Trends in Cognitive Sciences

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Review

Neurocognitive, physiological, and biophysical effects of transcranial alternating current stimulation

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Transcranial alternating current stimulation (tACS) can modulate human neural activity and behavior. Accordingly, tACS has vast potential for cognitive research and brain disorder therapies. The stimulation generates oscillating electric fields in the brain that can bias neural spike timing, causing changes in local neural oscillatory power and cross-frequency and cross-area coherence. tACS affects cognitive performance by modulating underlying single or nested brain rhythms, local or distal synchronization, and metabolic activity. Clinically, stimulation tailored to abnormal neural oscillations shows promising results in alleviating psychiatric and neurological symptoms. We summarize the findings of tACS mechanisms, its use for cognitive applications, and novel developments for personalized stimulation.

Highlights

Transcranial alternating current stimulation (tACS) is a non-invasive method for brain stimulation. It is the application of alternating currents to the scalp that pass through head tissues and create an electric field in the brain, which modulates neural activity.

The induced oscillatory electric fields can bias neural spike timing, synaptic plasticity, and long-range coherence.

Neurophysiological effects can translate into changes in brain oscillatory power, frequency, and phase connectivity. Thereby, tACS can modulate cognitive and behavioral processes.

tACS-induced brain modulation enables therapeutic applications in neurological and psychiatric conditions.

Personalizing stimulation parameters such as intensity, waveform, and location can improve tACS efficacy. Further, advances in higher-dose interventions, multi-electrode network stimulation, and adaptive closed-loop applications show promise for future research.

Controlling neural oscillations

The synchronous and periodically fluctuating balance between excitatory and inhibitory circuits of connected neuronal populations manifests as neural oscillations [1–3]. These rhythmic waves of brain activity drive multiple physiological and behavioral processes in the sensory, motor, and cognitive domains [4–9]. Further, abnormal oscillatory patterns have been observed in psychiatric and neurological disorders [10–14]. Thus, there is an increasing interest in developing tools to externally control neural oscillations for research and therapy.

tACS (see Glossary) is a method that can be used to manipulate neural rhythmicity in a non-invasive way. The past 5 years have seen a large increase in registered clinical trials to explore the beneficial effects of tACS on psychiatric and neurological symptoms [11,13–16]. This increase accompanies growing interest in the physiological and biophysical mechanisms of tACS. The original 'working hypothesis' was predicated on the idea of **entraining** neural populations [1–3]. Entrainment refers to the temporal locking of one signal or oscillation to another. For tACS, ongoing brain rhythms are aligned with an external **alternating current (AC)** (Figure 1). However, more recent work highlights the additional complex and non-linear interactions of the applied sinusoidal current with ongoing neural spiking activity [2,17].

This review first discusses *in vitro* single-neuron and computational studies and expands into whole-brain stimulation effects on *in vivo* intracranial recordings in rodents, non-human primates, and humans. We then present an ongoing debate regarding tACS mechanisms and their translation into cognitive-behavioral outcomes. Finally, we highlight upcoming tACS trends in cognitive research and clinical applications.

Biophysical and physiological mechanisms of alternating current stimulation

During tACS, weak oscillating electric currents are applied to the scalp, typically ranging from 1 to 4 mA in humans. Before reaching the brain, the currents partially shunt via tissues surrounding the

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brain such as skin and CSF because of limited skull **conductivity**. The **electric field** created in the brain, which is the acting force of AC stimulation [1,18], is expressed as **voltage** per meter (or millivolts per millimeter, mV/mm) and ranges between 0.1 and 1 mV/mm [19,20]. These externally generated fluctuating electric fields are weaker than required for generating an action potential in a steady-state neuron but are on the scale of intrinsic local field potentials (LFPs), which are measured at 1–4 mV/mm [21]. Thus, instead of generating action potentials, tACS causes rhythmic fluctuations in neuronal membrane potentials and can bias spike timing, as evidenced by *in vitro* and *in vivo* studies [1,18] (Figure 1).

Evidence from *in vitro* and *in vivo* rodent studies

Evidence that weak extracellular oscillating electric fields can change neuronal activity *in vitro* goes back 40 years [1,18,22–27]. Studies in anesthetized rodents and rodent slices have elegantly shown that oscillatory electric fields of ~0.7–1 mV/mm at natural brain rhythms (<100 Hz) cause fluctuations in neural transmembrane potentials [28]. These fluctuations significantly entrain neural activity [29–31]. Detailed reviews of tACS-induced entrainment at the cellular level and in rodents are available in the literature [21,32]. In the following we highlight key conclusions that can be drawn from these data.

First, although entrainment effects are typically frequency-dependent, the relationship between **stimulation frequency** and the neurophysiological response is not simple and remains under investigation [18,24,26,27]. Some studies demonstrated larger modulations of spike timing at lower frequencies (<10 Hz), whereas modulation at high frequencies (>20 Hz) required higher **stimulation intensities** [18,24]. Other studies found increased spike timing coherence using 30–50 Hz AC fields at intensities as low as 0.5 mV/mm [24,26,27]. Further, stimulation at frequencies precisely aligned to the intrinsic oscillations (e.g., individual alpha peak) showed higher stimulation effectiveness [29]. One hypothesis suggests that stimulation frequencies closer to the natural frequency are the most effective, following **Arnold tongue** phenomenology [33]; however, this dependency is not always seen [24].

Second, single-cell models showed that pyramidal neurons are more sensitive than other cells as a result of their elongated morphology [34–36]. Nevertheless, pyramidal neurons in isolation do not explain all tACS mechanisms. Neural network models with interacting inhibitory and excitatory neurons alter the responsiveness to tACS [25,37–39]. The specific cytoarchitecture and excitatory/inhibitory balance of a region will strongly determine susceptibility to tACS [23].

Finally, research in animals under anesthesia has the consequential limitation that brain metabolism and neural excitability are significantly suppressed [40]. Stimulation in behaving rats shows that lower minimal effective doses (electric fields of ~0.25–0.5 mV/mm) are necessary to induce entrainment [28]. However, the behavioral state of the animals plays a crucial role [29].

Evidence from non-human primate studies

The principal limitations of studies on small mammals are their lissencephalic and smaller brains [41] and cytological differences relative to primates [42,43]. As such, the most informative research model is an awake non-human primate [2,3,17,44,45]. Several recent studies demonstrated phase-locking of ongoing neural spiking to the tACS-induced oscillations at ≤0.3–0.4 mV/mm [2,3]. Both phase-locking and the percentage of entrained neurons increase with higher intensities [2] in a frequency-dependent manner [3]. Further, these effects arise even when peripheral somatosensory inputs are blocked [45]. None of these studies found a significant effect on the overall firing rate [2,3,17,45]. *In silico* results suggest that tACS induces an increase in firing rate only at doses well above the tolerable intensity range in humans [35].

