

What Can Transcranial Alternating Current Stimulation Tell Us About Brain Oscillations?

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Abstract

Purpose of the Review Transcranial alternating current stimulation (tACS) allows to interfere with oscillatory brain activity. Here, we provide an overview of novel approaches for removing the tACS artefact to elucidate the mechanisms responsible for on-line tACS effects. Furthermore, we review recent findings on tACS after-effects and clinical applications. *Recent Findings* tACS-induced entrainment of alpha oscillations was demonstrated in on-line electroencephalography (EEG) and magnetoencephalography (MEG) recordings. On-line effects have also been revealed by innovative tACS protocols utilizing amplitude modulation, cross-frequency coupling, non-sinusoidal waveforms, and non-electrical physiological measures. tACS after-effects on alpha power exceeding 1-h duration have been reported, and a behavioral relevance of these physiological changes was shown for the first time.

Summary Our understanding of tACS on-line effects greatly benefited from new artefact removal approaches. After-effects of varying duration have been consistently reported but the underlying mechanism is still unclear. tACS as a neurotherapeutic is only emerging, but first evidence for successful tACS interventions in neuropsychiatric and neurological disorders is encouraging.

Keywords Electroencephalogram · Brain oscillations · Transcranial electric stimulation · Transcranial alternating current stimulation · tACS artefact

Introduction

Non-invasive brain stimulation (NIBS) is based on transcranial application of either electric current or magnetic fields to interfere with cortical activity and, thereby, manipulate cognitive processes [1, 2]. Although these techniques require an electric current or magnetic field to pass through the scalp and skull, according to medical definitions, they do not qualify as being invasive, since the skin is not injured. In case of transcranial electric stimulation (tES), either direct current (transcranial direct current stimulation, tDCS) or alternating current (transcranial alternating current stimulation, tACS) of approximately 1–2 mA is delivered through Ag/AgCl electrodes or electrically conducting rubber electrodes. A combination of direct and alternating current is referred to as oscillatory tDCS (otDCS). In transcranial magnetic stimulation (TMS), on the other hand, strong and transient magnetic fields are delivered through a stimulating coil positioned over the head as either a single pulse (spTMS) or as a series of pulses (repetitive TMS/rTMS).

Although all of these NIBS methods are able to modulate brain activity and cognition in general [3, 4], a specific interference with oscillatory activity requires techniques allowing for rhythmic stimulation at a certain frequency (e.g., 10 Hz) like rTMS [5] or tACS/otDCS [6]. To drive ongoing brain oscillations with rTMS, brief bursts of ~100 μs are repeated at a specific frequency of interest, whereas tACS delivers sinusoidal currents at that frequency. Such an external manipulation of endogenous brain oscillations brings with it the possibility to go beyond the well-established association of brain

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oscillations with cognitive processes and to test for causal relationships [7]. In this review, we focus on tACS, one of the most recent NIBS methods, and one that is low-cost, easy to apply, and well tolerated. There is ample evidence for the effectiveness of tACS in modulating electroencephalographic (EEG) activity as well as various sensory, motor, and higher cognitive processes as documented by numerous recent reviews [2, 7–12].

Despite an ever increasing number of human tACS studies, the neurophysiological underpinnings of on-line effects during stimulation and off-line effects surviving stimulation offset (i.e., after-effects) are still poorly understood. Keys to a better understanding of how tACS impacts on oscillatory brain activity are simultaneous recordings of EEG or magnetoencephalography (MEG) that directly reflect the tACS effects. However, online recordings are severely complicated by the strong stimulation artefact contaminating the electrophysiological data. Although this fundamental problem has not been fully resolved yet, there are a number of recent advances exploring new avenues in the field of artefact removal. We will discuss novel techniques like cross-frequency tACS, amplitude modulated tACS, and stimulating with non-sinusoidal waveforms.

Whereas the problem of artefact removal is primarily related to on-line effects of tACS, we also describe the latest findings regarding tACS after-effects. Furthering our knowledge about the underlying mechanisms and relevant stimulation parameters regarding the origin of after-effects is essential for utilizing tACS in patient populations. Clinical tACS applications are still scarce, but recent years have witnessed an increasing interest in this important topic. Therefore, we will review the current state of rhythmic stimulation in neuropsychiatric and neurologic disorders in the final section.

