t(18) = -2.70$, $p = 0.015$], but not after sham stimulation [$t(18) = -0.98$, $p = 0.339$]. Hence, at least on this ERP component, tACS seems to have had some effect. While

we do not yet have a sound neurophysiological explanation on how tACS affected this ERP component, this possible effect clearly warrants further investigation for several reasons. First, previous studies found a relationship between the amplitude of the late negative ERP component N700 and the amount of attention allocated to stimuli (124–126). And second, there is evidence that the N700 amplitude is correlated with a dopamine transporter allele (127) which is considered as a risk factor for ADHD. Consequently, a targeted modulation of this component *via* tACS could also be interesting for the treatment of ADHD.

No Indication for a Stimulation-Induced Improvement of Attention

In line with the P300 null findings were also the neuropsychological outcomes in our study. For both, the VOT and d2 attention task, none of the assessed performance measures indicated any "Block" × "Intervention" interaction. Altogether, these results suggest that the application of tACS had little to no influence on the measured neuropsychological performance of our participants. This is, however, not surprising, given that the anticipated P300 amplification was already inefficient.

Successful Optimization of Our Visual Oddball Task

To enhance omission and commission errors, we changed the VOT used in the previous study (75). In particular, we changed the used stimuli, reduced the time period of stimulus presentation and, in addition, the response behavior. Our results suggest that this adaptation of the VOT has been successful in elevating the level of difficulty. In contrast to the previous study with almost no commission errors and a low omission error rate, we now encountered higher omission error rates (M_{pre} = 17.55%, SD_{pre} = 13.01% and M_{post} = 26.63%, SD_{post} = 17.49%) and commission rates (M_{pre} = 13.76%, SD_{pre} = 9.55% and M_{post} = 15.11%, SD_{post} = 11.64%), while still observing a plausible P300 ERP (40). For future follow-up studies on the same topic, we therefore propose to use our improved VOT variant instead of our original one.

Marginal Associations Between Main Experimental Parameters

Most of the major correlation parameters were non-significant. However, there was one significant positive correlation between late ERP mean amplitude and VOT RT [$r(18) = 0.70$, Bonferroni-Holm adjusted $p = 0.045$]. While preliminary, this finding might suggest that the amplitude change of the late ERP component could be influenced by the participant's RT during the VOT. Therefore, the modulation of this late ERP component could be a future target site to be investigated to influence responsiveness in ADHD individuals.

Limitations and Future Directions

One limitation of our study is that the experimental design is rather time critical and grounds on the presupposition that the participant's P300 latency remains stable across trials. If this requirement is violated too strongly, there is a risk that the tACS peaks do not sufficiently coincide with the P300 peaks, and thus the P300 cannot sufficiently be elevated. For the future, this problem could perhaps be attenuated by using an oddball task that induces a particularly low P300 latency variability, choosing a less time-critical target site instead of the P300 (e.g., an oscillation instead of an ERP component), or by implementing a closed loop system that may recognize P300 latency changes over time and may adapt the stimulation frequency accordingly.

In comparison to the study of Dallmer-Zerbe et al. (75), we changed various aspects in our present study. For example, we chose another study design (crossover design instead of between design), we used other electrodes for the application of tACS (rubber electrodes instead of EEG ring electrodes) and programmed a different visual oddball task with different stimuli and reaction patterns (for further details and differences cf. **Supplementary Table 1**). Therefore, it is not possible to directly compare both studies. However, with our experimental procedure, the application of tACS did not enhance low frequency power or the P300 amplitude, which challenges to some extent the robustness of the found effect in the previous study.

One aspect that needs further investigation is to find the optimal P300 time window to be extracted for the online analyses. A limitation of our online analyses was our rather narrowly chosen P300 time frame of 250 to 450 ms, since in four datasets the averaged ERP peaked maximally beyond our chosen P300 time frame. Therefore, for those four participants, the P300 latency, which is used for adjusting the stimulus presentation during the VOT, was not accurate enough. On the other hand, selecting a larger P300 time frame might have led to maximum peaks that fall below (e.g., <200) or exceed (e.g., >600) the usual P300 time window. Hence, future studies might expand the P300 time frame to 250–600 ms targeting ADHD patients.

Another caveat is that our study did not allow for full experimenter blinding, given that the neurostimulator had to be manually adjusted. Hence, an experimenter bias cannot fully be precluded. Therefore, for future studies, it would be helpful to control the neurostimulator automatically instead of manually entering the stimulation parameter.

Another limitation of our study is that our sample size is, unfortunately, not large enough to also allow for ADHD subtype analyses. Such an analysis would have been very interesting, though, because it could be that not all ADHD patients, but at least a certain ADHD subtype or subgroup of ADHD patients (e.g., the predominantly hyperactive/impulsive subtype) benefit from our tACS application. In addition, a sub analysis of patients with certain comorbidities may also have been interesting to look at, since our sample included, for example, ADHD patients with comorbid mild to moderate affective disorders or anxiety disorders. Similarly, the sample we collected may not have been large enough to detect even small tACS-induced changes. In this case, however, the question arises whether these undetected effects are clinically relevant.

Although ERP data give valuable insights into cognitive processing of ADHD patients, it is important to bear in mind that it is still unclear whether the P300 amplitude decrease in ADHD (41–48) is a cause, consequence, or compensatory process. Although first explanation attempts have been put forward (128), further studies are clearly necessary to shed more light on this unresolved question.

Moreover, a question that remains unanswered in our study is the question of possible tACS long-term effects. In particular, our study cannot exclude the possibility that the tACS effects we expected do not occur immediately, but perhaps not until after several sessions. For example, in the study Farokhzadi et al. (86), where alpha-tACS achieved higher reductions in inattention and impulsivity than Ritalin, the effect was measured after 24 sessions. Therefore, it would be interesting to compare various tACS conditions over more than one session. In this respect, it is also conceivable to vary the stimulation frequencies or electrode montages.

In addition, it should be considered that the application of tACS is accompanied by a large artifact in EEG data. It is a major challenge to recover artifact-free brain signals during tACS because it hinders direct insights into electrophysiological processing during stimulation. So far, current computational approaches still fail to obtain artifact-free data (129–132). In the future, however, it would be interesting to analyze EEG data during actual stimulation to lighten the current black box.

CONCLUSION

In conclusion, our study cannot provide further evidence that tACS can increase the P300 amplitude in ADHD patients and that by such P300 amplification an immediate improvement of neuropsychological attention parameters can be achieved. However, we found a possible effect of our tACS stimulation on a late ERP component and a positive correlation between this component and the participants' VOT RTs that both warrant further investigation. Moreover, our chosen setup included many actuation parameters (e.g., stimulation intensity, electrode mounting, waveform type) that could have been set differently. Therefore, there are still many alternative parameter settings for the application of tACS that can be tested and that may potentially yield more promising results.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the University of Bonn. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KK and CB designed the experiment under the supervision of NB, AP, and CH. CB conducted the tACS electrode simulations. KK collected and analyzed the data under the supervision of NB and CH, and intervision with CB. KK and NB wrote major parts of the manuscript. BA and HR recruited ADHD patients. AW, BS, CB, AP, SL, HR, BA, and CH contributed to reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.928145/full#supplementary-material

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Alpha modulation via transcranial alternating current stimulation in adults with attention-deficit hyperactivity disorder

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Background: One potential therapy treating attention-deficit/hyperactivity disorder (ADHD) is to modulate dysfunctional brain activations using brain stimulation techniques. While the number of studies investigating the effect of transcranial direct current stimulation on ADHD symptoms continues to increase, transcranial alternating current stimulation (tACS) is poorly examined. Previous studies reported impaired alpha brain oscillation (8–12 Hz) that may be associated with increased attention deficits in ADHD. Our aim was to enhance alpha power in adult ADHD patients via tACS, using different methods to explore potential therapeutic effects.

Methods: Undergoing a crossover design, adults with ADHD received active and sham stimulation on distinct days. Before and after each intervention, mean alpha power, attention performance, subjective symptom ratings, as well as head and gaze movement were examined.

Results: Frequency analyses revealed a significant power increase in the alpha band after both interventions. Despite a trend toward an interaction effect, this alpha power increase was, however, not significantly higher after active stimulation compared to sham stimulation. For the other measures, some additional pre-post effects were found, which were not intervention-related.

Conclusion: Our study cannot provide clear evidence for a tACS-induced increase in alpha power in adult ADHD patients, and thus no stimulation related improvement of attention parameters. We provide further recommendations for the future investigation of tACS as a potential ADHD treatment.

KEYWORDS

attention, ADHD, alpha, virtual reality, brain stimulation, tACS

1 Introduction

To alleviate their inattention, hyperactivity and impulsivity, adults with attention-deficit/hyperactivity disorder (ADHD) often receive long-lasting psychopharmacological treatment. While this form of treatment is still yielding the greatest success for adult ADHD, it can be accompanied by undesirable side effects, such as weight loss and sleep

disturbances (Graham et al., 2011; Wynchank et al., 2017; Kis et al., 2020). In addition, psychostimulants appear to be less effective in adult ADHD patients than in children and adolescents with ADHD (Wilens et al., 2011; Cortese et al., 2018). Although ADHD medication has shown high short-term efficacy in many studies (Mészáros et al., 2009; Cunill et al., 2016), their longer-term efficacy awaits further investigation (Cortese et al., 2018; Swanson, 2019) given that several patients seem to develop tolerance to psychostimulants (Handelman and Sumiya, 2022).