Glossary

Alternating current (AC): an electric current that periodically reverses its direction and changes its magnitude over time. Typically, AC refers to a sinusoidal current waveform without an offset.

Arnold tongue: a mathematical concept from dynamical systems theory that describes the susceptibility of an intrinsic oscillatory system to entrainment by an external force. Accordingly, the closer the frequency match between intrinsic and external oscillations, the less force is needed to cause entrainment.

Conductivity: the ability of tissues and materials to conduct electric current. Conductivity (in siemens per meter, S/m) is the opposite of impedance (in ohms).

Electric field: the physical vector field, the force that a charged particle would be subjected to at a given point of space. The electric field is directly proportional to the electric current and is measured in volts per meter (V/m) or, commonly in the tACS literature, in millivolts per millimeter (1 mV/mm = 1 V/m).

Electrode montage: an arrangement of tACS electrodes on the scalp and skin. It is typically referenced according to the 10–10 electroencephalographic nomenclature. Note that the stimulation electrodes can have various sizes and shapes, but often only the center location of the electrode is specified.

Entrainment: a temporal locking process in which the signal or oscillation of a system aligns with the signal of another system. For tACS, ongoing brain activity becomes temporally aligned with the external AC oscillation.

Stimulation frequency: a key parameter of tACS that indicates the number of AC cycles per second (in hertz, Hz). Most studies use frequencies in the electroencephalographic range (0.5–150 Hz), although some studies employ up to 10 kHz.

Stimulation intensity: the amplitude of the applied AC from the peak of the electric current waveform to the baseline (peak-to-baseline amplitude, in milliamperes, mA). Note that an alternative definition (peak-to-peak amplitude) also exists in the literature. The current intensity is the primary input parameter for tACS devices and typically is in the range of 0.2–4 mA.

Transcranial alternating current stimulation (tACS): the non-invasive application of an alternating electric current via scalp electrodes to affect brain activity.

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Together, non-human primate studies offer convincing evidence of tACS-induced neural entrainment at the practical electric field strengths of ~0.3 mV/mm [28], corresponding to ≥2 mA in humans [19,20] (Figure 2, left panel).

Although neural entrainment is a key mechanism, possible collateral effects were observed. First, investigators found increased neural spiking burstiness during tACS without affecting the overall firing rate [2]. This suggests a putative modulation of neural criticality. Second, it was shown that naturally entrained neurons (to intrinsic oscillations) can change their phase preference during tACS at the same frequency [17]. In such neurons, low stimulation doses can even disturb

Voltage: an electric potential between two points, in other words, 'pressure' on electric current to flow (in volts, V). When we aim to reach a specific stimulation intensity, the required voltage is inversely proportional to impedance (according to Ohm's law).