On-Line Effects of tACS on Brain Oscillations

Is tACS Sub- or Super-Threshold?

The rationale of using tACS in brain research is to modulate brain oscillations and, in turn, to influence those cognitive processes that rely on these brain oscillations. Therefore, it is of special interest to demonstrate how tACS modulates brain oscillations during the time of stimulation. One presupposition for tACS to produce such online effects is its capacity to modulate with brain activity at all. Because of its weak current intensities, this has been debated for a long time. Currently, tACS in humans is typically applied with intensities of 1 to 2 mA [13]. Animal studies suggested stimulation intensities as low as 0.2 V/m [14], 0.3 V/m [15], or 0.5 V/m [16] as thresholds for effectively modulating neural activity. Note that these animal studies usually report voltage gradients which cannot directly be compared to the intensity of tACS in human studies.

Therefore, the voltage gradient that results from tACS in humans has to be estimated. To this end, the intracranial current density has to be computed at first, e.g., by using finite element models [17]. It has been demonstrated that 1 mA of tACS results in maximum current densities of about 0.1 A/m². In a second step, this current density has to be multiplied with the conductivity of human brain tissue, i.e., 3 Ωm [18]. This leads to voltage gradients of about 0.3 V/m, which are well in the range of the abovementioned animal thresholds. It has to be stressed, however, that these values reflect intensities at which firing rates and spike timings are modulated by tACS, but not thresholds above which an otherwise silent neuron would start to fire. It should be noted that the head models require a sufficient amount of precision and tissue anisotropy should be taken into account, since conductivity is much higher along nerve fibers than perpendicular to them. In addition, the skull should be separated in compact and sponge-like compartments, since the latter conducts four times better than the former.

Only recently, cortical electric fields during tACS were measured *in vivo* in the human brain of surgical epilepsy patients [19••, 20••]. With 2 mA stimulation intensity, a maximal electric field magnitude of 0.4 V/m was achieved [20••]. When applying 1 mA, maximal electric field strengths varied between 0.5 V/m [19••] and 0.2 V/m [20••]. The different relations of extra-cranial currents to intra-cranial voltage gradients result from the different relative locations of extra-cranial tACS electrodes and intra-cranial recording electrodes. Importantly, these electric potentials that were measured intracranially in epilepsy patients reach the threshold of modulating neural activity as obtained in animal studies, even with only 1 mA. Thus, tACS at 1–2 mA can be considered effective in modulating neural activity in the human brain. Nevertheless, tACS is not comparable in intensity to transcranial magnetic stimulation (TMS) which elicits neural activity directly and can be considered super-threshold [2].

Entrainment and the Arnold Tongue

Entrainment of ongoing brain oscillations by the externally applied sine wave stimulation has been proposed as the responsible mechanism by which tACS modulates brain oscillations [10]. Entraining a brain oscillation implies that the phase and/or frequency of the brain oscillation are modulated to follow the external stimulation. At first glance, this sounds like a linear effect, where entrainment will only occur at neural oscillations at the frequency of stimulation. On the contrary, it is important to acknowledge that entrainment is non-linear. To explain this in a bit more detail, let us assume a neural oscillator which spontaneously oscillates at 10 Hz. If this neural oscillator is stimulated weakly, it follows the stimulation frequency within a narrow range around its intrinsic frequency, e.g., from 9 to 11 Hz. Outside this frequency range, it will return to its intrinsic frequency despite the ongoing stimulation at a different

frequency. If, however, the intensity of stimulation is increased, the frequency range around the intrinsic frequency in which the neural oscillator follows the stimulation frequency becomes wider, let us assume from 8 to 12 Hz [18].

The frequency band or region in which the neural oscillator follows the stimulation frequency is considered the synchronization region and is characterized by the occurrence of entrainment [21]. According to its triangular shape (wider frequency range at higher stimulation intensity) and the name of its discoverer, this region has been called the Arnold tongue (cf. Fig. 1). The Arnold tongue surrounding the intrinsic frequency of the neural oscillator is referred to as the 1:1 Arnold tongue, since stimulation frequency and the frequency of the neural oscillator have a 1:1 relation. All other n/m relations with n and m being integers, however, can also reveal synchronization of the neural oscillator to the stimulation frequency. If a neural oscillator with an intrinsic frequency of 10 Hz is driven at 5 Hz (1:2 Arnold tongue) or 20 Hz (2:1 Arnold tongue), it can also show synchronization. It will, however, always oscillate at m/n * intrinsic frequency. At the border of the Arnold tongues, the phase of the neural oscillator sometimes follows the stimulation and sometimes the intrinsic oscillation—another strongly non-linear effect [22].