In view of these drawbacks of psychopharmacological ADHD treatment, in the last decade various potential alternatives to non-pharmacological treatment have been investigated that enable ADHD treatment without or with fewer side effects. Besides psychotherapeutic approaches, for instance, physical activity training (Barudin-Carreiro et al., 2022; Montalva-Valenzuela et al., 2022; Seiffer et al., 2022), herbal treatments (Sarris et al., 2011), and digital health interventions (Lakes et al., 2022), including virtual reality (VR) interventions (for review, see Bashiri et al., 2017; Romero-Ayuso et al., 2021) and app-based psychoeducation (Selaskowski et al., 2022, 2023b) have been investigated. The probably most famous and controversially discussed alternative ADHD treatment approach, however, is still neurofeedback. This therapy intervention aims to improve the self-regulation of brain activity and has been under investigation for almost 50 years (Arns et al., 2014). While some researchers conclude positive effects of neurofeedback on ADHD symptoms (see, e.g., systematic review by Moreno-García et al., 2022) others have been more sceptical (for a systematic review and meta-analysis, see Louthrenoo et al., 2022; Rahmani et al., 2022). Therefore, its efficacy remains unclear. Accordingly, there is still a substantial need for developing more effective ADHD treatment approaches with less side effects.

Another treatment approach, though still in its infancy, is the idea of using brain stimulation techniques in place of, or as an adjunct to, traditional treatments. So far, the most established non-invasive brain stimulation techniques are transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES). While TMS is delivered by a pulsing electromagnetic coil that is held next to the skull, in TES, multiple electrodes are placed onto the scalp to apply an electrical current to decrease or increase neural activity (Vosskuhl et al., 2018). Prominent TES subtypes are transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). While under tDCS a constant current is applied, under tACS the current alternates at a specified frequency (Herrmann et al., 2013). Accordingly, the respective mechanism of action on brain activity is different: Whereas tDCS seeks to increase or decrease the general neuronal excitability in a stimulated brain area of interest depending on the type of stimulation used, tACS seeks to amplify a specific brain oscillation by stimulating the brain with the dominant frequency of the oscillation of interest. Notably, both methods are thereby considered safe and with few side effects (Vosskuhl et al., 2018; Westwood et al., 2021).

Although various studies have already investigated TMS and tDCS as possible treatment approaches for ADHD (for systematic reviews, see Salehinejad et al., 2020; Westwood et al., 2021; Chen et al., 2023), only few clinical investigations addressed the efficacy and tolerability of tACS for ADHD treatment. In fact, to our knowledge, only three studies have so far explored tACS as treatment for adult ADHD (Dallmer-Zerbe et al., 2020; Farokhzadi et al., 2020; Kannen et al., 2022). While one of the studies compared tACS to methylphenidate (Farokhzadi et al., 2020) and reported tACS as an effective treatment, the other two studies investigated tACS as an alternative treatment for ADHD by trying to increase the P300 amplitude (Dallmer-Zerbe et al., 2020; Kannen et al., 2022), which is considered to be diminished in ADHD patients (Hasler et al., 2016; Marquardt et al., 2018; Kaiser et al., 2020). Dallmer-Zerbe et al. (2020) observed an increase in the P300 amplitude accompanied by a decrease in omission errors among adult ADHD patients, whereas Kannen et al. (2022) did not confirm these results. Therefore, the extent to which tACS might be beneficial in treating ADHD remains unclear.

Besides the diminished P300, another possible neuronal target for the application of tACS could be the brain's alpha rhythm (8–12 Hz), which is known to be modulated during attention and considered as a potential biomarker for ADHD (Kiiski et al., 2020). In healthy individuals, alpha oscillations are dominant in posterior brain regions during relaxed wakefulness, and progressively relocate towards central and frontal cortical regions with increasing drowsiness (see, e.g., Goldman et al., 2002). The hypothesis thereby is that alpha oscillations enable basal cognitive functions and attentional processes (Klimesch, 2012). Moreover, of particular interest in the present context, alpha oscillations are reported to be reduced in ADHD patients in both power and frequency (Loo et al., 2009; Woltering et al., 2012; Poil et al., 2014; Liu et al., 2016; Deiber et al., 2020), although this finding could not be corroborated in other studies (for discussion, see Adamou et al., 2020). In addition, in line with this assumed alpha alleviation, some studies showed that increasing alpha power using neurofeedback resulted in clinical improvement of ADHD symptoms as well as in an increase of attentional performance (Bazanova et al., 2018; Deiber et al., 2020). Considering these findings, the question arises whether a tACS-induced increase of the participant's individual alpha activity might improve the attentional performance of ADHD patients.

To prove a tACS-induced improvement of impairments in attentional functions, however, the difficulty arises that such ADHD symptoms often cannot be reliably detected with standard neuropsychological tests. One potential factor for this limited diagnostic utility might be the low ecological validity, which might fail to mimic everyday life challenges of ADHD patients (Wasserman and Wasserman, 2012; Varao-Sousa et al., 2018). A possible solution for creating more reality-close test situations might be offered by VR technology. By creating three-dimensional, immersive, and interactive virtual environments which allow to mimic everyday life demands, ecological validity can be increased while maintaining a high level of standardization (Parsons, 2015).

The aim of the present study was to increase the individual alpha power in patients with adult ADHD and to investigate possible behavioral and neurophysiological changes resulting therefrom. To this end, a crossover trial was carried out, in which all patients underwent both an individual tACS-based alpha stimulation (active stimulation) and a placebo stimulation (sham stimulation). To simulate an everyday situation, a developed virtual seminar room (VSR) was used that allowed for a multimodal and standardized, but symptom-valid measurement of inattention,

hyperactivity and impulsivity (Wiebe et al., 2022, 2023; Selaskowski et al., 2023a).

2 Materials and methods

2.1 Participants

Twenty-seven ADHD patients volunteered in this study, out of which 24 (7 female; $M_{age} = 32.25$, $SD_{age} = 10.46$, aged between 19 and 53) completed the experiment. The recruitment of the sample was conducted via the specialized outpatient clinic for adult ADHD of the Department of Psychiatry and Psychotherapy at the University Hospital Bonn. Participants were either personally invited to the study during medical consultations or via a study applicant pool in which they had registered before. The study was approved by the medical ethics committee of the University of Bonn (protocol number: 195/20), conducted in accordance with the Declaration of Helsinki, and pre-registered at the German Clinical Trials Register (https://www.drks.de/, Trial-ID: DRKS00022927). Written informed consent was obtained from all participants and they all received a monetary compensation of 25 € for their participation.

2.2 Study design and general procedure

The trial was carried out as a crossover study with two interventions on three measurement days: "active stimulation" (the true tACS intervention) and "sham stimulation" (the placebo intervention). On Day 1, a comprehensive clinical examination was performed during which the ADHD diagnosis was validated, and comorbidities were evaluated. On Days 2 and 3, the stimulation experiment took place, with one of the two interventions being applied on each measurement day. The order of interventions (sham stimulation or active stimulation) was counterbalanced.

2.3 Eligibility assessment and clinical characterization

For confirmation of the ADHD diagnoses and further characterization of the individual ADHD symptom profiles, all participants were administered the structured clinical "Interview of Integrated Diagnosis of ADHD in Adulthood" (IDA-R; Retz et al., 2014). In addition, to check for exclusion criteria and to assess potential comorbidities, the German version of the "Diagnostic Short Interview for Mental Disorders" (Mini-Dips-OA; Margraf et al., 2017) was carried out. Both clinical interviews were conducted via video call using the online-platform RED medical.[1] Moreover, participants completed a battery of online-surveys, including, for instance, a demographic questionnaire, a questionnaire concerning quality of life (WHO-QOL; Harper et al., 1998) and the ADHD Self-Report-Scale (ADHS-SB; Rösler et al., 2004).

To be eligible for the study, participants needed to be right-handed (according to the Edinburgh Handedness Inventory; Oldfield, 1971), to be between 18 and 60 years old, and to have corrected-to-normal or normal vision. In addition, any of the following exclusion criteria had to be absent: current severe major depression or current substance dependence, psychosis, presence of a serious neurological disorder (especially epilepsy), presence of a dermatological disorder of the head, pregnancy, or no command of the German language. Intake of ADHD medication (reported by 12 participants of the final cohort) was discontinued 24 h prior to each of the laboratory sessions. Participants were instructed to abstain from caffeine and alcohol for at least 24 h before each laboratory session.

2.4 Experimental procedure

The experiment took place in the VR laboratory of the Department of Psychiatry and Psychotherapy at the University Hospital in Bonn and was scheduled at two separate appointments. On one appointment the active stimulation was applied, while on the other appointment only a sham stimulation was applied. Each appointment started with the preparation of tACS- and EEG-electrodes. Afterwards, participants took their seat in front of a 1 × 1 m table within a 3.70 m x 2.65 m VR play area. The active experiment started by measuring 2 min of resting state baseline EEG, followed by the determination of the individual alpha frequency (IAF). Once the IAF was determined, participants became equipped with the head mounted display *HTC Vive Pro Eye* (HTC Corporation, Taoyuan City, Taiwan) and entered the VSR. Immersed into the VSR, participants were familiarized with this new virtual environment as well as with the continuous performance task (CPT) that next would take place within the VSR (*cf.* section 2.5). In total, three CPT blocks were presented, whereby each CPT block lasted 18 min and was suspended by a two-minute resting state EEG measurement and a one-minute-long break. Moreover, after each block, the participants' subjective ADHD symptoms (one question regarding inattention, impulsivity, hyperactivity, respectively, answered on a 7-point Likert-scale) was prompted by a gesture-controlled user interface inside VR (for further details, see Wiebe et al., 2022). Finally, after the last CPT block ended, participants completed the Virtual Reality Sickness Questionnaire (VSRQ; Kim et al., 2018) and a questionnaire about tACS side effects (Brunoni et al., 2011). Also, to investigate if participants were blinded to the experimental condition, they were asked whether they thought they received the active stimulation or sham stimulation.

