REVIEW

Current challenges: the ups and downs of tACS

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Abstract

The non-invasive delivery of electric currents through the scalp (transcranial electrical stimulation) is a popular tool for neuromodulation, mostly due to its highly adaptable nature (waveform, montage) and tolerability at low intensities (< 2 mA). Applied rhythmically, transcranial alternating current stimulation (tACS) may entrain neural oscillations in a frequency- and phase-specific manner, providing a causal perspective on brain–behaviour relationships. While the past decade has seen many behavioural and electrophysiological effects of tACS that suggest entrainment-mediated effects in the brain, it has been difficult to reconcile such reports with the weak intracranial field strengths (< 1 V/m) achievable at conventional intensities. In this review, we first describe the ongoing challenges faced by users of tACS. We outline the biophysics of electrical brain stimulation and the factors that contribute to the weak field intensities achievable in the brain. Since the applied current predominantly shunts through the scalp—stimulating the nerves that innervate it—the plausibility of transcutaneous (rather than transcranial) effects of tACS is also discussed. In examining the effects of tACS on brain activity, the complex problem of salvaging electrophysiological recordings from artefacts of tACS is described. Nevertheless, these challenges by no means mark the rise and fall of tACS: the second part of this review outlines the recent advancements in the field. We describe some ways in which artefacts of tACS may be better managed using high-frequency protocols, and describe innovative methods for current interactions within the brain that offer either dynamic or more focal current distributions while also minimising transcutaneous effects.

Keywords Transcranial · Stimulation · Electric field · Oscillation · Artefact · Phase

Introduction

The central aim of cognitive neuroscience is to understand how the complex spatio-temporal dynamics of brain activity shape our consciousness and cognition. Historically, our knowledge about brain–behaviour relationships has been derived from correlational observations in both health and disease. While scientifically sound, theories driven by such evidence fail to prove the necessity or sufficiency of any brain-related phenomenon (e.g., a brain oscillation) beyond that of a correlate to some brain function, mental process, or behavioural outcome. A causal perspective on brain–behaviour relationships is possible, however, through manipulating the brain and observing the consequences (Herrmann et al. 2016; Polanía et al. 2018). This perspective is especially important in applied settings, where the utility of a neural measure depends on whether it is causally related to the outcome of interest (e.g., the diagnosis or treatment of some "oscillopathy;" Nimmrich et al. 2015; Başar et al. 2016). The ability to exogenously alter brain activity in humans and observe subsequent behavioural or electrophysiological effects is an exciting prospect for techniques of non-invasive brain stimulation (for recent reviews, see Thut et al. 2017; Polanía et al. 2018; Vosskuhl et al. 2018; Veniero et al. 2019)—with promising practical and clinical applications (Lefaucheur et al. 2014; Yavari et al. 2018).

Electrical stimulation of the human brain has a long medical and scientific history (see Priori 2003; Liu et al. 2018). High-intensity currents (~ 10–40 mA) were used to induce electrosleep and electroanesthesia from the early 1900s (Brown 1975), and later introduced to psychiatry in the 1930s for electrically inducing seizures (Payne and Prudic 2009), though with even higher intensities (~ 800–900 mA,

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Bikson et al. 2019). Transcranial electrical stimulation (tES) is defined by its non-invasive application through the intact scalp (see Bikson et al. 2019). For example, a very brief, high-intensity pulsed current (Merton and Morton 1980) can stimulate the healthy human brain (e.g., evoking a response in the hand when applied over the hand representation of the contralateral motor cortex) without surgery. Because of its transcutaneous delivery, however, tES is quite painful at the intensities necessary to evoke such responses (~ 1000 mA; see Edwards et al. 2013)—motivating the development of transcranial magnetic stimulation (TMS; Barker et al. 1985). Nevertheless, low-intensity variants of tES survived to modernity (Esmaeilpour et al. 2017). Because these weaker intensities (< 2 mA) are well tolerated by participants (Fertonani et al. 2015), application may continue for tens of minutes without adverse events (Bikson et al. 2016; Matsumoto and Ugawa 2017). In clinical settings, cranial electrotherapy stimulation (CES)—a type of pulsed low-intensity tES—has been used as a treatment for depression, anxiety, and insomnia since the early 1960s (though no compelling evidence for a therapeutic effect exists; see Kavirajan et al. 2014; Shekelle et al. 2018).