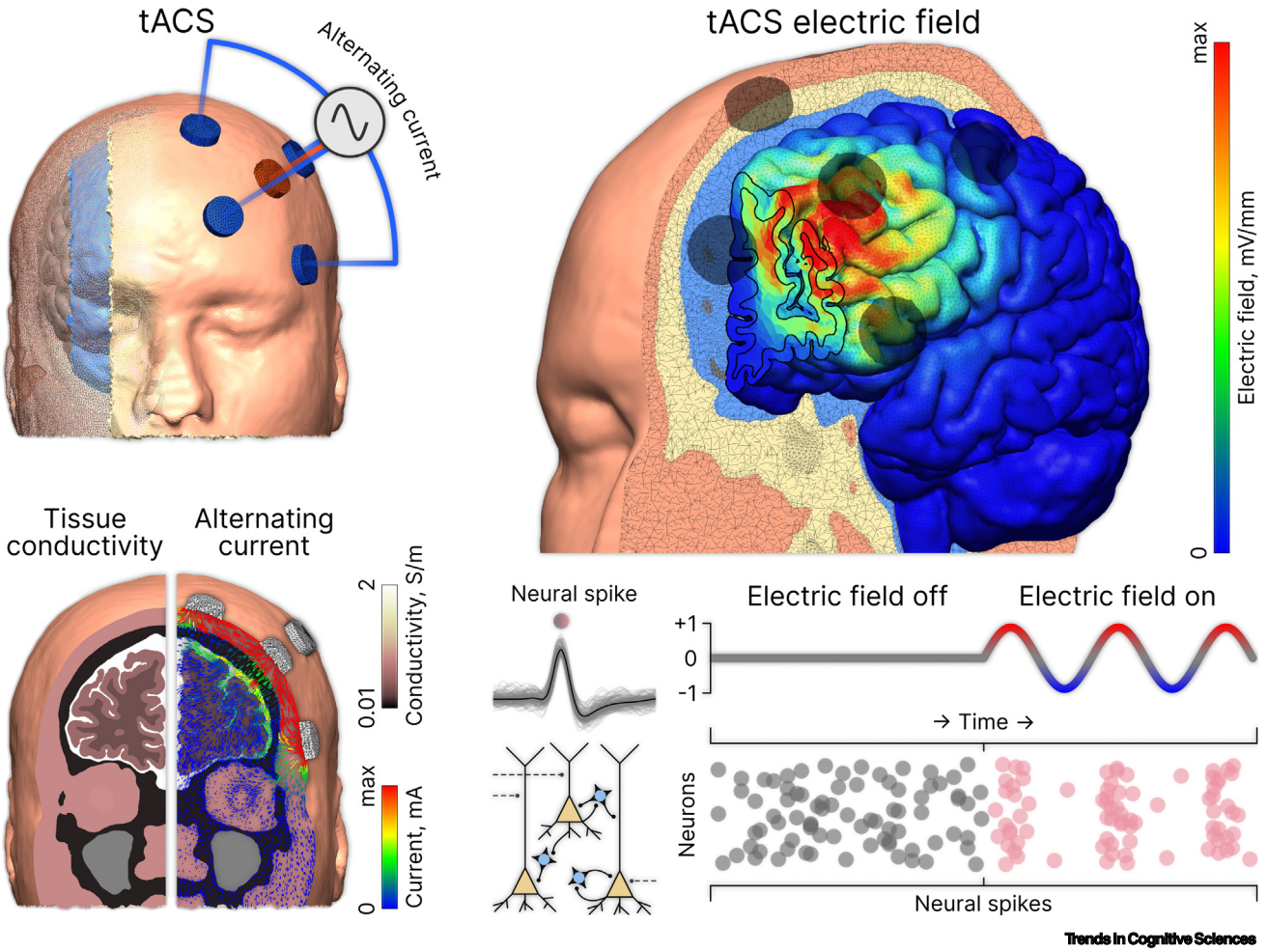

Figure 1. Biophysics of transcranial alternating current stimulation (tACS). (Top left) During tACS, an alternating current (AC) is applied between two or more electrodes placed on the scalp. Current flows between electrodes of opposing phase (indicated here with red and blue). The sum of electric currents at all stimulation electrodes needs to be zero (Kirchhoff's circuit rule). For multi-electrode montages, the stimulation intensity per electrode should be adjusted accordingly. AC passes through the scalp, skull, and cerebrospinal fluid and penetrates the brain. (Bottom left) The resulting electric current in the head depends on the stimulation 'montage' (electrode locations and current intensity per electrode) and the conductivity of the biological tissues. Owing to the low conductivity of the skull, shunting in the scalp can occur if electrodes are placed too close to each other (approximately <3 cm), resulting in close-to-zero electric field intensity in the brain [149]. Although we can control the montage, conductivity is a biophysical property. It is noteworthy that conductivity values differ between individuals, meaning that computational modeling of electric field intensities should be viewed as an estimate [143,144]. (Top right) The AC creates an electric field (in mV/mm) which is the acting force (i.e., 'dose') of neuromodulation. Electric fields generally become weaker in deeper cortical structures. (Bottom right) When the electric field strength in the brain is sufficient, it biases the timing of neural action potentials (i.e., neural spikes) [2,3]. The total spike count per time most often remains constant at the effective doses reached in human research, namely ~0.3–1 mV/mm, corresponding to a total external current intensity of 1–4 mA.

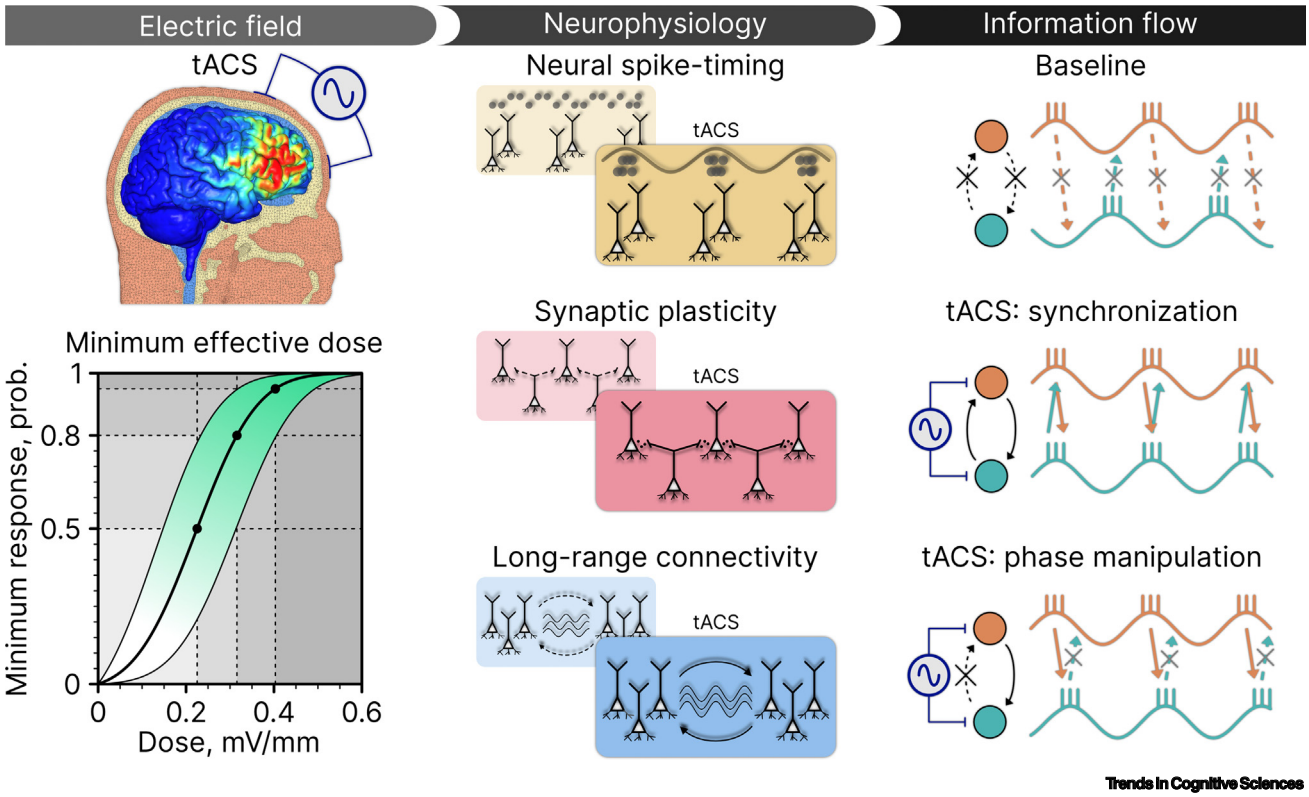

Figure 2. Physiological mechanisms of action. Transcranial alternating current stimulation (tACS) electric fields in the brain can affect information flow, and thus cognition, through various neural mechanisms. (Left) Reaching sufficient electric field strength is crucial for successful intervention. A recent meta-analysis [28] on awake rodent and non-human primate data has shown that a dose of ~0.3 mV/mm has an 80% probability of modulating brain activity. A 95% probability (prob.) corresponds to ~0.4 mV/mm across the whole region of interest. These levels form an estimate of the minimum effective dose of tACS. (Middle) With sufficient dosage, tACS can affect brain physiology in three ways. First, tACS can modulate neural spike timing, causing biased neural spiking and local neural entrainment [2,3]. This effect primarily occurs online, during the stimulation. Second, tACS can induce NMDA receptor-mediated synaptic plasticity with long-lasting effects [53]. Third, tACS over two or more regions can strengthen or weaken long-range connectivity by synchronizing affected areas to the same or different alternating current (AC) phases [6,60,107]. Multiple mechanisms can be engaged at the same time. (Right) By modulating oscillations, tACS can affect brain communication through coherence [58]. That is, tACS can synchronize the time-windows of neural depolarization when cells are more likely to generate action potentials, thus promoting information flow. Specifically, the effects of tACS on neural entrainment and synaptic plasticity can promote communication within local networks and regional task-related processes. Enhancing long-range connectivity through phase-dependent tACS can strengthen communication between distant networks and task-specific network activity. Choices of tACS parameters (electrode locations, waveforms, dose) and concurrent brain state influence the involvement of different mechanisms, which will determine the effects on cognition and behavior.

local synchrony, whereas higher doses eventually overwrite the baseline phase relationship and entrain neural activity [17]. Because low-dose tACS can both increase [2] and decrease [17] entrainment depending on the baseline neural activity, future research should consider a non-linear dose dependency. Higher doses of 2–4 mA in humans can be favorable for achieving robust net-positive entrainment.