2.5 Virtual seminar room and continuous performance task

The VSR and the implemented CPT are depicted in Figure 1 and have been described in detail previously (Wiebe et al., 2022). In brief, based on existing assets (i.a. the "School Classroom" from 3D everything available in the Unity Asset Store), the VSR was developed under Unity 3D version 2019.1.10f1 (Unity technologies, San Francisco, CA, United Staes) and contained the typical furniture found in a seminar room, including chairs and tables as well as a canvas at the front of the VSR. Moreover, the VSR comprised virtual classmates that performed unobtrusive idle movements during

1 https://www.redmedical.de

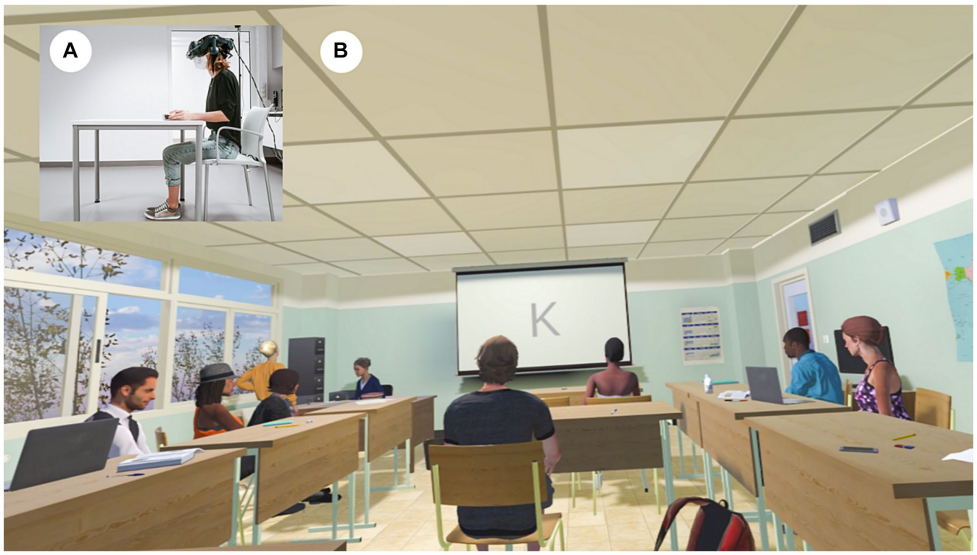

FIGURE 1
The virtual seminar room (VSR). **(A)** Real-world third-person perspective and **(B)** virtual-environment first person perspective. Adults with ADHD were immersed into the VSR, in which the continuous performance task (CPT) was presented at the canvas. **(A)** is an exemplary depiction and thus without attached tACS. For programming the virtual seminar room we only used non-restricted assets. "School Classroom" (Reprinted from 3D Everything via Unity Asset Store, licensed under Standard Unity Asset Store EULA).

non-distractor phases (NDP) and more complex actions during distractor phases (DP; details below). The virtual table where the participants found themselves seated, was thereby located in the back of the VSR, so that participants had a good overview of the entire VSR.

The CPT itself was presented on the canvas and consisted of a pseudorandomly-presented series of letters ranging from "A" to "Z", each presented with a 1.1 s inter-stimulus-interval and 100 ms duration. The task was to press the space bar as soon as the letter "A" was followed by the letter "K", while in all other cases, a response had to be withhold (Neguț et al., 2017; Mühlberger et al., 2020). After a practice run of 20 trials, the actual CPT began, which was split into three consecutive blocks: A pre-intervention block that occurred before active or sham stimulation was applied; a during-intervention block in which the active or sham stimulation was applied; and a post-intervention block that occurred after the active or sham stimulation.

Each of the CPT-blocks thereby lasted approximately 18 min and included 450 letter pairs, partitioned into 135 target sequences (~30%) and 315 non-target sequences (~70%). To elevate task difficulty, non-target sequences included 158 pseudo target sequences ("K" not preceded by "A"). Furthermore, each CPT block consisted of three DP and three NDP, each lasting three min. While during NDP no distractors were played, during DP, 54 different distracting events were played in total, of which 18 were exclusively visual (e.g., a paper airplane), another 18 solely auditory (e.g., a bell noise) and the remaining 18 audiovisual (e.g., passing fire trucks). Across participants, the order of distractors was thereby randomized, and the order of phases counterbalanced.

For analyzing CPT-performances, three main parameters of interest were defined: Omission error rate (i.e., the percentage of missed responses to target stimuli), commission error rate (i.e., the percentage of invalid responses to non-target stimuli) and reaction time variability (RTV, i.e., the standard deviation of reaction times towards correct hit trials divided by the mean reaction time). While omission error rates are regarded to reflect inattention, commission error rates are considered to reflect impulsive behavior (Nichols and Waschbusch, 2004), and RTV is considered a measure of vigilance (Llevy et al., 2018).

2.6 Electrical brain stimulation and electrode montage

The tACS was delivered by a battery-operated stimulator system (DC Stimulator Plus, Neuroconn, Illmenau, Germany). With the help of an electrically conductive paste (ten20 conductive paste, Weaver and Co., Aurora, CO, United States), two rubber electrodes were attached to the participants' scalp. Since former studies reported significant differences in the alpha band power of posterior brain regions between ADHD patients and healthy controls (see scalp plots, e.g., Woltering et al., 2012; Deiber et al., 2020), one electrode was placed above Cz (5 × 7 cm) and another above Oz (4 × 4 cm). Modeling studies have shown that this montage achieves the highest current densities in posterior brain regions (Neuling et al., 2012) and elicits aftereffects in alpha band power (Neuling et al., 2013; Kasten et al., 2016). Impedances were kept below 15 kΩ ($M = 4.55$, $SD = 2.92$). Participants were stimulated at their IAF (9.63 Hz ± 0.69 Hz active stimulation, 9.67 Hz ± 0.98 Hz sham stimulation) with an intensity of 1.5 mA. Baseline resting-EEG measurements (2 min, eyes open) for determining the IAF were performed before the actual experiment and outside VR (for analysis steps *cf.* section 2.4.1). After the first CPT block, participants received either 18 min of tACS (active stimulation) or 10 s of tACS (sham stimulation) with 10 s fade-in and fade-out (30 s in total to evoke a light tingling sensation in both conditions, implemented for blinding purposes). This sham stimulation procedure

is one of the commonly used placebo stimulation techniques (Davis et al., 2013).

2.7 EEG recording and analysis

To acquire electroencephalography (EEG) data, we used a wireless EEG system (Smarting®, mBrainTrain®, Belgrade, Serbia) with 22 Ag/AgCl sintered ring electrodes (Fp1, Fp2, AFz, F3, Fz, F4, T7, C3, Cz, C4, T8, CPz, P7, P3, Pz, P4, P8, POz, O1, O2, M1, M2) of the international 10/20 system that were mounted to an elastic EEG cap (Easycap, Herrsching, Germany). While electrode FPz served as ground, FCz served as reference electrode. The amplifier was connected via Bluetooth with the recording computer. Data was sampled at 500 Hz frequency via Lab Streaming Layer (LSL)[2] and all impedances were kept below 15 kΩ. EEG data were processed with Matlab 2021b (MathWorks Inc., Natick, MA, United States), using EEGLAB 2021.0 (Delorme and Makeig, 2004) and in-house scripts.

2.7.1 On-site analysis of IAF

For the evaluation of the individual stimulation frequency, resting EEG at channel Pz was filtered between 0.1 and 40 Hz and epoched into 2 s long segments. Afterwards, non-stereotyped artifacts were removed using built-in EEGLAB functions (joint probability test, ±1.7-SD single-channel and global-channel thresholds) before an independent-component-analysis (ICA) ("fastica" version) was conducted. After visual inspection of the generated ICA components, artifacts like vertical and horizontal eye movements were identified and removed in the continuous EEG data set. Clean continuous EEG data from channel Pz was epoched into 2 s long segments and the frequency power spectrum was extracted by Matlab's *pspectrum()* function between 0 and 40 Hz. The resulting frequency resolution was 0.05 Hz, while the resulting time resolution amounted to 0.25 s. Next, the power spectra were logarithmized and averaged across trials. Finally, the maximum alpha frequency between 7 and 13 Hz was used for the calculation of stimulation parameters.

2.7.2 Stereotyped artifact removal for offline wavelet analysis

Before wavelet analyses were performed, the EEG datasets were cleaned from stereotypic artifacts by the following steps: First, the EEG data was resampled to 250 Hz, filtered between 1 and 40 Hz, and detrended. Second, due to tACS artifacts during stimulation, the second CPT block was removed. Third, noisy EEG channels were detected (6 datasets, $M = 1.67$, $SD = 0.82$) and replaced via spherical interpolation. Fourth, for computing an independent component analysis (ICA), the continuous EEG data was segmented into 2 s time windows and non-stereotypic artifacts were removed using built-in EEGLAB functions (joint probability test, ± 2-SD single-channel and global-channel thresholds). Fifth, the ICA ("extended" version) was computed on the epoched data and components reflecting horizontal or vertical eye movements, heartbeat, muscle activity, or electrode artifacts were visually identified, backprojected to the continuous EEG data, and then rejected. All components that included a 10 Hz peak were retained.