Entrainment and the Problem of tACS Artefact Removal

A major problem that arises from tACS application during electrophysiological recordings, such as EEG, is the huge stimulation

artefact superimposed on the EEG activity which is several magnitudes larger than the EEG signal. Therefore, special care is required to prevent the EEG amplifier from reaching saturation levels by keeping the impedance of the stimulation electrodes and the intensity sufficiently low. If this is achieved, the tACS artefact can be removed by similar methods that have been developed for subtracting the gradient artefact from EEG activity when simultaneously recorded with functional magnetic resonance imaging (fMRI).

This approach was successfully adapted to on-line tACS/EEG measurements by Helfrich and colleagues [23]. After removing the tACS artefact, the authors were able to compute event-related potentials evoked by light-emitting diodes and could show that they closely resemble those in a sham group that did not receive stimulation. The cleaned EEG data showed that the EEG spectrum during 10 Hz tACS revealed an increased peak at 10 Hz after artefact correction as compared to before stimulation. This study represents the first direct evidence for tACS-induced entrainment of oscillatory activity in the human brain.

Approaches to Avoid or Remove tACS Artefacts

One approach to avoid tACS artefacts is to measure physiological activity which is not contaminated by tACS. This can be achieved, for example, by recording motor-evoked potentials (MEPs) at the hand that are evoked by TMS impulses to the motor cortex while the motor cortex is simultaneously stimulated with tACS. Moliadze and colleagues [24] have

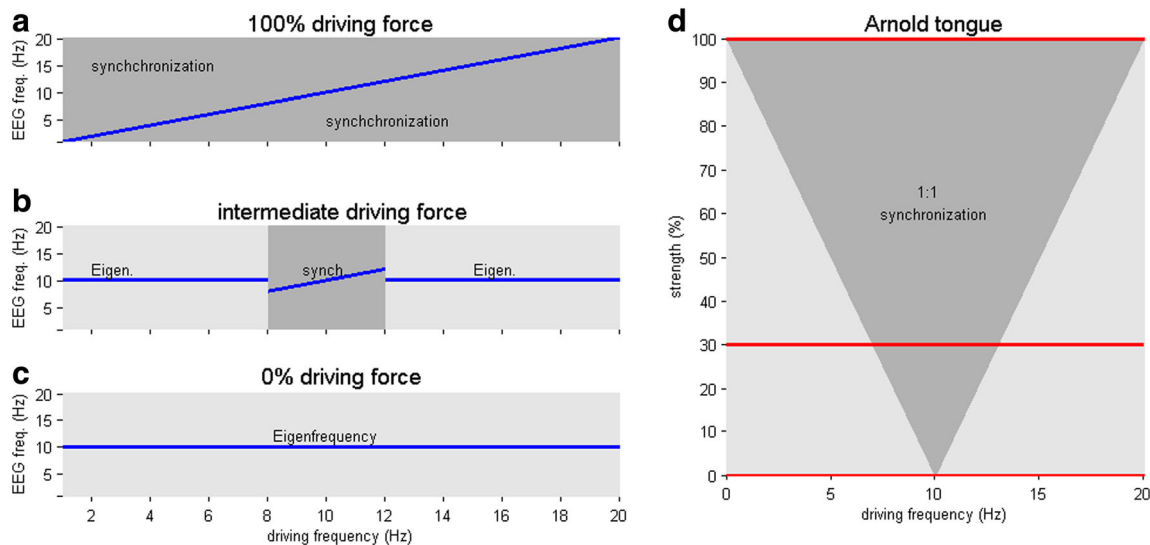


Fig. 1 **a** 100% driving force. If the brain is stimulated with a repetitive stimulus at high intensity, the EEG will synchronize to the frequency of the driving force (e.g., flickering light or tACS) across all frequencies. **b** Intermediate driving force. For intermediate stimulation intensities, a mixture of the two regimes will occur: if the driving frequency is close to the Eigenfrequency (e.g., 10 Hz), the EEG will oscillate at the frequency of the driving force (middle). Only when the EEG frequency follows the driving frequency, it is said to be synchronized (*diagonal blue*