Over the past two decades, low-intensity (< 2 mA) tES has become an increasingly popular tool for neuromodulation in the laboratory (for balanced reviews, see Bestmann et al. 2015; Soekadar et al. 2016; Bestmann and Walsh 2017; Fertonani and Miniussi 2017; Karabanov et al. 2019). This renaissance of tES research has been motivated by its highly adaptable nature (both in terms of waveform and montage; see Bikson et al. 2019), and its portability, tolerability, and low cost relative to TMS. At the core of tES (see Box 1), the imposition of an electric field in the brain—given sufficient intensity—will influence the rate or timing of neural activity, though its mechanisms of action are only rudimentarily understood (for a recent review, see Liu et al. 2018). The two most common forms of low-intensity tES involve the application of either direct or alternating currents (transcranial direct current stimulation, tDCS; transcranial alternating current stimulation, tACS; see Box 1), typically used to excite or inhibit cortex in a polarity-dependent manner (as in tDCS, Nitsche et al. 2008; Filmer et al. 2014) or entrain a particular neural rhythm (as in tACS, Antal and Paulus 2013; Antal and Herrmann 2016). However, as quickly as researchers adopted these weaker forms of tES were they met with great scepticism and criticism (perhaps most famously for tDCS by Horvath et al. 2015a, b; and for tACS by Lafon et al. 2017)—a sentiment apparent even in early commentary on CES (e.g., Brown 1975).

In its relatively short life, tACS—the term coming into mainstream use from 2008 (~ 10 years after tDCS)—boasts a series of successes across an impressively diverse range of research applications (e.g., learning, memory, creativity, intelligence, and risk taking; for reviews, see Veniero et al.

2015, 2019; Abd Hamid et al. 2015; Schutter and Wischnewski 2016; Herrmann and Strüber 2017). Moreover, there are recent examples of compelling electrophysiological and perceptual phase-dependent effects of tACS (see Vosskuhl et al. 2018), suggesting entrainment-like effects on endogenous neural oscillations. However, there are continuing issues with its use that remain open problems in the field of tES research. In this review, we outline the ups and downs of tACS as a tool for neuromodulation, with timely commentary on these issues: weak cortical currents (Lafon et al. 2017; Vöröslakos et al. 2018); indirect (e.g., transcutaneous) effects (Asamoah et al. 2019a); poor focality (Wagner et al. 2013; Opitz et al. 2015), frequency-specificity (Veniero et al. 2015), and reproducibility (Héroux et al. 2017; Bikson et al. 2018); and the complex problem of removing its artefacts from concurrent electrophysiological recordings (Noury et al. 2016; Neuling et al. 2017; Noury and Siegel 2017, 2018). Still, the outlook for tACS is not wholly bleak, with many exciting advances in both its application and the measurement of its effects discussed at the end of this review.

Box 1: Terminology

Transcranial electrical stimulation (tES): The imposition of an electric field in the brain through the intact scalp in an attempt to influence neural activity. With sufficient intensity, tES can directly alter the rate or timing of neural activity, but its transcutaneous delivery can be painful. Modern forms of tES therefore use much lower intensities (~ 1–2 mA), though at a cost of also weakening the cortical effects. At these low intensities, tES cannot directly evoke action potentials, and is instead thought to induce subthreshold changes in neural excitability (i.e., biasing either the rate or timing of such action potentials). However, since low-intensity tES is well tolerated, it can be applied for much longer periods compared to high-intensity variants. A lowercase t is used throughout this article to emphasise subthreshold variants of tES and distinguish these from a form of suprathreshold stimulation with the same name: TES (uppercase T) is a high-intensity pulsed current tES protocol (e.g., Merton and Morton 1980).