2.7.3 Offline wavelet analysis of alpha activity during CPT blocks

One wavelet analysis focused on potential differences in alpha activity between blocks (pre-intervention vs. post-intervention block) and interventions (active stimulation vs. sham stimulation) during CPT performance. To this end, the ICA-corrected continuous EEG datasets were split into four segmented subsets, such that each subset represented one of the four compared conditions and entailed as many non-overlapping 2 s EEG segments as available within the CPT block of the respecting condition. Next, the following identical pre-processing and analysis steps were performed on each subset: First, the same non-stereotypic artifact removal was conducted that had already been conducted for the ICA calculation. Second, additional non-stereotypic artifact removal was conducted with the help of an eeglab plugin (Ben-Shachar, 2020), in that within each epoch, channels that exceeded 150 μV were marked for rejection. If the channels being marked for rejection were noisy in more than 15% of all epochs, the channels were excluded. In addition, epochs with more than 10 identified bad channels were rejected, while epochs with less than 10 bad channels were included, whereby bad-channel data was replaced by spherical interpolation. Third, a continuous wavelet transformation (CWT) was calculated on each retained epoch of the respective dataset (intervention) for channels Pz, POz, CPz, P3, P4. The frequency range obtained thereby reached from 0.27 Hz to 30.00 Hz in 69 steps on a log scale and the time resolution amounted to 0.004 s. After that, the derived power spectra were logarithmized and a mean power spectrum was derived by averaging across all derived power spectra. Finally, for statistical analyses, the mean alpha power (7–13 Hz) across all five channels for both blocks (pre intervention/post intervention) and both interventions (active stimulation/sham stimulation) was derived by taking the average power across all frequency bins falling into the respecting frequency range and time range between 0.2 and 1.8 s. To check for outliers, the pre-to-post-difference for alpha power was calculated and it was examined whether any datasets differed ±2 standard deviations from the mean alpha power change.

2.7.4 Offline wavelet analysis of alpha activity during resting states

Another wavelet analysis focused on potential differences in alpha activity between blocks and interventions during the 2 min resting state phases. Here, the preprocessing steps were identical to the just described wavelet analysis on the CPT blocks, with the only exception that the segmentation into the four individual subsets was not based on the CPT blocks themselves, but on the 2 min resting state phases. The obtained frequency range and time range was the same as reported above (*cf.* section 2.4.3).

2.7.5 Eye tracking recording and analyses

Eye tracking analyses focused on differences in gaze behavior between blocks (pre-intervention vs. post-intervention) and interventions (active stimulation vs. sham stimulation). To acquire eye tracking data, eye movements were recorded with a sampling rate of ~50 Hz and an accuracy of approximately 0.5°-1.1° via the infrared-based Tobii eye tracker built into the head-mounted display

2 https://github.com/sccn/labstreaminglayer

(HMD). While the software developmental kit (SDK) SRanipal version 1.3.1.1 (HTC Corporation, Taoyuan, Taiwan) procured access to the eye tracking raw data within Unity, the Tobii XR SDK version 1.16.36.0 (Tobii Technology, Stockholm, Sweden) allowed to track the participant's momentary gaze on specified virtual objects within the VSR. Specifically, it was tracked when and for how long the participants looked at the canvas as well as on 3D objects that were implemented as distracting events (during DP). Offline analyses were run in Matlab 2021b (MathWorks Inc., Natick, MA, United States). To statistically compare gaze locations for each block and intervention, three parameters were extracted (Selaskowski et al., 2023a): Time looking at canvas (as a measure of task focus), time looking at distractors (as a measure of focus on specific distractors) and time of gaze wandering (i.e., that time amount the participants neither looked at a distractor nor at the canvas). Moreover, based on these three derived parameters, a composite distractibility score was calculated by dividing the sum of the time of looking at distractors (in %) and time of gaze-wandering (in %) by the time of looking at canvas (in %), with higher values indicating a higher level of distraction.

2.7.6 Actigraphy recording and analyses

Actigraphy analyses focused on differences in head position shifts and head rotations between blocks (pre-intervention vs. post-intervention) and interventions (sham stimulation vs. active stimulation). The two actigraphy parameters were inferred from the built-in positional tracking of the Vive system by means of which the HMDs momentary positions and rotations during the experiment were each recorded with a ~ 90 Hz sampling rate in three-dimensional Euclidean space coordinates. For offline analyses, actigraphy data was first down-sampled to 10 Hz. Next, the Euclidean distance between each sample point (three-dimensional position or rotation vector) and its preceding sample point was specifically calculated for the HMD position and HMD rotation data. Finally, to statistically compare the amount of head position shifts and rotations between conditions, the mean Euclidean distance in respect to head position shifts and head rotations was derived for each block and intervention.

2.8 Data exclusion

Twelve participants had to be excluded from the overall analyses: three because they refrained from the study after the diagnostic appointment or first measurement date; four because of technical difficulties (on at least one experimental day, EEG measurements were aborted or key presses were not recorded), four because the CPT in these subjects accidentally had a different number of pseudo-targets, and one because there were large outliers in CPT performance. Hence, 15 participants (4 female, $M_{age} = 32.53$, $SD = 11.07$) remained for analyses. Two datasets did not contain eye tracking data, hence only 13 datasets remained for these analyses. Considering a power analysis for a within-between interaction, a sample size of $n = 16$ would be required to establish reliable results with an effect size of $\eta^2 = 0.14$ and a power of 0.80. The effect sizes of our study exceeded these with $\eta^2 = 0.23$ for the EEG alpha power interaction effect, thereby determining the *post-hoc* power to 97.5% for this model (see section 3.4). Therefore, the obtained sample should be sufficient to detect potential tACS effects.

2.9 Statistical analyses

For statistical analyses with Matlab 2021b (MathWorks Inc., Natick, MA, United States), the following outcome variables were included: omission error rate, commission error rate, and RTV for the CPT analysis; hyperactivity, inattention, and impulsivity ratings for the subjective ADHD symptom evaluation; mean alpha power for the wavelet analysis; composite distractibility score, gaze time on canvas, gaze time on distractors and gaze-wandering time for eye tracking analysis; and head movement and rotation for actigraphy analyses. For each main dependent variable, a two-way repeated measures ANOVA with the two within-factors "Block" (pre-intervention vs. post-intervention) and "Intervention" (active stimulation vs. sham stimulation) was conducted, with an α-level of 0.05. In case of a significant interaction, we followed up this interaction via *post-hoc* *t*-tests (sham pre vs. sham post; active pre vs. active post; sham pre vs. active pre; sham post vs. active post). In order to correct for multiple comparison by Bonferroni correction, only those $p < 0.0125$ (α-level of 0.05/4 *post-hoc* tests) were considered as statistically significant.

3 Results

3.1 Sample characteristics

Results of the eligibility assessment and clinical characterization are reported in Table 1. Out of the 15 participants analyzed (4 female, $M_{age} = 32.53$, $SD = 11.07$), 14 participants (93.3%) were found to have a combined ADHD presentation and one participant (6.7%) had a predominantly inattentive presentation. None of our participants were assigned to the impulsive–hyperactive subtype. An ADHD diagnosis had been evident since childhood in 12 participants (80%). Six patients received ADHD-medication. Moreover, five patients took selective serotonin reuptake inhibitors or selective serotonin-noradrenalin-reuptake-inhibitors for the treatment of depression or anxiety. Most participants had a higher education entrance qualification (73.3%). The most common current comorbidities found were anxiety disorders (53.3%) and affective disorders (46.7%). According to the depression-anxiety-scales (DASS-21; Nilges and Essau, 2015), participants revealed, on average, only low scores for symptoms of depression ($M = 12.73$; $SD = 2.91$), anxiety ($M = 12.13$; $SD = 3.11$) and stress ($M = 15.00$; $SD = 3.70$).

Most frequently reported tACS side effects, according to the questionnaire about tACS side effects (Brunoni et al., 2011), were fatigue ($n = 12$ per condition, 80%), whereby only two participants (13.4%) in the active stimulation condition associated fatigue symptoms with tACS, but rather linking it to the experiment duration. In addition, difficulties in concentration and headaches were reported (for detailed results, see Supplementary material 2). This implies that during the experiment, participants experienced some discomfort, but no one aborted the experiment and no serious adverse events occurred. Checking for blinding, analyses revealed that for active stimulation 9 participants (60%) detected the condition correctly.

3.2 Behavioral performance

Results of the CPT analyses are shown in Figure 2. Regarding omission error rate (Figure 2A), the ANOVA revealed neither a

TABLE 1 Demographic and clinical characteristics of the sample.

Total sample (*n*)	15
Female [*n* (%)]	4 (26.67)
Age [*M* (*SD*)]	32.53 (11.07)

Interview data		
IDA-R		**Maximum scores**
ADHD presentations [n (%)]		
Combined type	14 (93.33)	
Predominantly hyperactive–impulsive type	0	
Predominantly inattentive type	1 (6.67)	
ADHD scores [M (SD)]		
Total	35.60 (6.20)	54
Inattention	19.80 (3.41)	27
Hyperactivity	9.13 (2.88)	15
Impulsivity	6.67 (3.09)	12

Mini-DIPS*		
	Current diagnosis (*n*)	**Previous diagnosis (*n*)**
Affective disorder	6	2
Anxiety disorder	5	0
Somatoform disorder	1	0
Sleep disorder	2	1

Questionnaire data:		
ADHS-SB	***M* (*SD*)**	**Maximum scores**
Total	45.67 (9.54)	54
Inattention	24.67 (4.59)	27
Hyperactivity	11.87 (3.42)	15
Impulsivity	9.13 (2.90)	12
WHOQOL		**Maximum scores**
Total	61.08 (13.44)	100
Physical health	59.66 (18.12)	100
Psychological health	49.72 (19.70)	100
Social relationships	62.22 (16.33)	100
Environment	72.71 (14.87)	100
DASS-21		**Maximum scores**
Total	13.29 (2.26)	21
Depression	12.73 (2.91)	21
Anxiety	12.13 (3.11)	21
Stress	15.00 (3.70)	21

Results of the eligibility assessment and clinical characterization of the sample. *Only comorbidities with > 0 occurrences are reported. Maximum scores for IDA-R and ADHD-SB depict sum scores, while for WHQOL and DASS mean scores.

significant main effect of "Block" (F (1, 14) = 0.96, p = 0.347, η_p^2 = 0.06), nor a main effect of "Intervention" (F (1, 14) = 1.48, p = 0.244, η_p^2 = 0.10) and no interaction effect (F (1, 14) = 0.22, p = 0.647, η_p^2 = 0.02). Also, for commission error rate (Figure 2B), the ANOVA revealed neither a significant effect of "Block" (F (1, 14) = 3.27, p = 0.092, η_p^2 = 0.19), nor a significant effect of "Intervention" (F (1, 14) = 0.36, p = 0.557, η_p^2 = 0.03), and no interaction effect (F (1, 14) = 0.04, p = 0.848, η_p^2 = 0.00) was found. And finally, the ANOVA for reaction time variability (Figure 2C) yielded neither a significant main effect of "Block" (F (1, 14) = 0.33, p = 0.577, η_p^2 = 0.02) or "Intervention" (F (1, 14) = 0.14, p = 0.712, η_p^2 = 0.01), nor an interaction effect (F (1, 14) = 1.12, p = 0.307, η_p^2 = 0.07).