Intracranial human evidence

Despite the crucial insights that awake animal studies have provided, remaining cytoarchitectonic and anatomical differences in the brain and surrounding head tissues [41,46] complicate the translation of results to humans. Fundamental human research relies on surgical epilepsy patients for their invaluable invasive brain recordings [19,20,47] because non-invasive recordings using magneto/electroencephalography (MEG and EEG; referred to as M/EEG for both) are highly contaminated with technical artifacts from tACS [48,49]. Key insights into tACS dosing have come from surgical epilepsy patient studies [19,20], and these found an approximate relationship

between the stimulation intensity and the maximum generated electric field ('dose') that was in the range ~0.4–0.5 mV/mm per 1 mA from peak to baseline. Despite substantial variability between individuals and **electrode montages** [50], these findings further validated computational electric field modeling (Box 1) and linked physiological mechanistic studies to human applications. Further, one study aimed to entrain sleep spindles (10–14 Hz activity) in epilepsy patients using tACS at a slow wave frequency (0.75–1 Hz) with electric fields in the brain ≤0.16 mV/mm [47]. Possibly owing to low dose or indirect measurement, because sleep spindles are imperfectly correlated to slow waves, the study found no stimulation effects. The dose-response and tACS mechanisms in humans remain under investigation, leaving fundamental studies in awake mammals as the most reliable source for planning and interpreting human studies.

Interactions of tACS, human brain, and cognition

Even though tACS affects single-neuron activity, a crucial follow-up question concerns how it interacts with ongoing neural dynamics in the active human brain (Figure 2). We describe several non-mutually exclusive mechanisms.

Effects on neuronal spike timing

The original hypothesis of tACS states that exogenous AC could entrain endogenous neural firing (Figure 2, middle panel). As discussed before, entrainment occurs consistently in a significant number of neurons when tACS electric field values are above 0.3–0.4 mV/mm, and stronger electric fields recruit more neurons [2,3,17] (Figure 2, left panel). In human experiments performed to date, electric fields rarely exceed and are often smaller than these values, meaning that strong

Box 1. Computational head modeling for tACS

Computational models can predict the tACS-induced electric field in the brain. Numerical modeling software has become standard in human research to plan stimulation protocols. A typical modeling pipeline includes whole-head anatomical MRI, tissue segmentation, 3D model generation, electrode placement, assignment of tissue conductivities, and numerical solution. The outcome is an electric field vector E at all brain locations that can be further analyzed.

Magnitude: the electric field magnitude $|E|$ indicates the stimulation strength at a given location (in volts per meter, V/m), a key parameter for dosing.

Focality: stimulation focality is the area or volume where $|E|$ exceeds a given threshold, for example, 50% of the maximum in the brain. Focality can be expressed in absolute (cm^2 or cm^3) or relative units as a fraction of the total brain volume.

Direction: neurons are typically most sensitive to the electric field along their somatodendritic axis. In the neocortex, large pyramidal neurons are oriented perpendicular to the cortical surface. Thus, investigating the angle of E relative to the brain surface can be insightful for neurophysiological interpretation. In practice, this can be implemented by separating E in directional components such as the tangential and perpendicular electric fields.

Computational models have greatly improved our understanding of the tACS biophysics and can inform stimulation design and dosing. However, modeling technologies are still being actively developed, and current models have limitations. First, anatomical MRI and segmentation (required for model generation) have a limited spatial resolution. Thus, thin structures such as CSF and meninges, which are important for modeling results, might not be well represented. Second, tissue conductivities are often based on *ex vivo* measurements and population averages. Nevertheless, individual differences in tissue conductivities are substantial and can result in considerable uncertainty in the electric field estimates per individual. Finally, experimental factors, such as precise electrode placement or leakage of electrode gel or saline, will result in further uncertainties.

Despite these limitations, modeling results are usually robust to minor uncertainties. Further, uncertainty quantification methods can estimate an error bound of modeling results using probabilistic simulations. Typically, within-subject comparisons are more reliable, because they share the same model uncertainties, than between-subject comparisons.

In conclusion, computational modeling is crucial for tACS experimental design and interpretation. New multiscale models combining electric field simulations with neuronal models are a promising avenue for future developments in computational dosing selection.

entrainment is unlikely. However, even in the absence of entrainment, weak fluctuations in neural membrane potentials can temporally bias spike timing [2,3,17]. This means that action potentials are more likely to occur during some states of an AC oscillation than at others, thus synchronizing spiking in the affected brain area. This effect may be further amplified when the targeted brain rhythm is already task-engaged and the frequency and phase of endogenous and exogenous oscillations align [9,51]. Therefore, in human cognitive experiments, biasing spike timing in task-engaged neural circuits with tailored tACS may not require outright strong entrainment.

Effects on synaptic plasticity

A crucial question for clinical translation concerns whether tACS effects outlast the duration of stimulation. Data suggesting neuroplastic effects show, for instance, that alpha tACS over the visual cortex increases alpha power and visual evoked responses after the stimulation ended [9,52]. One study provided direct evidence for synaptic plasticity mediated by *N*-methyl-D-aspartate (NMDA) receptors following tACS [53]. Whereas sensorimotor stimulation at 20 Hz facilitated motor-evoked potentials and EEG spectral activity in humans for 60 min after tACS, a pharmacological NMDA receptor antagonist suppressed the after-effect. These studies support the hypothesis that tACS acts on spike timing-dependent plasticity, which arises from rhythmic coactivation with minimal temporal delay in recurrent neuronal networks [54–57]. Systematic and empirical verification of this concept is a prospective avenue for future research.

Network effects

Based on the idea that increased coherence within oscillatory networks will promote intra- and inter-regional interactions [58], various studies have investigated potential tACS effects over a single or several brain areas on network connectivity [6,53,59–63] (Figure 2, middle panel). Studies have reported tACS-induced changes in long-range EEG coherence at the stimulation frequency [53,64]. Furthermore, tACS may also promote cross-frequency coupling [5,65], for example, by superimposing two tACS rhythms of interest [5,7,66]. In fMRI connectivity analyses, tACS effects have been found on interhemispheric [61,62], intrahemispheric [59,67], and whole-brain functional connectivity [68]. Notably, these network effects are region-, frequency-, and task-specific. Thus, instead of enforcing coherence between disconnected networks, tACS modulates ongoing network activity.

Effects of tACS on cognition

tACS can affect cognitive functions through various mechanisms (Figure 2). For successful cognitive modulation, optimizing tACS parameters and targeting the direct neural source implied in the behavior of interest is paramount (Box 2). In practice, we should use experimental outcome measures and statistical approaches sensitive to neuromodulation. Ceiling and floor effects of cognitive tests should be avoided by, for example, choosing task difficulty where baseline performance is at the center of the performance range (e.g., ~75% correct in a two-choice task). When all criteria are met, tACS can change performance on tasks involving short-term and working memory [5,6,60,69–74], long-term memory [65,75–77], perception and attention [8,78–81], decision-making and learning [4,7,51,66,82–86], and language [61,87–90]. tACS effects on specific cognitive modalities are reviewed in [91,92]. Analysis of stimulation location, frequency, and task changes can elucidate the causality of brain oscillations in cognitive mechanisms. However, it is crucial to have an *ad hoc* mechanistic cognitive hypothesis and select tACS parameters accordingly. We consider below four principal approaches to cognitive modulation.