Transcranial direct current stimulation (tDCS): The delivery of a weak (< 2 mA) direct current between electrodes on the scalp. The current flows from anode (positive) to cathode (negative), with polarity-dependent effects on underlying cortex. Nearest the anode, widespread subthreshold depolarisation is expected (increased neural excitability); nearest the cathode, widespread subthreshold hyperpolarisation is expected (decreased neural excitability). However, these effects can be complicated

by the orientation of the electric field relative to the stimulated tissue (e.g., by cortical folding).

Transcranial alternating current stimulation (tACS): The delivery of a weak (< 2 mA) alternating current between electrodes on the scalp. The direction of current flow changes cyclically, with the anode and cathode alternating per half-cycle. tACS is thought to foster neural activity that approximates the rhythmicity of the induced current: biasing the ongoing timing of action potentials with periodic states of subthreshold depolarisation and hyperpolarisation. The intensity of tACS usually refers to the peak-to-peak amplitude (i.e., '2 mA tACS' has a maximum current equal to that of '1 mA tDCS').

There exist many other variations of tES that are described elsewhere (see Bikson et al. 2019). For example, an offset can be added during tACS, typically such that one electrode remains anodal throughout stimulation ('oscillating' transcranial direct current stimulation, otDCS). During otDCS, the current amplitude (but not its polarity) is modulated cyclically. A random zero-mean waveform—typically with bounded frequency content (e.g., 100–640 Hz)—is called transcranial random noise stimulation (tRNS).

Transcranial magnetic stimulation (TMS): A form of non-invasive brain stimulation that exploits electromagnetic induction to briefly induce strong, focal currents in the brain that can directly evoke action potentials.

Biophysics of tES

Beginning in the 1950s, a swathe of in vitro and in vivo animal work formed the basis for understanding the biophysics of tES (Ruffini et al. 2013; Jackson et al. 2016; Liu et al. 2018). However, translating this research to humans has been historically very challenging due to the vastly weaker tES-induced electric field strengths in humans (Modolo et al. 2018; Alekseichuk et al. 2019b). At the core of tES, the imposition of an electric field in the brain will affect the polarisation of cellular membranes in a polarity-dependent manner, which in turn can alter neural excitability and evoked responses (Reato et al. 2013; Jackson et al. 2016). The strength of this field in the brain (measured in V/m) is directly proportional to the intensity of the current applied at the scalp (measured in mA). For every 1 V/m of applied field, a transmembrane polarisation change of no more than ~ 0.2 mV is expected (Bikson et al. 2004; Radman et al. 2009; see the 'coupling constant' in Jackson et al. 2016)—a value far smaller than required to bring a neuron from rest to threshold (~ 15 mV depolarisation). However, there is no theoretical minimum intensity effective in modulating neural activity, since any exogenous polarisation caused by tES

(< 1 V/m for most research applications) will add to existing physiological mechanisms (Radman et al. 2007; Anastassiou et al. 2010; Ozen et al. 2010). Even a very small electric field may bias the discharge timing or probability of neurons near their spiking threshold—a phenomenon known as 'stochastic resonance' (Geisler and Goldberg 1966).

Direct currents

The effects of direct currents on neural excitability have been studied extensively within animal models, both in vivo and in vitro (Reato et al. 2013)—the latter providing an environment to deliver uniform electric fields across slice preparations (Bikson et al. 2004). Field-induced effects on firing rate are detectable at field intensities as low as 0.8 V/m (Terzuolo and Bullock 1956), though much greater intensities are required to evoke action potentials from quiescent neurons (~ 30–100 V/m; Radman et al. 2009). These effects are polarity-dependent, whereby the direction of polarisation depends on the morphology of the neuronal compartments relative to the electric field (Chan et al. 1988; Jackson et al. 2016). For example, a surface anode (i.e., generating an inward current flow) over a typical cortical pyramidal cell will hyperpolarise the apical dendrite (pointing toward the cortical surface) but will depolarise the soma (Radman et al. 2009). Somatic depolarisation by a surface anode increases neural firing rate and somatic hyperpolarisation by a surface cathode decreases it (Creutzfeldt et al. 1962; Bindman et al. 1964; Purpura and McMurtry 1965), even beyond stimulation (Bindman et al. 1962; Gartside 1968a, b).