3.3 Subjective ADHD symptom evaluation

Results of the subjective evaluations are shown in Figure 3. For reported hyperactivity (Figure 3A), the ANOVA revealed a significant effect of "Block" (F (1, 14) = 5.38, p = 0.036, η_p^2 = 0.28), but no significant effect of "Intervention" (F (1, 14) = 2.34, p = 0.148, η_p^2 = 0.14) and no interaction effect (F (1, 14) = 2.13, p = 0.167, η_p^2 = 0.13). The significant "Block" effect consisted of higher hyperactivity scores during the pre-intervention (M = 1.19; SD = 0.45) than post-intervention (M = 1.03; SD = 0.45) block.

For reported inattention (Figure 3B), in turn, the ANOVA revealed neither a significant effect of "Block" (F (1, 14) = 0.03, p = 0.862, η_p^2 = 0.00) nor an effect of "Intervention" (F (1, 14) = 0.01, p = 0.939, η_p^2 = 0.00), and no interaction effect (F (1, 14) = 3.81, p = 0.071, η_p^2 = 0.21). Finally, regarding reported impulsivity (Figure 3C), the ANOVA revealed no significant main effect of "Block" (F (1, 14) = 0.44, p = 0.648, η_p^2 = 0.03), or "Intervention" (F (1, 14) = 1.91, p = 0.188, η_p^2 = 0.12), but a significant interaction effect (F (1, 14) = 3.40, p = 0.048, η_p^2 = 0.20). Following up this interaction effect, Bonferroni corrected paired t-tests neither revealed a significant difference between pre- to post- intervention for active stimulation (t (14) = 0.33, p = 0.746) nor sham stimulation (t (14) = −1.99, p = 0.067). All other follow-up t-test were non-significant.

3.4 Wavelet analysis

Before starting the actual experiment, the mean alpha frequency outside VR amounted to M = 9.63 (SD = 0.69) in the stimulation group and M = 9.67 (SD = 0.98) in the sham group. Results of the wavelet analysis during CPT are shown in Figure 4, while the individual mean alpha power during CPT before and after both interventions are depicted in Figure 5. The ANOVA on the mean alpha power revealed no significant main effect for "Intervention" (F (1, 14) = 0.97, p = 0.342, η_p^2 = 0.06), but a significant main effect of "Block" (F (1, 14) = 23.11, p < 0.001, η_p^2 = 0.62), and a trend for an interaction effect (F (1, 14) = 4.19, p = 0.060, η_p^2 = 0.23). The block effect resulted from higher amplitude values during the post-intervention block (M = 3.61, SD = 1.25) compared to the pre-intervention block (M = 3.13, SD = 0.10). Following up the trend for an interaction exploratively, we see a significant increase from pre- to post-measurements during sham stimulation (t (14) = −3.14, p = 0.007) and active stimulation (t (14) = −5.64, p = <0.001), even after Bonferroni correction. All other follow-up t-test were non-significant.

Results of the wavelet analyses during the two-minutes resting phases, are, in turn, depicted in the Supplementary material 1. Here, the ANOVA revealed a significant main effect of "Block" (F (1, 14) = 9.87, p = 0.007, η_p^2 = 0.41), but no significant effect for

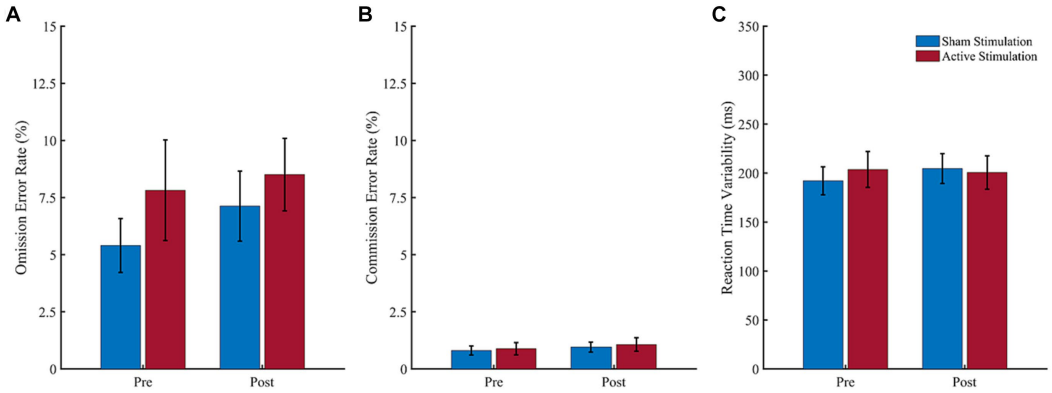

FIGURE 2
Results of the CPT. Values depict means for the **(A)** omission error rate, **(B)** commission error rate and **(C)** reaction time variability before (pre) and after (post) sham stimulation (blue bars) and active stimulation (red bars). Error bars represent the standard error of the mean.

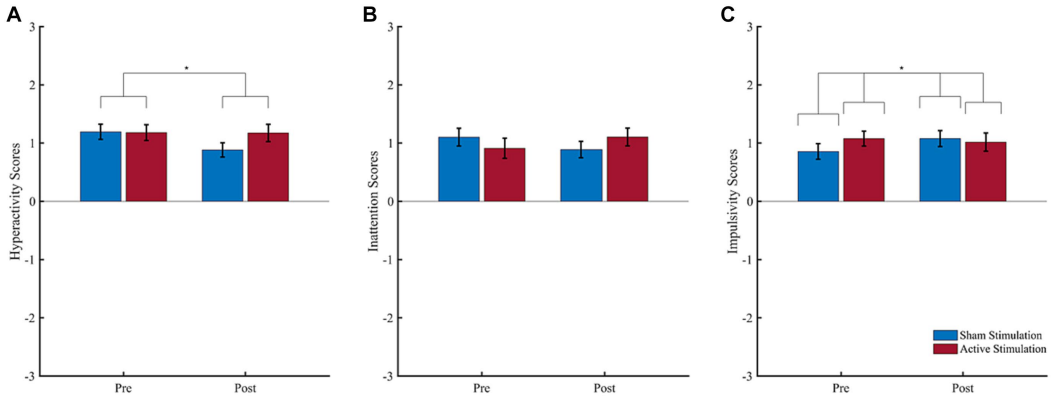

FIGURE 3
Subjective ratings of core ADHD symptoms. Patient-rated symptoms of **(A)** hyperactivity, **(B)** inattention, and **(C)** impulsivity before (pre) and after (post) intervention. Scores ranged from −3 (strongly disagree) to 3 (strongly agree). Error bars represent the standard error of the mean. *$p < 0.05$.

"Intervention" (F (1, 14) = 3.60, p = 0.079, η_p^2 = 0.20), and only a trend for an interaction effect (F (1, 14) = 4.09, p = 0.063, η_p^2 = 0.23). Following up on the trend for an interaction exploratively, after applying the Bonferroni correction, none of the paired t-tests yielded statistically significant differences in any of the tests conducted.

3.5 Eye tracking

Results of the eye tracking analyses are depicted in Figure 6. The ANOVA for gaze time on canvas revealed no significant main effect of "Block" (F (1, 12) = 2.23, p = 0.161, η_p^2 = 0.16), or "Intervention" (F (1, 12) = 0.01, p = 0.914, η_p^2 = 0.00), and no significant interaction (F (1, 12) = 0.01, p = 0.942, η_p^2 = 0.00). For the gaze time looking on distractors, in turn, there was a trend for "Block" (F (1, 12) = 4.47, p = 0.056, η_p^2 = 0.27), but no effect for "Intervention" (F (1, 12) = 0.32, p = 0.580, η_p^2 = 0.03) or the interaction (F (1, 12) = 3.21, p = 0.098, η_p^2 = 0.21). The trend effect indicated potentially higher gaze time on distractors during the post-intervention block (M = 4.75, SD = 3.71) compared to the pre-intervention block (M = 3.60, SD = 2.61). The ANOVA for gaze wandering revealed no significant main effect of "Block" (F (1, 12) = 0.77, p = 0.396, η_p^2 = 0.06), or "Intervention" (F (1, 12) = 0.05, p = 0.824, η_p^2 = 0.00), and no significant interaction (F (1, 12) = 0.16, p = 0.700, η_p^2 = 0.01).