line, dark gray region). **c** 0% driving force. If the stimulation intensity is close to zero, the EEG will be dominated by its Eigenfrequency, i.e., the individual alpha activity around 10 Hz (bottom). **d** Arnold tongue. If the width of the synchronization region is depicted as a function of stimulation intensity, this results in the so-called Arnold tongue. At low intensities, the synchronization region is small while at higher intensities, it becomes wider

applied this method to demonstrate that different intensities of 140 Hz tACS can have different effects on cortical excitation.

Combining MEG and Beamforming

In general, using MEG instead of EEG to investigate the on-line effects of tACS bears the advantage that MEG sensors are not in physical contact with the skin, and therefore, the tACS artefact is much smaller in amplitude as compared to EEG. Utilizing this effect, Neuling and colleagues [25] demonstrated that it is feasible to filter out the tACS artefact in MEG data by means of a linearly constrained minimum variance (LCMV) beamformer. With this method, brain activity inside the skull is separated from the tACS artefact which is present mainly in the electrode wires outside the skull. After artefact removal, the authors were able to compute visual and auditory event-related potentials (ERPs). In addition, they were able to monitor the changes of alpha activity in response to participants' opening and closing their eyes despite simultaneously applying tACS at the individual alpha frequency. In a follow-up study, Ruhnau and colleagues [26] provided direct evidence for entrainment of MEG alpha oscillations in visual cortex during tACS at participants' individual alpha frequency. Interestingly, this entrainment was state-dependent in that it was much stronger for states of small alpha amplitudes during open eyes as compared to stronger alpha amplitudes with eyes closed.

Recently, however, criticisms have been raised that the removal of tACS-artefacts from EEG and MEG data is not as straight forward as suggested in the aforementioned studies [27]. In their study, Noury and colleagues demonstrated that in addition to the expected tACS artifact at the frequency of stimulation, side-bands occurred in the vicinity of the stimulation frequency when plotting their spectra logarithmically. The authors argued that these side-bands reflect heart-beat and respiration both modulating the conductivity of tissue, which in turn leads to an amplitude-modulated sinusoidal stimulation due to the constant-current character of the tACS stimulator. If the current is kept constant while the resistance changes, this will result in a modulation of the stimulation voltage. See Fig. 2 for a depiction of side-bands. In response to this critique, Neuling and colleagues [28] re-analyzed their MEG data and, indeed, found such side-bands in some of their participants but only in those who were stimulated at high intensities. In contrast to Noury and colleagues, however, they were able to remove these side-bands with the beamforming approach when choosing the right parameters. In addition, it should be noted that both groups used different hardware for stimulation and recording of physiology which might also contribute to the differences. It seems advisable to consider these side-bands already during EEG/MEG recording and to possibly avoid them, i.e., by lowering current intensity.

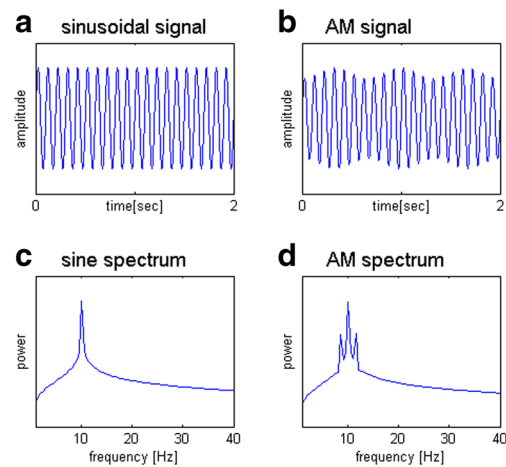


Fig. 2 **a** Sinusoidal signal. A 10 Hz sine as is often used for tACS. **b** AM signal. If the electrode impedance of the stimulation electrodes is modulated at 1.5 Hz, an amplitude-modulated signal results. **c** Sine spectrum. The frequency spectrum of the 10 Hz sine in **a** will show one prominent peak at the stimulation frequency of 10 Hz. **d** AM spectrum. The frequency spectrum of the AM signal in **b** will introduce side-bands at 8.5 Hz ($10 - 1.5$) and 11.5 Hz ($10 + 1.5$)