In humans, studies using TMS to probe the excitability of motor cortex after exposure to direct currents broadly supported this view: anodal tDCS increased the amplitude of TMS-evoked muscle responses (increased excitability; Nitsche and Paulus 2000, 2001), while cathodal tDCS had the opposite effect (decreased excitability; Nitsche et al. 2003). These early studies led many clinicians and researchers to invoke a 'sliding-scale' anode–excitation/cathode–inhibition view of tDCS on neural excitability (the 'somatic doctrine'; Jackson et al. 2016). However, the orientation of the electric field relative to the stimulated neuron's somatodentritic axis can affect the magnitude or the direction of these effects (e.g., by cortical folding, Rahman et al. 2013), and the widespread tES-induced intracranial field will affect other neuronal compartments (e.g., dendrites, axon) and glia (e.g., astrocytes) with varied sensitivities to stimulation (Bikson et al. 2004; Jackson et al. 2016). These factors may contribute to the complex, non-linear dose–response relationship observed for tDCS-induced changes in corticomotor excitability (see Batsikadze et al. 2013; Goldsworthy and Hordacre 2017; Rawji et al. 2018). During tDCS, the distributed current may lead to widespread membrane polarisation, which may alter ongoing *oscillatory* activity within stimulated networks—even in

the absence of modulations to neural firing rate (e.g., Krause et al. 2017; see also Vöröslakos et al. 2018).

Alternating currents

The fundamentally oscillatory nature of neural activity renders it susceptible to manipulation by the imposition of rhythmically alternating currents, offering a means to entrain oscillations in the brain in a frequency- and phase-specific manner (Ali et al. 2013). Like tDCS, much of our understanding of how tACS influences neural activity comes from animal studies (Reato et al. 2013). tACS is conventionally thought to alter the ongoing timing of discharges without affecting their overall rate. For example, field intensities of 0.7–5 V/m applied in vitro can phase-lock (entrain) spiking to the oscillating (1–30 Hz) external field (Anastassiou et al. 2011). Over successive cycles, this alternation may induce cumulative effects on spike timing (Liu et al. 2018). At low frequencies, tACS may induce periodic tDCS-like effects on discharge frequency per half-cycle (Chan and Nicholson 1986; Chan et al. 1988; Reato et al. 2010). However, a neuron's susceptibility to membrane polarisation (mV of polarisation per mV/mm electric field, or simply mm) decreases with increasing frequency: ~ 0.2 mm with a direct current versus ~ 0.1 mm with a 50 Hz alternating current (Deans et al. 2007). This is due to a 20–60 ms transmembrane time constant for polarisation by the applied field (Jefferys et al. 2003; Bikson et al. 2004; Deans et al. 2007). This capacitive low-pass filtering property of the membrane underpins the need for greater stimulation intensities to entrain activity at higher frequencies (e.g., Anastassiou et al. 2010, 2011).

Voltage gradients of 1–2 V/m would cause membrane polarisation comparable in magnitude to intrinsic, non-synaptic, internally generated neuronal noise (0.2–0.5 mV; Jacobson et al. 2005), but these small fluctuations are dwarfed by synaptic background activity in vivo (Liu et al. 2018). To affect endogenous network oscillations, field intensities greater than 1 V/m are typically needed (e.g., Fröhlich and McCormick 2010; Ozen et al. 2010; Berényi et al. 2012; Vöröslakos et al. 2018) in order to compete with native brain rhythms (2–4 V/m; Fröhlich and McCormick 2010). For example, endogenous field strengths of 2–3 V/m are observed during theta oscillations in rat hippocampus, with 10–15 V/m fields observed during hippocampal sharp waves (Anastassiou et al. 2010). However, when the frequency of the external current matches the endogenous rhythm, spike timing can be biased by field intensities as low as 0.2–0.5 V/m (Francis et al. 2003; Deans et al. 2007; Reato et al. 2010). For example, Krause et al. (2019) observed entrainment of single-unit activity in the primate brain to tACS-induced fields of only 0.2–0.3 V/m at all frequencies examined: 5, 10, 20, and 40 Hz. These field strengths are in the realm of what can be achieved with tACS in humans (see "Weak cortical currents").