3.6 Actigraphy

Results of the actigraphy analyses are depicted in Figure 7. For head position, there was a significant effect for "Block" (F (1, 14) = 18.83, p < 0.001, η_p^2 = 0.57) but neither for "Intervention" (F (1, 14) = 0.70, p = 0.418, η_p^2 = 0.05) nor for the interaction (F (1, 14) = 0.08, p = 0.776, η_p^2 = 0.01). The block effect resulted from higher head position scores in the post-intervention block (M = 4.01, SD = 2.26) compared to the pre-intervention block (M = 3.00, SD = 2.10). For head rotation, there was no significant effect for "Block" (F (1, 14) = 0.02, p = 0.897, η_p^2 = 0.00) or "Intervention" (F (1, 14) = 0.01, p = 911, η_p^2 = 0.00), and no significant interaction (F (1, 14) = 3.61, p = 0.078, η_p^2 = 0.21).

4 Discussion

Given the evidence for a decreased EEG alpha power in adult ADHD (Loo et al., 2009; Woltering et al., 2012; Poil et al., 2014; Liu

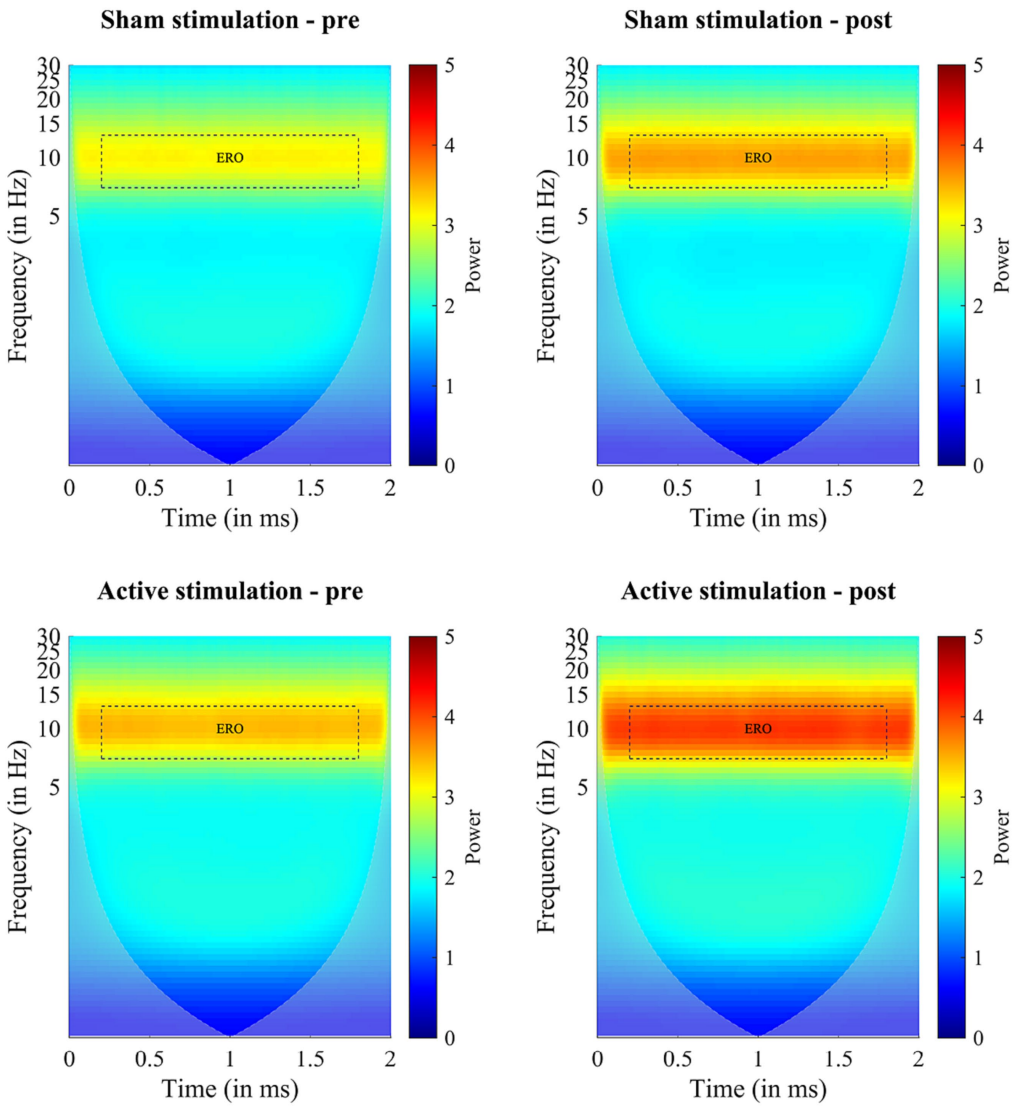

FIGURE 4
Results of the Wavelet analyses during CPT performance before (pre) and after (post) intervention (sham stimulation vs. active stimulation). Data analyses based on $n = 15$ datasets. ERO = event related potential.

et al., 2016; Deiber et al., 2020), the objective of the current study was to increase the alpha power of adult ADHD patients and to explore possible resulting neurophysiological and/or behavioral changes. Therefore, we carried out a crossover trial, in which a final sample of $n = 15$ adult patients with ADHD underwent both an individual tACS-based alpha stimulation (active stimulation) and a placebo stimulation (sham stimulation) while performing a CPT in a VSR scenario. We examined the mean alpha power at rest (2 min each) and during CPT conductance (18 min each), CPT performances, subjective ADHD symptoms, head movement and rotation, and gaze behavior before and after both interventions.

While alpha power significantly increased from pre- to post-interventions, we were not able to find a significantly stronger increase in alpha power due to active stimulation compared to sham stimulation, neither at rest nor during CPT execution. Although both statistical analyses each yielded a trend for a significant interaction, exploratively assessed trend interactions indicated time differences rather than intervention effects. While the block effect can be attributed to a natural alpha rise in both groups, which is a well-known phenomenon during a prolonged cognitive task as a function of time on task and mental fatigue (Fan et al., 2015; Gharagozlou et al., 2015; Trejo et al., 2015; Benwell et al., 2019), it is not clear why we do not find a significant difference in the participants' alpha power comparing the application of active and sham stimulation. Nevertheless, since we only expect a small effect of tACS anyway and, in addition, the effect of tACS is quite variable, the small sample size is a constraint in our study. It seems that a larger sample size could have resulted in a significant effect.

In addition, patients with different ADHD presentations seem to show varying levels of alpha power. Most studies suggest a decreased alpha power in patients with ADHD (Loo et al., 2009; Woltering et al., 2012; Poil et al., 2014; Liu et al., 2016; Deiber et al., 2020), but some studies also report an increased alpha power (Koehler et al., 2009; Poil et al., 2014; Deiber et al., 2020), especially for those suffering from

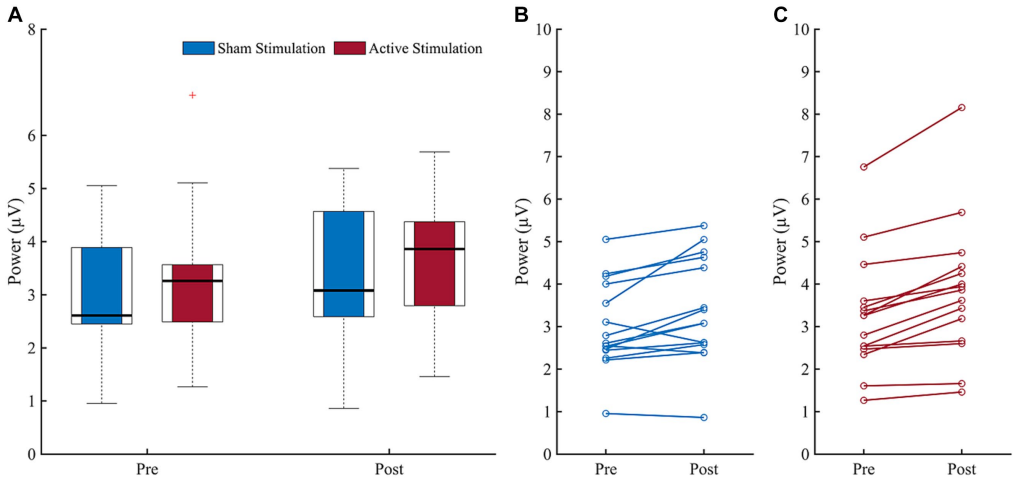

FIGURE 5
Block comparison (pre vs. post) of individual mean alpha power. **(A)** Boxplots depict mean alpha power before (pre) and after (post) for sham stimulation (blue) and active stimulation (red). **(B)** Pre to post change of individual mean alpha power for sham stimulation and **(C)** for active stimulation. Data analyses based on $n = 15$ datasets. Error bars represent the standard error of the mean.