Cross-Frequency tACS

Brain activity usually does not consist of only one neural oscillation at one frequency but of multiple oscillations at multiple frequencies. Interestingly, different frequencies (e.g., in the theta and gamma range) interact with one another—a mechanism referred to as cross-frequency coupling [29]. Recently, a novel cross-frequency tACS protocol was introduced for demonstrating a causal role of phase-amplitude coupling between theta and gamma oscillations in working memory [30•]. Interestingly, the strongest effect on memory was found if gamma power was coupled to the peak of the theta waves (cf. Fig. 3, top), whereas gamma bursts at the trough of the theta waves had no effect (cf. Fig. 3, bottom). In the context of artefact removal, the effect of cross-frequency coupling can be used in order to modulate a brain oscillation at one frequency without stimulating at this frequency. Thus, this approach offers a further way of investigating on-line effects by separating tACS effect and artefact by means of a low-pass filter. The effectiveness of this method has been demonstrated recently by Helfrich and colleagues [31], who found an alpha amplitude reduction during 40 Hz tACS. This finding strongly supports the proposed antagonistic relationship between alpha and gamma oscillations [32].

Amplitude-Modulated tACS

Recently, another approach was taken to disentangle the tACS-artefact and its effects on electrophysiology by using

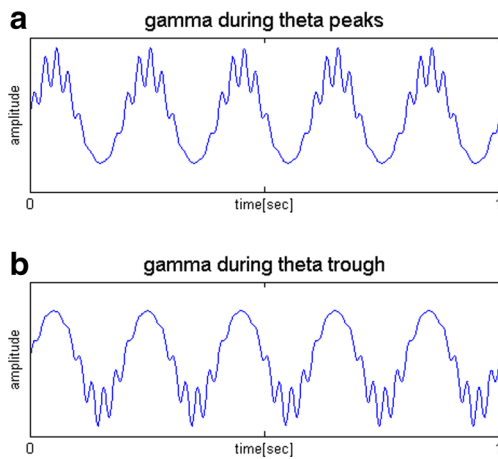


Fig. 3 **a** Gamma during theta peaks: the amplitude of a fast gamma oscillation (40 Hz) is modulated by the phase of a slower theta oscillation (5 Hz) such that the gamma amplitude is maximal during the peaks of the theta oscillation. This is referred to as phase-amplitude coupling. **b** Gamma during theta troughs: here, the gamma amplitude is maximal during the peaks of the theta oscillation

amplitude-modulated (AM) sine waves [33]. This approach allows for separating the stimulation frequency from the frequency of interest by choosing a modulating sine wave at the frequency of interest and a high-frequency carrier wave. For instance, if an AM sine wave is generated by modulating a 220 Hz carrier wave with an 11 Hz modulatory wave and used for tACS stimulation, the spectrum of the stimulation signal will reveal peaks at 209, 220, and 231 Hz, i.e., the carrier frequency and the carrier frequency plus and minus the modulation frequency.

Importantly, no spectral energy is present in the stimulation signal at the modulation frequency of 11 Hz. Due to the non-linear threshold behavior of neurons, however, an effect on neural activity is expected also at the modulation frequency of 11 Hz. Thus, a low-pass filter can nicely disentangle the observation of the AM-tACS effects at 11 Hz from the tACS-artefact in the frequency range from 200 to 240 Hz. Using MEG, it could be shown recently that this approach is feasible in principle [33]. So far, however, there is no direct evidence for entrainment of neural activity at the modulation frequency. Future studies should take into account that the membranes of neurons act like low-pass filters and effects of AM-tACS are most likely if the carrier frequency is chosen below 100 Hz rather than above 200 Hz [34].

tACS with Non-sinusoidal Waveforms

Alagapan and colleagues [35] have applied electrical stimulus trains consisting of brief pulses of 200 μ s duration every 100 ms resembling a 10 Hz stimulation—albeit more similar to rTMS than to sinusoidal tACS. The brief pulses resulted only in brief artefacts which were eliminated by a template

matching algorithm. In addition, this study was very elegant in using intra-cranial electrodes in epilepsy patients for stimulation as well as recording. Similar to previous findings, this study demonstrated enhanced power at the frequency of stimulation.