Weak cortical currents

Perhaps the greatest source of controversy for modern tES is to what extent weak scalp-applied currents can influence neural activity. At conventional intensities (~ 1–2 mA), intracranial recordings show that tES is able to induce maximal electric field strengths of 0.1–0.8 V/m in targeted tissue (Opitz et al. 2016, 2017; Huang et al. 2017; Lafon et al. 2017; Chhatbar et al. 2018; Ruhnau et al. 2018; Vöröslakos et al. 2018; Krause et al. 2019), with large variability due to other important factors (e.g., participant anatomy and montage of application; Kim et al. 2014; Opitz et al. 2015; Alekseichuk et al. 2019b). Realistic current flow simulations (Miranda et al. 2006, 2013; Datta et al. 2009, 2013; Sadleir et al. 2010; Alekseichuk et al. 2019b) also predict tES induces field strengths of no more than ~ 0.5 V/m for every 1 mA applied to the scalp, and these models are well corroborated by invasive recordings (see Huang et al. 2017; Lafon et al. 2017; Ruhnau et al. 2018). To put these weak (subthreshold) effects in context, a voltage gradient of 100–200 V/m is required in motor cortex to evoke a muscle response (which is achievable with TMS, Alekseichuk et al. 2019b; or with ~ 1000 mA tES, Edwards et al. 2013).

Since the electric field strengths achievable with low-intensity tES are on the lower end of what has been shown to induce detectable changes in neural activity under ideal conditions, it is not obvious how these weak currents lead to the plethora of behavioural and electrophysiological effects observed in humans (Asamoah et al. 2019a). Assuming 2 mA tDCS can generate a peak electric field in the brain of 1 V/m (corresponding to 0.2 mV somatic polarisation), a change in firing rate of ~ 1.5 Hz is plausible (Jackson et al. 2016). This estimate comes from an observed change in firing rate of ~ 7 Hz per mV of membrane polarisation (Carandini and Ferster 2000). However, this estimate is for isolated neurons, and yet the distributed effects of tDCS will induce widespread polarisation in the brain that may amplify these otherwise weak effects (e.g., Reato et al. 2010)—an argument that can also be made for tACS. The somatic polarisation observed by 1 V/m during tACS will be inevitably lower than that observed by 1 V/m during tDCS. Due to the 20–60 ms transmembrane time constant, the sensitivity drops as an exponential decay function of frequency (Deans et al. 2007). While this suggests that generally stronger currents may be required to observe effects of tACS (especially at high frequencies; Anastassiou et al. 2011), the ongoing spike timing of neurons appears to be highly sensitive to persistent rhythmic fluctuations introduced by tACS (e.g., Krause et al. 2019).
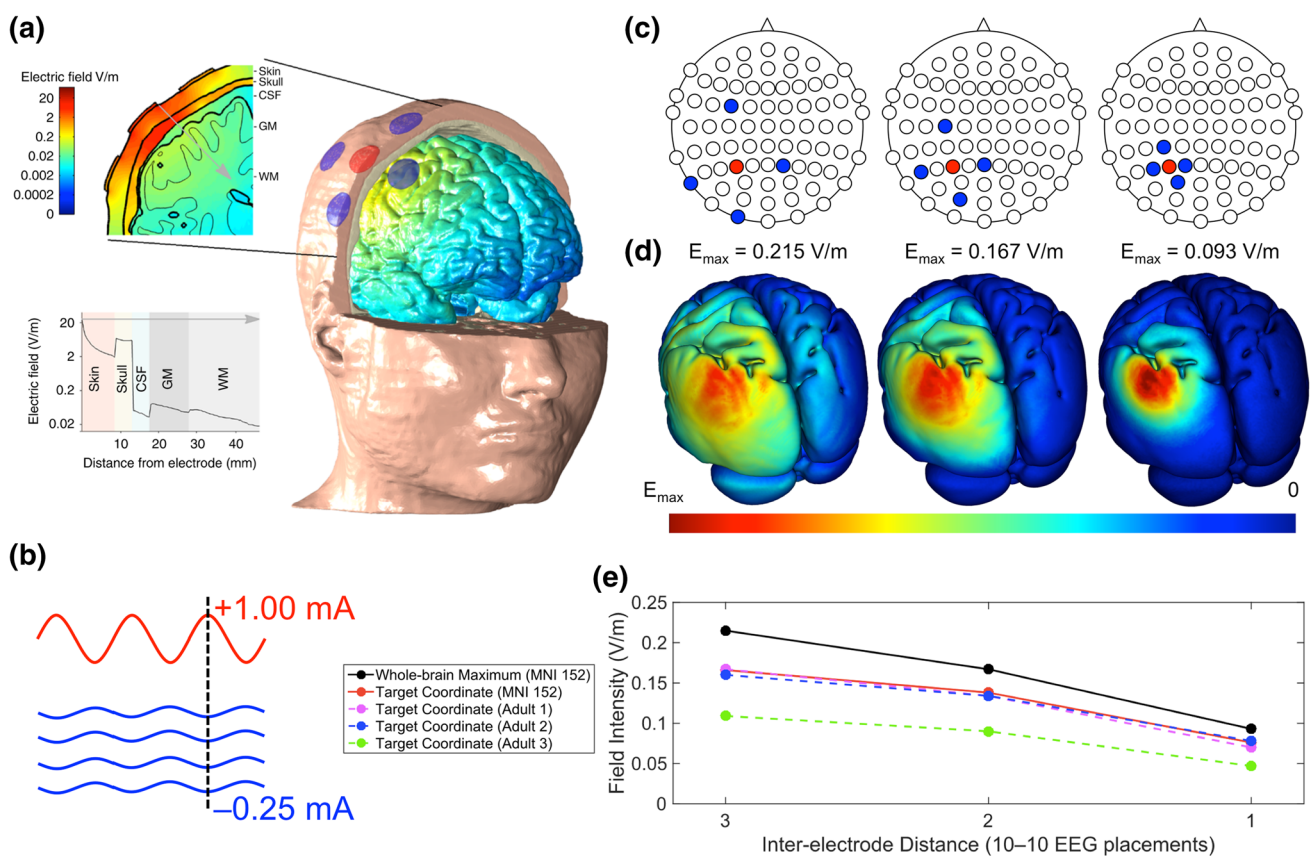
Shunting