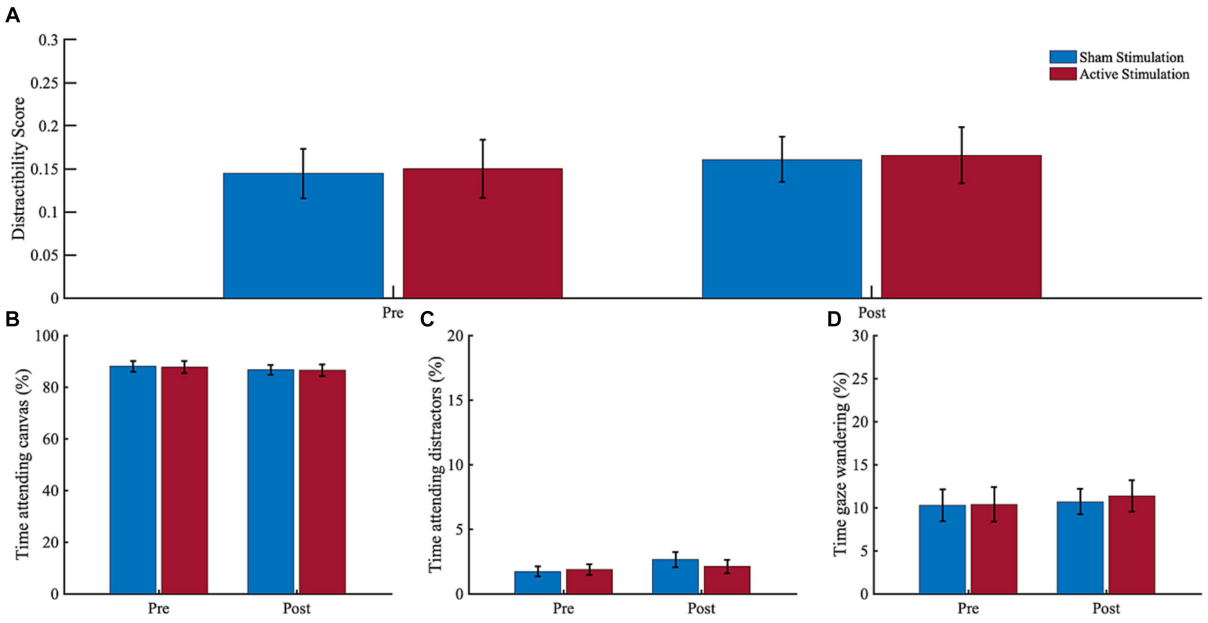

FIGURE 6
Eye tracking results. **(A)** Distractibility score, **(B)** Time attending canvas, **(C)** Time attending distractors, and **(D)** Time gaze wandering. Dwell time percentages before (pre) and after (post) sham stimulation (blue bars) and active stimulation (red bars). Data analyses based on $n = 13$ datasets. Error bars represent the standard error of the mean.

hyperactivity/impulsivity (Deiber et al., 2020). Of note, our ADHD sample almost exclusively consisted of patients with the combined ADHD presentation. Hence, almost all our patients also exhibited a level of hyperactivity, which might be associated with a higher and therefore not strongly further increasable alpha power. This indicates that a subgroup of ADHD patients (e.g., a predominantly inattentive sample) associated with a diminished alpha power, might have benefited more from the tACS application. However, since our data seem to show a high variability in the alpha power pre-to-post change (*cf.* Figures 5B,C), further basic research is needed to clarify whether abnormal alpha power is a neuromarker for a specific ADHD subtype, and to what extent subtype-specific neural activity patterns need to be taken more into account in the application of tACS.

Finally, the success of brain stimulation might have been influenced by inter- and intraindividual variability, e.g., by an unfavorable brain state during the application of tACS or by using a non-individualized

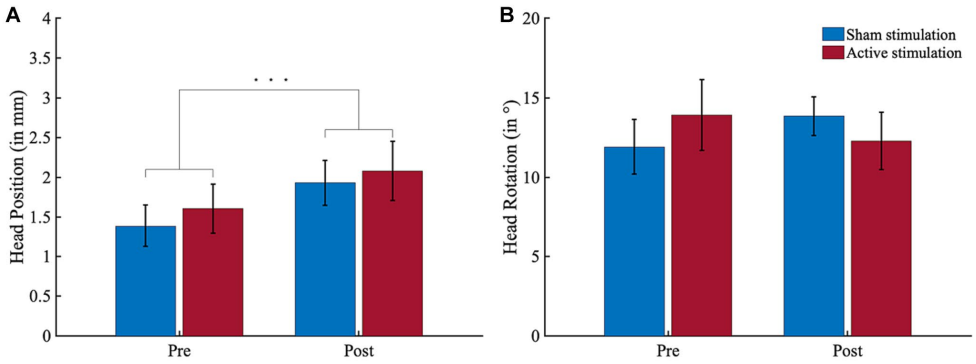

FIGURE 7
Actigraphy results. **(A)** Head position (in mm per 100 ms) and **(B)** head ration (in ° per 100 ms) shifts in block 1 (pre-intervention) and block 3 (post-intervention). All participants conducted greater head position shifts during block 3 than block 1. Error bars represent the standard error of the mean. ***$p < 0.001$.

electrode montage that failed to target the correct source (Bergmann, 2018; von Conta et al., 2021; Kasten and Herrmann, 2022). This could have affected the subsequent aftereffects (the so called "offline effects" that we have investigated) of induced synaptic changes by non-invasive brain stimulation (for details, see, e.g., Vossen et al., 2015). One possible innovative approach to overcome the individual variability would be to use a closed loop system that tracks brain activity during tACS application and adjusts the stimulation accordingly (Zrenner et al., 2016). Since there are only few studies investigating online adaptation of stimulation parameters depending on current brain activity so far, the efficiency and practicability of such closed loop systems needs to be further evaluated (Bergmann et al., 2016; Karabanov et al., 2016; Thut et al., 2017; Stecher et al., 2021).

Regarding behavioral measures, we found no indication for a tACS-induced cognitive improvement for any of our CPT performance, eye tracking, actigraphy or subjective measures. In sum, our tACS application does not appear to have induced any clinically meaningful effect in terms of behavioral changes.

4.1 Task related time-on-task effects

Regarding pre-post effects, one interesting finding is that there was a higher gaze time spent on distractors as well as a higher amount of head position movements in the post-intervention block as compared to the pre-intervention block. The latter result is consistent with the results of a virtual classroom study in ADHD children by Mühlberger et al. (2020) as well as with our own VSR study in healthy controls (Wiebe et al., 2022), which both yielded very similar time-on-task head movement effects. Regarding gaze duration on distractors, the outcome agrees with Wiebe et al. (2023), who found that unmedicated ADHD patients spent significantly more time gazing at distracting stimuli while being immersed into the VSR, compared to healthy controls. Interpreting both results, it could be assumed that our participants became increasingly inattentive and/or restless over the duration of the experiment. This, in turn, may suggest that our VSR setup was able to induce the neuropsychologically-desired boredom and monotony in our participants that may provoke inattention, hyperactivity, and impulsivity in adults with ADHD. If this is true, this induction of monotony was, however, insufficiently small, as no pre-post effect was found for any of the CPT performance measures.

Another finding is that in contrast to the pre-post increase of head movements, participants reported to be less hyperactive in the post-intervention block as compared to the pre-intervention block. In other words, while the participants perceived that their motor activity decreased over the course of the experiment, their motor activity increased. One possible explanation for this mismatch between active and experienced movement behavior might be a "positive illusory bias" (i.e., an overestimation of one's own competence that does not correspond to one's active performance) that has already been repeatedly reported for ADHD children (Owens et al., 2007; Prevatt et al., 2012; Volz-Sidiropoulou et al., 2016) and recently also for ADHD adults (Butzbach et al., 2021). Another alternative explanation might be habituation. That is, our participants got used to the experimental procedure and virtual surrounding and thereby became less excited over time, what resulted in diminished feeling of restlessness. Likewise, it is also conceivable that head movements might not be a reliable marker of hyperactivity in patients with ADHD. Nevertheless, these diverging outcomes underline the importance of a multimodal assessment when testing the efficacy of tACS or other therapeutic interventions in ADHD, as our data suggests that one cannot rely on subjective data alone.

4.2 Limitations and future directions

A limitation of this study is the small final sample size ($n = 15$). Reasons for this included our technically challenging multimodal VR paradigm, which caused some technical difficulties during data acquisition, as well as an impeded ADHD patient access due to the Corona pandemic. Our data suggest that a stimulation effect might have been found with a larger sample. Moreover, a larger sample could indicate the extent to which the specific ADHD presentation might be associated with a significant stimulation effect.

Another aspect to be considered is that, in addition to the studies cited for decreased alpha power (Loo et al., 2009; Woltering et al., 2012; Poil et al., 2014; Liu et al., 2016; Deiber et al., 2020), there is also some evidence for equal (van Dongen-Boomsma et al., 2010) or even increased alpha power (Bresnahan and Barry, 2002; Koehler et al.,

2009) in adult ADHD patients compared to healthy individuals. Assuming that the alpha power is increased, the mechanism of action proposed in this study to achieve attentional improvement through alpha amplification might be ineffective, since an already elevated endogenous alpha power cannot be further increased by tACS (Neuling et al., 2013). To account for heterogeneity, future studies might evaluate the alpha power of adult ADHD patients beforehand and allocate them accordingly into groups of low and high alpha power before applying tACS to test its therapeutic effect. Additionally, further work is needed to explore the potential differential effects of tACS on the different ADHD subtypes, thereby contributing to a more detailed understanding of its potential therapeutic applicability. Unfortunately, in the present study it was not possible to conduct such an analysis, as the majority of our participants was diagnosed with the combined ADHD type and only one participant with the predominantly inattentive subtype, thereby precluding a subgroup analysis.

It is also conceivable that other potential ADHD neuromarkers could be considered for tACS. One possibility might be the theta-beta-ratio (TBR), which seems encouraging since TBR differences between children with ADHD and healthy controls appear to exist (Monastra et al., 2001; Snyder and Hall, 2006; Zhang et al., 2017). The prospect of using tACS to correct this ratio would offer a non-invasive therapeutic approach aimed at improving attention and cognitive deficits in the ADHD population. Another promising option would be to enhance the P300 (Prox et al., 2007; Itagaki et al., 2011; Marquardt et al., 2018) by the application of tACS. Some studies already aimed for this goal (Dallmer-Zerbe et al., 2020; Kannen et al., 2022). A recent study by Boetzel et al. (2023) accomplished to increase the P300 amplitude in healthy controls but revealed no dependent effect on behavioral performance parameters yet.

Finally, to our knowledge, this study is one of the first attempting to increase the alpha power of adult ADHD patients using tACS. In addition, we combined the application of tACS with a multimodal VR assessment, creating a functional setup in which various measurement techniques (EEG, eye tracking, actigraphy, behavioral performance, subjective measures) are used to investigate a potential stimulation effect in psychophysiological, behavioral, and subjective domains. In fact, there are many different possibilities to apply tACS by changing stimulation parameters (e.g., stimulation intensity), electrode positions, electrode size, or stimulation frequency, which is why further studies will need to be undertaken.