Yet, another approach for removing the stimulation artefact was taken by Dowsett and Herrmann [36], who applied tACS with sawtooth waves instead of sine waves. These sawtooth waves offer the advantage that they are piece-wise linear which makes the removal of the artefact easier. The results showed that positive ramp sawtooth stimulation, but not negative ramp sawtooth stimulation, significantly enhanced alpha power during stimulation as compared to a sham condition. This finding is in line with network simulations and animal recordings having revealed that not only the absolute amplitude of stimulation but also the steepness of transients are relevant parameters [16].

On a more general note, the stimulation effects generated by sawtooth waves highlight the widely neglected fact that brain oscillations are not purely sinusoidal although current analysis and stimulation techniques are mostly based on this assumption [37, 38]. Taking differences in oscillatory waveform shape into account might therefore improve the alignment between online brain activity and tACS signal during entrainment in future work.

Combining tACS and fMRI

With fMRI, the physiological effects of tACS on hemodynamic processes can be investigated. This method bears the advantage that the blood oxygen level dependent (BOLD) response of the brain—as measured with fMRI—is not electric and thus not susceptible to the tACS-artefact. Importantly, tACS does not introduce artefacts into the BOLD signal [39]. Vosskuhl and colleagues [40] were able to demonstrate that tACS at participants' individual alpha frequency down-regulates the BOLD response to visual stimuli, i.e., another on-line effect of tACS stimulation. Due to the antagonistic relationship between the amplitude of EEG alpha activity and the BOLD response, it was assumed that entrainment of EEG alpha oscillations by tACS results in the observed decrease of the BOLD response. A subsequent study, however, used 10 Hz tACS instead of the individual alpha frequency and could not replicate the on-line effect but found an off-line effect [41].

By comparing different tACS frequencies (10, 16, and 40 Hz), it could be demonstrated that effects of 10 Hz tACS were indeed opposite to those of 40 Hz tACS [42], supporting the notion that tACS-entrained oscillations follow the abovementioned antagonism between alpha and gamma oscillations [31]. In another study of this group, it was shown that tACS in the beta frequency range modulated BOLD in a fronto-parietal network [43].

Off-Line Effects of tACS: Duration and Mechanism

Given that tACS impacts on oscillatory brain activity through entrainment, how long do these on-line effects remain and what mechanisms might underlie their persistence? These are important questions not only in basic neuroscience but especially for translational research and clinical tACS applications. Therefore, it is an important observation that brain activity remains altered for some time even after the end of prolonged stimulation with tACS [10, 44]. These so-called off-line or after-effects are not disturbed by artefacts and are statistically compared to the brain activity before stimulation which is also clean of artefacts.

Duration of Physiological tACS After-Effects

Most existing tACS studies did not systematically analyze the maximum possible after-effect duration but used a pre-post stimulation comparison for demonstrating tACS effects. Therefore, only the duration of the post-stimulation EEG/MEG recording period can be used to estimate the minimum possible after-effect duration [44, 45]. However, with this procedure, the time course of the after-effect in case of an extended post-recording time period remains elusive.

Some progress was made in a series of studies on the after-effect duration of enhanced alpha power. Building on the first demonstration that tACS at participants' individual alpha frequency resulted in a significant alpha power enhancement for at least 3 min after the end of 10-min stimulation [6], Neuling and colleagues [46] increased the stimulation duration to 20 min and used a prolonged recording period of 30 min to analyze the post-tACS alpha activity. Under these conditions, an after-effect duration of at least 30 min was reported, i.e., the alpha power did not return to baseline within the observation period. Interestingly, the size of this effect depended on the level of the endogenous alpha power, i.e., it was state-dependent [46]. A follow-up experiment with 20 min of tACS stimulation further increased the post-stimulation EEG recording time to 90 min and demonstrated an after-effect duration of about 70 min [47].