Modulating homeostatic cognitive systems

tACS can enhance a dominant or task-specific neural rhythm that is otherwise reflected in local EEG power [4,9,74,77]. This is typically done in a single local brain area using a simple two- or

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Box 2. Brain imaging of tACS effects in humans

The non-invasiveness of tACS is a methodological strength for cognitive and clinical applications but a challenge for basic research which aims to understand tACS mechanisms at the finest level that only invasive imaging can offer. Nevertheless, several non-invasive neuroimaging modalities can partially elucidate the neural mechanisms of tACS by connecting it with cognitive and behavioral measurements. These modalities differ in their spatiotemporal properties and in the interpretation of the underlying neural activity.

Electrophysiology

Magneto- and electroencephalography (MEG and EEG; referred to as M/EEG for both) provide direct and widely available recordings of large-scale electrophysiology in humans. These methods measure the neuroelectrical activity with high temporal and limited spatial resolution. M/EEG could give clear insights into tACS mechanisms; however, studying immediate or online effects is immensely challenging due to large stimulation artifacts that obscure the physiological responses. Most studies using M/EEG resort to pre-/post-stimulation measurements of brain oscillations, known as offline designs, that capture outlasting entrainment echos and putative neuroplastic changes. Thus, standard electrophysiological techniques can provide a direct but offline readout of tACS effects.

Hemodynamics

fMRI and near-IR spectroscopy (NIRS) can characterize the changes in cerebral blood flow which are coupled to local neural activity. Hemodynamic neuroimaging provides moderate-to-high spatial resolution and is less affected by stimulation artifacts than M/EEG. Thus, both online (immediate) and offline measurements are employed. These advantages come at the cost of low temporal resolution, high analytical complexity, and inherent uncertainty regarding the interpretation of hemodynamic changes across diverse cytoarchitectonic brain areas. Although indirect, hemodynamic neuroimaging is a viable option for online non-invasive measurements of tACS-induced neurophysiological changes across the whole brain.

Brain reactivity

One way to infer a brain state is by perturbing it and observing the response. Applying a suprathreshold stimulation to a specific brain region with transcranial magnetic stimulation (TMS) is a popular option. TMS probing is particularly informative in the motor cortex, where one can measure a motor evoked potential (MEP). An MEP reflects the strength of the muscle response following a standardized single pulse to the brain, thus providing a measure of corticospinal excitability. It is straightforward to assess motor cortex reactivity concurrently (online) or pre-/post-tACS (offline). In other brain areas, offline M/EEG can capture changes in TMS-evoked potentials similar to event-related potentials. TMS-evoked potential amplitudes can approximate the local excitability, although measurement noise and somatosensory confounds remain a challenge.

multi-electrode montage (Figure 2). Such stimulation enables causal tests of correlations between the M/EEG power and behavior. For example, one group recorded sleep spindles, which are essential for memory consolidation, and applied frontal tACS at the sleep spindle frequency (12 Hz) [77]. The tACS-induced increase in sleep spindle activity resulted in improved procedural memory consolidation, showing direct causality.

However, some cognitive functions underlie the activation of a brain network with multiple neural oscillatory generators at different frequencies. These different oscillations may reflect concurrent processes that represent a trade-off. Various research has shown that delta/alpha, delta/beta, and theta/beta ratios predict cognitive performance following an inverted U-shape [4,93,94]. That is, the optimal balance or homeostasis between neural oscillations leads to optimal performance, and overactivity of either oscillation leads to suboptimal performance [4,10,93,95]. This relates to behavioral compromises, such as a trade-off between speed and accuracy [4,84], effort versus reward [96], stability versus flexibility [10,97], or exploration versus exploitation [86]. Consequently, single-frequency tACS can improve performance in one domain over another (Figure 3). For instance, in the stability versus flexibility case, frontal low-frequency oscillations (delta/theta) encode uncertainty, conflict, novelty, and errors, and thus drive behavioral flexibility [97]. Delta/theta tACS increases exploratory behavior and cognitive flexibility but may disrupt response inhibition [4,10]. High-frequency oscillations (beta/gamma) are associated with cognitive

control and maintenance of information [98]. Beta/gamma tACS improves distractor inhibition and exploitative behavior but may reduce flexibility [84,99].

Thus, when researchers use single-frequency tACS, they should examine homeostatic effects on the entire brain system. If M/EEG is used to test tACS after-effects, it is sensible to analyze all frequency bands across the whole head. Similarly, a whole-head analysis should be conducted for tACS–fMRI studies. Given the limitations of physiological resources, an increase in local power may lead to a power decrease elsewhere [95]. It can also be valuable to distinguish tACS effects on periodic and aperiodic M/EEG signals [100]. If a cognitive task involves behavioral trade-offs, both dimensions should be considered and reported (e.g., accuracy and reaction time). Standard analyses of outcome measures may benefit from computational modeling analyses such as drift diffusion modeling [67,85,101].

Modulating nested oscillations

Whereas for some cognitive mechanisms brain oscillations compete or are independent, for other functions they operate in harmony (Figure 2). Intraregional cross-frequency coupling between theta and gamma oscillations or between delta and beta are prominent examples [5,7,66,102]. Specifically, the phase of the low-frequency oscillation can modulate the amplitude of high-frequency oscillations, known as phase–amplitude coupling or nesting [103]. This synchronization between global and local oscillatory processes is crucial for optimal inter-regional communication (Figure 3). For example, frontoparietal synchronization underlies global communication reflected by theta activity and local processes associated with gamma activity. One hypothesis about local nested oscillations is that the gamma/theta ratio encodes the storage of memory engrams, where the number of gamma cycles per theta oscillation defines capacity [104]. As such, tACS at a frequency below the endogenous theta rhythm may be effective in improving executive functions [73,105]. This tentative hypothesis calls for further investigation, but it suggests that the optimal stimulation frequency for some tasks is not the same as the natural peak frequency. Instead, cognitive enhancement may result from a down- or upshift of ongoing oscillations [73].

Furthermore, instead of stimulating either a low- or high-frequency component, one can apply cross-frequency tACS. Initial research found that an electric current with gamma oscillations (40–200 Hz) nested in a theta cycle (6 Hz) improves spatial working memory performance [5]. The effect was particularly pronounced for nested oscillations in the high gamma range, peaking at 80–100 Hz. Furthermore, cross-frequency tACS was shown to interfere with long-term memory [106] and improve cognitive control [66], binaural integration [61], and motor skill acquisition [7].