Since tES is by definition delivered transcutaneously, a large proportion of the scalp-applied current (~75%) is attenuated by soft tissues and the skull (Vöröslakos et al. 2018). This proportion can be even higher when the stimulating electrodes are in close proximity (low anode–cathode distance), since the current is even more likely to shunt across the scalp (Miranda et al. 2006; Faria et al. 2011; see Fig. 1). Multi-electrode, 'high-definition' (or 'high-density') tES montages have been used to optimise the focality and intensity of stimulation (Dmochowski et al. 2011; Cancelli et al. 2016). However, there is a fundamental trade-off between focality and intensity such that the multi-electrode montages (typically

with decreased inter-electrode distance) tend to reduce the strengths of tES-induced intracranial fields (e.g., Saturnino et al. 2017; Asamoah et al. 2019a). Generally speaking, increasing the distance between anodal and cathodal electrodes will: (a) decrease the proportion of current shunting across the scalp, (b) increase the depth and magnitude of intracranial fields, but (c) induce more distributed (non-focal) electric fields in the brain.

Current limits

An obvious way to increase the tES-induced field strengths in the brain is to apply more current, since these are directly proportional to one another (i.e., doubling the mA applied

Fig. 1 Electrode proximity and the proportion of current shunting through the scalp. **a** Only a small proportion of the transcutaneously applied current reaches the brain, resulting in field intensities orders of magnitude greater in the scalp (Asamoah et al. 2019a). **b** The current intensity cyclically changes during tACS, but is typically modelled at its extrema: tACS with an amplitude of 2 mA peak-to-peak is delivered through a 4×1 ring electrode configuration, and modelled at a single time point (1 mA entering at the centroid; exiting equally across four peripheral electrodes). **c** Changing the distance between the centre electrode (EEG position P3; red) and its four returns (blue) influences the intensity and focality of intracranial electric fields, despite keeping the scalp-applied current intensity equal for all montages (i.e., 1 mA). **d** As the inter-electrode distance decreases,