Whereas these studies suggest a robust physiological tACS after-effect of more than 1-h duration, the behavioral relevance of such enduring alpha power increase is not clear, because no demanding task was introduced so far. This gap was filled only recently by another study that monitored alpha activity and performance in a mental rotation task simultaneously for a 50-min post-stimulation time period [48]. In addition to the previously described after-effect for alpha power, the task performance was also enhanced during the off-line effect (Fig. 4), indicating a behavioral relevance of alpha power for the performance in a mental rotation task which is known to depend upon the amplitude of EEG alpha oscillations [49, 50].

Underlying Mechanisms of tACS After-Effects

It is still unknown how to set the different stimulation parameters such as duration, intensity, frequency, and electrode montage in order to effectively trigger the physiological processes that generate long-lasting after-effects. Until now, only the duration of tACS has been varied. Strüber and colleagues [45] repeated the abovementioned experiment using 20 min of tACS [46], but reduced stimulation duration to intermittent trains of only 1 s. No after-effects were obtained with these short stimulation periods.

Another study applied intermittent alpha tACS of either 3 or 8 s and found after-effects only for the 8-s condition [51]. In this study, the degree of phase continuity between successive trains of tACS was also varied, but had no further effect in addition to stimulation duration. The authors interpreted this pattern of results as indicative of plasticity-related changes rather than entrainment as the responsible mechanism for after-effects. This is in line with previous work proposing a computational model of spike-timing dependent plasticity as the relevant physiological process [6].

Regardless of the specific type of plasticity involved in the origin of after-effects, current research speaks for the differentiation of the mechanisms underlying on-line and after-effects with entrainment responsible for on-line effects and plasticity for after-effects. Therefore, the so far unanswered question arises how exactly entrainment-based on-line effects transfer into plasticity-based after-effects [44].

tACS in Neuropsychiatric and Neurological Disorders

Beside their fundamental role in normal sensory, motor, and cognitive functioning, brain oscillations have also been related to neuropsychiatric disease. The underlying logic is that pathological changes of brain oscillations for which a strong link to specific sensory-motor or cognitive processes has been demonstrated in the healthy brain may serve as clinical phenotypes or biomarkers in psychiatric disorders [52, 53]. Prominent examples of such 'oscillopathies' are abnormal gamma oscillations in schizophrenia [54] and impaired alpha oscillations in affective and post-traumatic stress disorders [55]. Oscillatory alterations in specific frequency bands or in the interaction between different frequencies have also been associated with Parkinson's disease (PD), attention deficit/hyperactivity disorder (ADHD), Alzheimer's disease (AD), bipolar disorder (BD), dyslexia, and autism [56–58].

Given this connection between oscillatory brain activity and psychiatric illnesses together with the documented effectiveness of tACS in modulating brain oscillations as the main mediators of cognition, it has been proposed recently to use tACS for the treatment of pathological brain rhythms in mental illness [9, 59]. However, compared to other tES methods [60], the development of tACS as a neurotherapeutic tool is