Modulating long-range coherence

According to the communication through coherence hypothesis, information transfer occurs through the oscillatory synchronization of two distal brain regions [58]. Therefore, the oscillation phase is an important variable when using tACS to strengthen long-range connectivity between several areas (Figure 2). Multi-electrode stimulation can manipulate the phase of brain oscillations in distinct cortical targets [107,108]. The initial hypothesis was that tACS over two regions with in-phase stimulation synchronizes the regions, whereas desynchronization occurs when an opposing phase is used [60]. Consequently, synchronization improves long-range communication and should boost behavioral performance (Figure 3). In-phase frontoparietal tACS has been shown to improve working memory performance, whereas anti-phase stimulation did not [6,60]. In another example, bihemispheric visual cortex in-phase, but not anti-phase, tACS led to improved performance on a stroboscopic alternative motion task [78]. However, others have found no clear dichotomy in behavioral performance [67,84,109]. Binary phase manipulation (in- vs. anti-phase) is limited in its translation to biophysical mechanisms and does not consider electric fields

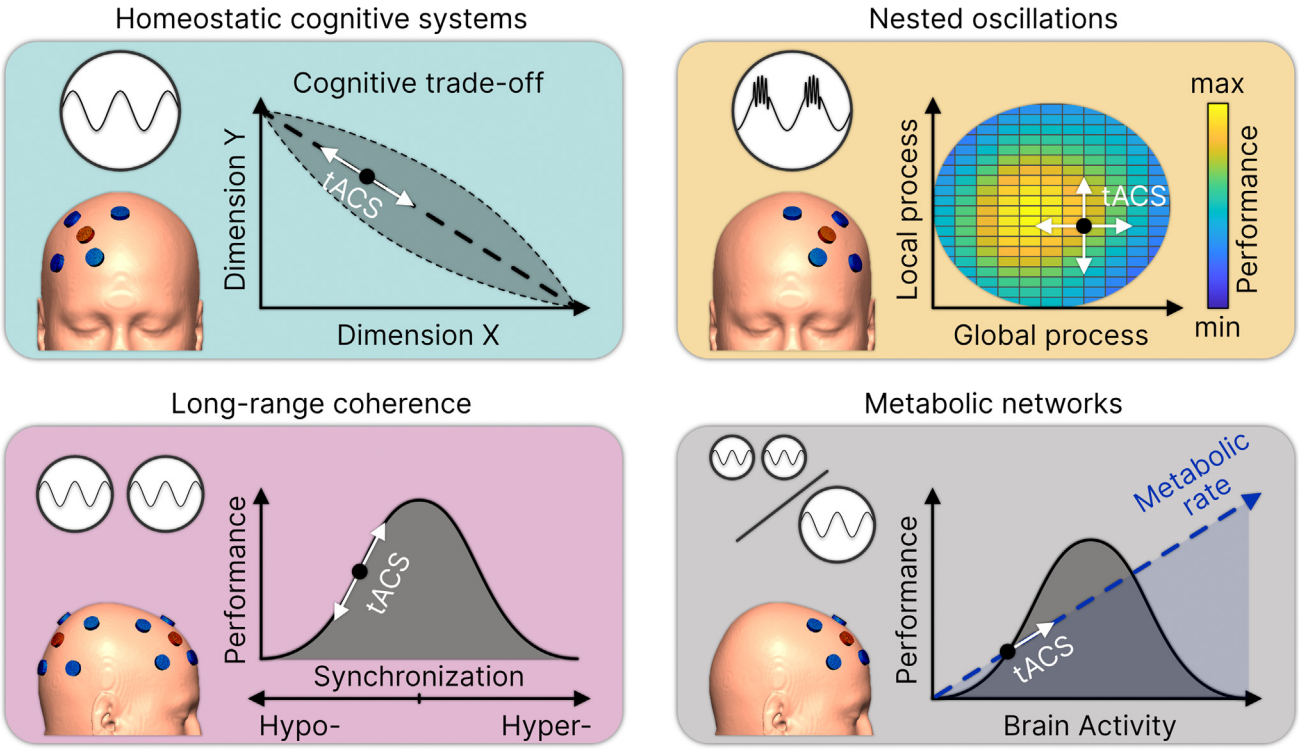

Figure 3. Effects of transcranial alternating current stimulation (tACS) on cognitive performance. How tACS modulates behavior depends on the stimulation parameters, target brain area, and cognitive domain. We present four non-mutually exclusive hypotheses for tACS mechanisms. (Left upper) Some cognitive domains underlie a trade-off between competing processes, for example, speed versus accuracy or stability versus flexibility in decision-making [4,93]. If distinct neural oscillatory generators drive these competing processes, single-frequency tACS may improve one dimension and shift the balance between them. (Right upper) Phase–amplitude coupling or nesting of multiple oscillations reflects the integration of global and local processes in brain networks [102,103]. Canonically, high-frequency oscillations characterize local information processing, whereas low-frequency oscillations involve inter-regional communication. Cross-frequency tACS can modulate nested oscillatory activity towards an optimal ratio, which improves cognitive performance [5,7,66]. (Left lower) Long-range synchronization is crucial for information exchange between distal brain regions. Hypo- or hypersynchronization yields suboptimal behavioral performance. Multi-area tACS can modulate the phase of several oscillatory generators by driving them in-phase, anti-phase, or with a phase shift [6,60,107]. (Right lower) Enhanced brain activity can demand higher metabolic activity, including glucose and oxygen uptake. Early-stage evidence suggests that tACS may affect metabolic activity [112,113]. As such, changes in metabolic rate through tACS could drive cognitive performance.

and biological signal transmission times, as demonstrated by phase lags between regions [110,111] (Figure 2, right panel). One should optimize the phase of induced oscillating electric fields rather than the phase of applied current, which can differ depending on the electrode montage [107]. When optimized, multi-electrode tACS can impose smooth gradients of phase changes, known as traveling waves [107]. As such, investigators can match the natural phase connectivity using phase-shifted stimulation.

In addition to phase differences, inter-regional differences in frequency need to be considered when modulating behavior. As elegantly shown by several research groups, investigating separate but interacting oscillations improves our understanding of cognitive phenomena. For instance, Reinhart and Nguyen [71] showed that frontotemporal theta tACS improves theta–gamma phase coupling between these regions and, by extension, working memory in elderly individuals.