5 Conclusion

In conclusion, our study provides no evidence that tACS can increase the alpha power in adult ADHD patients. With a larger sample, however, there might have been a significant difference, since the analyses revealed large effect sizes. Since alpha power in adult ADHD has not yet been investigated in depth and since there are still many conceivable parameter settings for the application of tACS, more research is needed to clarify whether alpha power enhancement via tACS could be advantageous as a possible therapeutic intervention for ADHD. Overall, we have succeeded in creating a multimodal experimental design including multiple measures (subjective, behavioral, electrophysiological, actigraphy, and eyetracking) to test the potential effects of tACS on adult ADHD and our research has raised numerous questions that require further investigation.

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 Medical ethics committee of the University of Bonn. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

KK: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. JR: Investigation, Writing – review & editing. AF: Investigation, Writing – review & editing. AW: Formal analysis, Writing – review & editing. BS: Formal analysis, Writing – review & editing. LA: Writing – review & editing. BA: Writing – review & editing. SL: Writing – review & editing. CSH: Conceptualization, Methodology, Supervision, Writing – review & editing. AP: Conceptualization, Funding acquisition, Supervision, Writing – review & editing, Methodology. NB: Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

Over the past 3 years, AP received funding by the German Federal Ministry of Education and Research, Horizon 2020, Medice and DFG; she reports serving on advisory boards for Takeda, Medice and Boehringer; delivering lectures sponsored by Medice and Takeda; and being the author of books and articles on ADHD. CSH holds a patent on brain stimulation.

The remaining 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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1280397/full#supplementary-material

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4. Discussion with References

4.1 Summary

The current dissertation focuses on assessing ADHD core symptoms (inattention, hyperactivity, and impulsivity) in a standardized, realistic, and multi-modal testing environment and explores tACS, a new NiBS technique, as a potential alternative therapeutic intervention for adult ADHD.

The first study investigates the potential of utilizing the VSR, a VR-based multi-modal assessment, for adult ADHD. This system simulates a real-life seminar room with various distractions, creating a more realistic and complex but standardized testing environment. Testing the VSR with a healthy control group confirmed the feasibility of the VR-based approach. It provides a comprehensive and ecologically valid assessment tool, capturing the complexity of ADHD symptomatology. The developed VSR was afterwards utilized to investigate potential differences in task performance, actigraphy, EEG, eye tracking and fNIRS measurements between adult ADHD patients and healthy controls. Demonstrating its efficacy, the VSR significantly distinguished between patients and healthy controls, with notable differences observed in several parameters (Wiebe et al., 2023).

The second study investigated whether brain stimulation via tACS can increase the P300 amplitude in adults with ADHD, potentially leading to symptom improvement. Examination of active and sham tACS conditions revealed no evidence of an enhanced P300 amplitude following active stimulation compared to sham. Although active tACS stimulation significantly increased the N700 amplitude unlike sham stimulation, this increase was not reflected in any improvement in attention performance measures. In sum, our findings do not support the previous research conducted by Dallmer-Zerbe et al. (2020), which reported symptom improvement in adult ADHD patients through an increase in mean P300 amplitude using tACS.

In the third study, we examined the potential of tACS as a treatment for adult ADHD in combination with the developed VSR. After both, sham and active tACS, a significant increase in alpha band power was observed. Although there was a trend towards an interaction effect, the increase in symptom improvement was not significantly higher after active stimulation compared to sham stimulation. Overall, we did not find any intervention-related symptom improvement.

4.2 Electrical Brain Stimulation as a Therapeutic Approach for Psychiatric Disorders

Several studies have demonstrated the effectiveness of tACS as a therapeutic intervention for various psychiatric disorders (Elyamany et al., 2021; Biačková et al., 2023). For instance, Grover et al. (2023) reported a meta-analysis showing improvements in cognitive functions such as working memory, long-term memory, attention, executive control, and fluid intelligence. The most promising results have been observed in patients with schizophrenia and depression (Frohlich and Townsend, 2021; Lee et al., 2022). However, there is only limited evidence to support the therapeutic efficacy of tACS for the treatment of ADHD (Dallmer-Zerbe et al., 2020; Farokhzadi et al., 2021). In contrast, tDCS, which is a similar brain stimulation technique, has undergone extensive study (Rubia, 2018). Salehinejad et al. (2019) found significant improvements in inhibitory control and working memory in ADHD patients following tDCS application, with a small-to-medium effect size. These findings were supported by a subsequent meta-analysis (Salehinejad et al., 2020). Breitling et al. (2016) also noted improvements in the interference control of patients with ADHD by administering anodal tDCS over the right inferior frontal gyrus. Overall, tDCS is a promising alternative to psychopharmacological therapy. However, further clinical investigations are needed to confirm its efficacy.

4.3 Limitations and Future Perspective

NiBS techniques can modulate targeted brain oscillations by applying a weak current to the scalp (for details see, Antal and Herrmann, 2016). Developing NiBS therapies tailored to ADHD patients requires a comprehensive understanding of ADHD neuromakers. With the application of tACS, it is particularly important to identify the altered brain oscillations underlying ADHD. However, there is no definite consensus on ADHD neuromarkers at present (for an overview, see Kiiski et al., 2020), and recent evidence suggests that neuromarkers can differ between ADHD subtypes (for review, cf. Slater et al., 2022). To examine the therapeutic benefits of tACS, large-scale and highly individualized clinical trials are required. These trials should account for potential differences in neuromarkers for ADHD subtypes. Moreover, further studies focusing on individual neuroanatomy and brain state are needed (Kasten et al., 2019; Laakso et al., 2015, 2019; Opitz et al., 2018; Zanto et al., 2021). Through interdisciplinary collaboration, translational research can make such studies feasible. Nonetheless, translational research faces several obstacles that may add

to the complexity and burden of these time-consuming research projects (Pober et al., 2001). Moreover, integrating tACS in a closed-loop system that simultaneously monitors the patient's brain activity and adjust stimulation parameters based on real-time EEG measurements could be beneficial (Leite et al., 2017; Stecher et al., 2021). The second study of this dissertation aimed to increase the P300 amplitude, which made the experiment time-sensitive as the positive wave of the sinusoidal current had to align with the P300's positive deflection. Future studies should be less time-sensitive, initially focusing on targeting brain oscillations rather than ERPs to avoid overcomplicating the already complex experimental setup. Since transcranial electrical stimulation (TES) is safely tolerated, even in repeated sessions (Nikolin et al., 2018; Riddle et al., 2019; Wilkening et al., 2019), longitudinal studies should investigate whether tACS can sustainably improve ADHD symptoms and ensure that these effects are enduring. Overall, there are several parameters that need further investigation to develop an effective alternative therapy approach for ADHD.

4.4 Implications for Clinical Application of tACS

To introduce tACS into the health care system and especially for the treatment of ADHD, several aspects need to be considered (for tDCS, see Charvet et al., 2020). The main goals are to identify and optimize stimulation parameters to enhance the effectiveness and safety of tACS for symptom improvement, ensuring compliance with the medical device regulations (Elyamany et al., 2021). To this end, randomized controlled trials are necessary to evaluate the therapeutic efficacy and long-term safety of tACS. Following research consensus, it is essential to develop a medical therapy device customizable to each patient, taking into account factors such as age, neuroanatomy, and ADHD subtype. The design focus should encompass user-centered principles, such as participatory design, to create a medical product that meets the actual users' needs (for a systematic review, see Vandekerckhove et al., 2020). Ideally, the design should be compact, cost-effective, and mobile to facilitate its accessibility. In addition, the stimulation system should be simple to apply, eliminating the need for complex and time-consuming electrode adjustments, and enhancing time-efficient treatment of psychiatric disorders. Thus, improving the overall user experience and enable continues application at home. Patient safety is crucial in the development and deployment of a medical product. As such the

compliance with regulatory requirements for medical devices is vital to maintain high-quality standards and prevent unexpected side effects. To ensure the ongoing safety and effectiveness, long-term safety monitoring and adverse event reporting mechanisms, for instance a reliable assessment of side effects, should be established. Additionally, clear user guidelines, safety tutorials, and robust trainings as well as instructional programs for medical staff and patients are necessary, particularly for home-based intervention, to ensure the device is used safely and correctly with emphasize on adherence to prescribed stimulation parameters. Safety features, like mechanisms to restrict unlimited access to stimulation settings (e.g., current intensity, duration, number of sessions), should be built into the device to prevent manual changes of stimulation parameters. Moreover, emergency mechanisms are essential to stop the stimulation automatically if the contact quality between the stimulation electrodes and scalp reaches a critical level (shut down mechanism). Finally, healthcare providers and patients should be supported through programs that ensure the safety and efficacy of the device. In conclusion, introducing tACS into the health care system, especially for the treatment of ADHD, requires an initial clinical proof of concept.

4.5 Conclusion

The main objectives of this dissertation were to investigate the feasibility of a multi-modal, realistic, and standardized testing environment to assess ADHD symptoms and to evaluate the potential therapeutic effect of the NiBS technique tACS. Although we were not able to confirm a benefit of tACS for ADHD patients so far, our research highlights the need for further fundamental research on ADHD neuromarkers, a detailed understanding of the tACS mechanisms and applications, and the development of multimodal assessment tools for ADHD. For the latter, the developed VSR appears suitable. As indicated previously, tACS is a new NiBS technique that has shown potential in alleviating cognitive impairment in various psychiatric disorders. The studies presented here provide a foundation for future research on using tACS for treating ADHD, although further investigations are needed to tailor tACS therapies for ADHD.

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