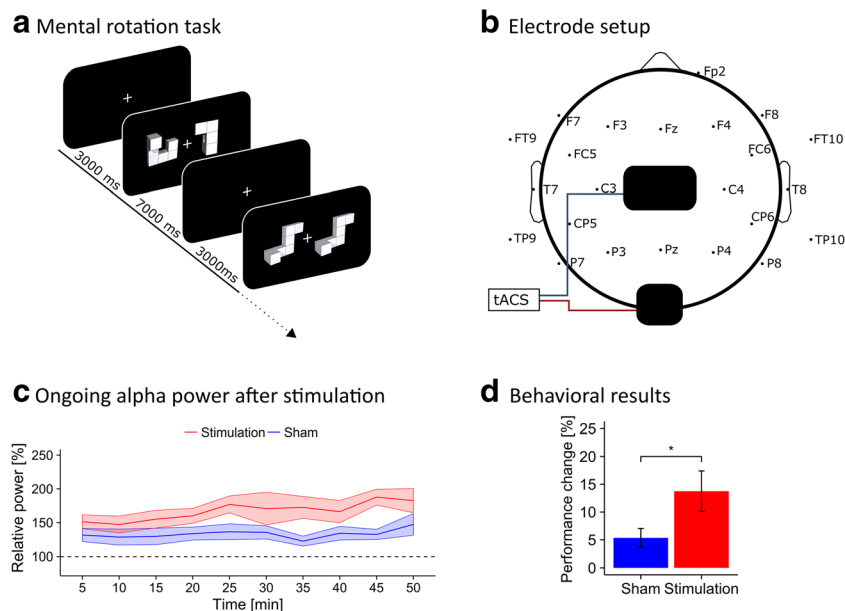


Fig. 4 **a** Mental rotation task. Each trial started with the presentation of a white fixation cross at the center of the screen. After 3000 ms, a mental rotation stimulus appeared and remained on screen for 7000 ms. During this time, participants had to decide whether the two presented figures were identical (but rotated) or different. **b** Electrode setup. tACS electrodes (black) were located at Cz and Oz. EEG was measured from 23 positions following the international 10–10 system with electrode sites above or close to tACS electrodes left blank. **c** Ongoing alpha power after

the end of stimulation relative to a baseline period prior to stimulation. Time-course of ongoing alpha power after tACS at individual alpha frequency (red) or sham stimulation (blue). The dashed line indicates the ongoing alpha power before stimulation (baseline period). Shaded areas depict SEM. **d** Behavioral Results. Overall performance increase of the mental rotation task for stimulation (red bar) and sham (blue bar) group. Asterisks depict significant differences ($* < 0.05$). Error bars depict SEM. Adapted from Kasten and Herrmann [48•]

still at its very beginning and direct evidence for successful tACS interventions in neuropsychiatric patients with cognitive impairment is scarce, but first promising examples are emerging.

Building on the first published report of declarative memory enhancement following slow otDCS at 0.75 Hz during sleep in healthy participants [61], similar effects could be demonstrated in patients with temporal lobe epilepsy [62], schizophrenia [63], and ADHD [64]. Whereas these findings underline the role of slow-wave sleep for memory consolidation in different patient populations displaying memory deficits, a recent study successfully applied frontal slow otDCS at night to improve daytime behavioral inhibition in boys with ADHD [65•].

In addition to these sleep-related otDCS protocols for treating cognitive impairments, the therapeutic potential of tACS has also been demonstrated in neurological disorders for vision rehabilitation in optic neuropathy or after unilateral occipital stroke [66, 67], reduction of dystonic symptoms and pain in idiopathic cervical dystonia [68], and for influencing dysfunctional oscillatory networks in PD [69, 70]. For tinnitus suppression, however, tACS was largely ineffective as compared to other forms of tES [71, 72].

In an elegant study using a closed loop design to reduce tremor amplitude in PD, tACS was applied at the individual tremor frequency [73••]. In this study, a continuous

adjustment of the phase relationship between tACS over the motor cortex and individual tremor frequency induced an optimal phase cancellation between online and induced oscillatory activity resulting in a 50% reduction of tremor amplitude.

Conclusion

The main obstacle for a better understanding of how tACS impacts on oscillatory brain activity during stimulation is the huge artefact contaminating the simultaneously recorded EEG/MEG data. One approach to resolve this problem is the development of artefact correction algorithms, which allowed the first direct evidence for tACS-induced entrainment. However, current artefact removal methods are not perfect and residual artefacts may remain in the data or over-correction may occur. Therefore, researchers should estimate the size of residual artefacts resulting from their method of artefact removal and should demonstrate that the effects of tACS stimulation exceed the possible residual artefact. A fruitful complementary approach to post hoc artefact removal is to enable a dissociation of artefact and on-line effect as recently exemplified by amplitude modulated tACS, cross-frequency tACS, and tACS using non-sinusoidal waveforms. Even the avoidance of tACS artefacts was demonstrated recently by utilizing non-electrical physiological measures

that are obtainable by fMRI. Along the same lines, future tACS studies might profit from a combination with near-infrared spectroscopy (NIRS). tACS after-effects of varying duration have been consistently reported but the underlying mechanism is still far from being clear. One possibility is that entrainment during stimulation has to continue for a minimum time before it leads to the subsequent off-line effect, probably via some form of neural plasticity. However, future studies in animals are required to reveal how tACS on-line effects translate into after-effects. This would not only help to better understand the functional roles of brain oscillations but also to develop more targeted clinical stimulation protocols.

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Compliance with Ethical Standards

Conflict of Interest Dr. Herrmann has received honoraria as editor from Elsevier Publishers and has filed a patent application for transcranial electric stimulation.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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