Modulating metabolic networks

There is early-stage evidence that transcranial electric stimulation directly or indirectly influences metabolic brain networks and neurovascular coupling [112,113], and this has profound

implications for cognitive processes [114]. A direct effect can arise because the electric current density in the brain at the microscopic level is locally stronger across the blood–brain barrier owing to sharp differences in conductivity between the blood and brain parenchyma. As a result, the local electric field may be sufficient to affect vascular structures and induce vasodilation [112]. Investigators found frequency- and dose-dependent changes in cerebral blood flow during tACS in basic research [115] and human cognitive studies using fMRI [59,63,72,116–118]. Human research shows that the stimulation impact can be spatially specific to the target location or spread outside it along the default mode, frontoparietal, or dorsal attention networks. These data are consistent with the abovementioned observations that tACS can improve long-range brain connectivity. Nevertheless, there is no systematic understanding of metabolic findings to date, and individual studies suggest either an increase [6,59,117,118] or a decrease in blood oxygenation signals [6,59,63,72,118] that can last during the stimulation [6,72,118] or significantly longer [59,63,117]. This variability arises from variable brain states (task vs. rest), stimulation frequencies, and fMRI modalities, and this aspect warrants further research.

Clinical translation of tACS

Given the possibility of modulating behavior, tACS has excellent potential as a low-cost clinical tool in treating psychiatric and neurological disorders [11–16,74,99,119–125]. However, because tACS targets neural oscillations, a clear picture of oscillatory abnormalities is paramount. Clinical scientists should identify local or global deficits or overactivity in specific oscillations to formulate testable hypotheses (Figure 3). In addition, it is important to remember the limitations and best practices of the method (Box 3). For example, suboptimal cognitive performance and mental disorders can be characterized by frequency-unspecific hypo- or hyperactive brain regions. Although tACS can entrain neural populations, it does not significantly alter firing rate [2,3,17,35]. In such cases, other neuromodulation tools (e.g., transcranial magnetic stimulation or direct current stimulation; TMS or tDCS) are preferred over tACS (reviewed in [92]). Furthermore, the limited focality of modern tACS means that sub-gyrus targeting is not yet possible. In addition, patient populations are more heterogeneous than healthy individuals [126]. The precise neural origin of symptoms is likely to vary on top of pre-existing interindividual differences in brain morphology and function [126]. As such, personalized stimulation location, intensity, and frequency could improve tACS treatment. Possible sources of personalization are individual brain morphology (via computational head modeling; e.g., [127]), ongoing activity and functional connectivity (fMRI and M/EEG; e.g., [128]), and behavioral symptoms (cognitive modeling; e.g., [119]).

Location specificity

All electrodes contribute to the distribution of current in the brain. Investigators should carefully select the location of tACS electrodes to ensure that the study design accounts for all affected areas, which could be between the electrodes or underneath them [50,129]. For example, a comparison of commonly used tACS montages targeting the primary motor cortex has shown them to result in drastically different effects on physiological tremor [130,131]. Further, anatomical idiosyncrasies have a significant impact on electric field distributions [50,129]. This problem is compounded in the case of structural brain damage (e.g., stroke) because abnormal tissues will significantly alter the current path [126]. If possible, investigators should optimize tACS electrode placement based on individual MRI scans and modeling [132]. For instance, bilateral frontoparietal fMRI-guided tACS reduces craving more effectively in methamphetamine use disorder patients than a standard frontoparietal montage [128]. Further, multi-electrode montages allow the isolated targeting of brain regions. A nine-electrode montage targeting the dorsolateral prefrontal cortex and inferior parietal cortex, respectively, was used to test effects on memory in elderly volunteers [74]. By this, it was shown that the effects of tACS depend on the region, neural rhythm, and memory type.

Box 3. Best practices for tACS in humans

Suggested best practices below arise from the ambition to conclude that 'modulation of the brain oscillation *X* in the brain area *Y* at the electric field strength *Z* during the brain state *W* leads to a specific outcome'. Implementing all measures may not always be feasible, but they all deserve attention.

Know!

Electric field

The electric field across brain tissues is the primary driver of the neurophysiological effects of tACS. Thus, it is important to know and report the electric field strength and direction in target and off-target brain areas. Computational modeling tools can give reasonable estimates, thereby informing stimulation dose and montage.

Brain state

Regulating brain states reduces inter- and intrasubject variability. Aim to keep experimental procedures (e.g., cognitive/behavioral tasks) and pre-experimental conditions (e.g., activity level, stimulants) constant. In addition, adding functional neuroimaging or electroencephalography can inform about ongoing brain activity.

Timeline

Immediate and outlasting neuromodulatory effects, whether for single or multiple sessions, should be distinguishable by study design. Randomization, follow-up assessments, and sufficient time between conditions can mitigate carry-over effects in crossover studies.

Target effects

Consider which brain function represents the study target (e.g., memory performance) and which functions are collateral (e.g., attention, perception, motor response). A careful study design should isolate target effects. Control tests and computational cognitive modeling can be useful.

Control!

Stimulation frequency

Direct tACS effects are frequency-specific. Their interpretation as such requires evidence that stimulation at another frequency would lead to different outcomes.

Target location

Interpretation of findings as specific to the target brain area is stronger if contrasted with off-target stimulation outcomes or a control montage.

Placebo

Sham stimulation using fade-in/fade-out or actiSham paradigms can provide a realistic baseline for measurements. Note that stimulation using off-target locations or frequencies may replace sham stimulation in some study designs.

Somatosensory effects

tACS can coactivate cranial nerves and retinal cells, thus nonspecifically modulating arousal and perception. Control conditions should mimic such activation.

Implement!

Training

Be proficient in correctly applying tACS. Onsite training for all personnel and multiple pilot experiments are highly encouraged.

Technical logs

At every session, record the exact electrode locations (e.g., using neuronavigation, individualized caps), the applied current per electrode, and impedances to reduce variability and check for technical issues.

Blinding

Ensure blinding of participants by using realistic sham conditions. Experimenters should also be blinded.

Tolerability reports

Side and adverse effects should be collected using written questionnaires which allow safety and success of blinding to be assessed.

Frequency specificity

Symptoms of brain disorders can arise due to reduced power in particular frequency bands (Figure 3). For example, alpha tACS benefits affective symptoms, whereas gamma tACS benefits cognitive symptoms in major depressive disorder (MDD) patients [14,16,119]. This shows that identifying and tailoring tACS to the specific symptomatology is important. Individualization of frequency may be particularly important at lower frequency bands where small changes can affect the behavioral efficacy of tACS [56,105]. Individual tACS in the beta/gamma range improves reward learning, and a 5-day application led to lasting reduced obsessive-compulsive behavior in a subclinical population [99]. Another example of frequency specificity is shown in the application of tACS in Alzheimer's disease (AD) [13,122,123]. Optogenetic stimulation in AD model mice at 40 Hz, but not at other frequencies, was shown to alleviate the deposition of adverse protein build-up and improve microglial functioning [133]. Correspondingly, parietal 40 Hz tACS improved short-term memory and verbal learning performance in AD patients [13,122].

Synchronization and desynchronization

Phase-dependent tACS can synchronize or desynchronize oscillations when aligning with or opposing endogenous oscillations [60,107,134] (Figure 3). Several brain disorders, including Parkinson's disease and epilepsy, are characterized by excessive or abnormal oscillatory synchronization [12,15,120,121]. In particular, Parkinson's disease leads to beta hypersynchronization, and beta tACS that further promotes synchrony worsens motor symptoms [15]. Conversely, using a closed-loop phase-dependent tACS approach, researchers applied beta tACS to desynchronize brain oscillations related to peripheral tremor, which led to tremor suppression of 42% [12]. A similar closed-loop approach shows promise in reducing epileptic brain activity [124,125] and is presently undergoing clinical trials.

Present challenges

With the growing popularity of tACS, null findings and ineffective protocols also emerge. The lack of a relationship between brain oscillations and cognitive processes should be differentiated from inadequate stimulation. Converging evidence emphasizes the importance of adequate dosing [2,3,17,19,28]. The minimum effective dose of tACS for clear physiological effects is ~0.3–0.4 mV/mm [2,3,28,29]. What stimulation intensity achieves this electric field strength depends on the target brain region and required spatial focality [19,20]. However, many studies using well below 2 mA will not reach sufficient electric field strength. Application of electric currents up to 4 mA is safe [135], but higher-end stimulation doses remain largely untapped in human studies although it promises qualitatively improved interventions [2,17].

High-intensity tACS doses can be accompanied by peripheral side effects such as visual flickering and somatosensory discomfort [31]. Although peripheral effects can interfere with cognitive performance, adjusting the applied current to below the perception threshold creates a risk of underdosing. Instead, researchers should consider realistic, active sham stimulation protocols [136] and additional control experiments using task-irrelevant brain areas and stimulation frequencies. Stimulation approaches utilizing distributed small electrode arrays [137] or topical anesthetics can enable higher doses and mitigate possible discomfort [81].

Further, the cumulative effects of multi-session tACS remain largely unknown. A few clinical trials have applied tACS for up to 2 weeks, with some promising and lasting results [14,99]. However, FDA-approved brain stimulation protocols, such as repetitive TMS in depression, deliver 20+ sessions over 4+ weeks [138]. To date, such extended human trials with tACS are lacking.

Finally, although the frequency dependency of tACS effects is apparent, as discussed throughout this review, the exact relationship remains debated. One hypothesis of tACS suggested an Arnold tongue pattern [33] in which primary tACS effects were at the endogenous oscillatory peak frequency. Nevertheless, positive effects on cognition and neural plasticity are observed at tACS frequencies under or above peaks of endogenous oscillatory activity [57,73,105]. Some brain oscillations, such as the gamma rhythm, lack a clear spectral peak, but gamma-range tACS shows positive effects [15,69,74,109,123,139]. Thus, granular exploration of frequency specificity presents an exciting research direction.

Future directions

Given its ample ability to control stimulation parameters, tACS has the potential for personalization. However, its vast parameter space is also a challenge. Computational head models can facilitate individual dosing [140,141] and electrode montage selection [142]. However, uncertainties in model estimates due to variability in head tissue conductivities [143,144] and electrode locations [50] call for further improvements in modeling-based dose schemes [145]. Personalizing tACS frequencies to individual brain rhythms could further reduce variability and improve tACS efficacy [146]. In addition to frequency, the stimulation waveform itself can be individualized to brain activity, leading to improved outcomes [1]. Such personalization can go beyond a single frequency stimulation and use a whole oscillatory frequency band (e.g., alpha band) to recruit a sizeable neural population, likely composed of several subpopulations with slightly different peak oscillations [147]. Advanced personalization requires dynamically adjusting tACS regarding measurements that capture ongoing brain states through a closed-loop approach [12,76,77,134]. Further, precise manipulation of phase relations may hold the key to optimally targeting phase connectivity between distal brain areas. In addition, phase synchronization of tACS with other neuromodulation methods can lead to more optimal modulation of behavior [148]. It was demonstrated that tACS peak-, but not trough-, synchronized 10 Hz repetitive TMS leads to sustained increases in EEG power [148].

Previous tACS studies focused on two brain areas and exact in-phase (0° synchronization) or anti-phase (180° desynchronization) stimulation [60,67,84,108]. However, recent developments have shown the feasibility of tACS in manipulating the local phase with fine-grained precision, generating phase gradients or traveling waves [107]. Such traveling wave stimulation protocols can mimic and possibly modulate intrinsic cortical traveling waves [110]. One can also manipulate long-range phase connectivity and local cross-frequency connectivity [5,71] simultaneously with potentially greater effect.

Concluding remarks

In conclusion, tACS is a promising tool in cognitive and clinical research. It can selectively modulate ongoing neural synchrony and evoke neuroplasticity in local brain areas or networks with substantial precision by combining spatial and frequency specificity. The latter effectively translates into contextual specificity because tACS can only modulate the existing neural oscillations and cannot evoke *de novo* activity from steady-state brains. Although the extent of tACS capabilities and dose-response dependency remains under active investigation (see Outstanding questions), dozens of well-designed cognitive studies already implement tACS to explore the association between brain oscillations and behavior, validate neuroimaging findings regarding a cognitive process with the causal evidence, and translate fundamental neurocognitive theories into unique mental health therapeutic tools.

Outstanding questions

What is the optimal effective dose of tACS? Present estimates of minimum effective dosing, ~0.3–0.4 mV/mm, follow animal research and do not consider complex neural states intrinsic to cognitive engagement in humans. Furthermore, an upper level of tACS intensity that maximizes behavioral effects with minimal adverse effects remains to be determined.

What are the long-term benefits of tACS? For clinical utility, tACS effects must be long-lasting, but most research focuses on immediate effects to short-term after-effects. Lasting changes likely require multi-session multi-day protocols.

How can we maximize the personalization of tACS? Great efforts have been made towards individualized stimulation parameters (location, dose, and waveform) using computational models and non-invasive neuroimaging (EEG, fMRI). Nevertheless, modern computational models and neuroimaging outcomes still come with *a priori* assumptions and considerable uncertainty. Future studies utilizing more advanced personalization schemes, including real-time closed-loop adaptations, will significantly impact on the research field.

What new questions about brain electrophysiology can we address using tACS? Cross-frequency coupling and traveling wave tACS are recent advances based on influential neuroscientific theories about brain organization. Future variants of tACS may allow us to answer novel research questions about brain organization that presently lack causal proof.

Can we achieve a synergetic effect on the brain and behavior using tACS in combination with cognitive-behavioral or pharmacological interventions? If tACS potentiates neural plasticity, putting the brain in the right state may strengthen the efficacy of other brain targeting modalities.

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Declaration of interests

The authors declare no conflicts of interest.

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