a greater proportion of current shunts through the scalp (i.e., never reaching the brain). Note that the electric field strength is scaled to the whole-brain maximum, which differs dramatically across the three montages. **e** The whole-brain maximum decreases as the inter-electrode (anode–cathode) distance decreases, as does the field intensity observed at a fixed (target) location within the left angular gyrus—MNI coordinates $\{-50, -64, 42\}$. Field spread was computed for a composite (MNI 152), and for individual structural scans of three healthy adult males using Soterix Medical HD–Explore software. Panel **a** was reproduced without changes from Asamoah et al. (Asamoah et al. 2019a) under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

to the scalp doubles the intracranial V/m). However, the use of < 2 mA tES is mostly due to its tolerability by participants (Fertonani et al. 2015), and thus jointly due to being able to successfully sham stimulation at these lower intensities. Due to its transcutaneous application, tES becomes uncomfortable at higher intensities. While the sensations felt during tES will differ based on current intensity, current waveform and frequency, electrode type and location, and scalp impedance (Fertonani et al. 2015), a pinching or burning sensation under the stimulating pads is common above 1 mA (Poreisz et al. 2007). At higher intensities, participants can also report dizziness, illusory flickering lights (phosphenes), and a metallic taste in the mouth (> 4 mA, Vöröslakos et al. 2018). These peripheral effects typically act as a limiting factor on the current intensities clinicians and researchers can use, especially for prolonged applications of tES in healthy (and usually unanaesthetised) participants. However, the use of high-frequency alternating currents (or short pulses of direct current) with a frequency above the neuronal membrane time constant might mitigate some of these unwanted effects (see "Interfering currents"). For a review of the safety of tDCS with respect to dose and tissue damage, see Bikson et al. (2016).

Indirect effects

Most studies employing tES tacitly or explicitly assume any effect of stimulation originates from tES-induced electric fields in the brain (i.e., stimulation is *transcranial*). However, scalp-applied currents will predominantly shunt across the scalp, stimulating the cranial nerves that innervate it, and flow through the orbits and ear canals (Liu et al. 2018; Vöröslakos et al. 2018). It is therefore plausible that many tES effects instead have a *transcutaneous* origin. Given the weak fields (0.1–0.8 V/m) tES is able to induce in cortex at intensities of 1–2 mA, these indirect effects have been posited as a potential solution to the "tACS paradox" (Asamoah et al. 2019a): How can we reconcile the plethora of reported cognitive, perceptual, and electrophysiological effects of tACS with the likely very weak cortical effects of stimulation? Some reported effects might therefore occur via indirect mechanisms rather than via direct cortical stimulation. While this notion has only recently emerged in the tACS literature (e.g., Schutter 2016; Asamoah et al. 2019a), peripheral effects of low-intensity currents have been exploited for decades by users of galvanic vestibular stimulation (Kwan et al. 2019) and transcutaneous electrical nerve stimulation (DeSantana et al. 2008). It should also be noted that even if tES-induced intracranial fields are the cause of observed effects, these might not have a strictly neuronal origin (e.g., effects could be indirectly mediated by glia; Ruohonen and Karhu 2012; Monai and Hirase 2018).

Retinal stimulation

The application of 0.25–1 mA tACS over visual cortex (Kanai et al. 2008) can induce visual flashes (phosphenes), which are evoked maximally by tACS frequencies in the low beta band (14–20 Hz; illuminated room) and alpha band (10–12 Hz; dark room). Because endogenous alpha oscillations naturally increase in darkness, the shift toward phosphene perception during alpha tACS was thought to reflect a direct interaction with endogenous oscillations in visual cortex (Kanai et al. 2008). However, subsequent studies suggested a retinal and not a cortical origin of these tACS-evoked phosphenes (Schwiedrzik 2009): they increased in intensity when tACS was applied closer to the eyes (Schutter and Hortensius 2010), the lower frequencies that evoked phosphenes in darkness reflected increased sensitivity of retinal ganglion cells (Kar and Krekelberg 2012), and field intensities sufficient to evoke retinal phosphenes were observed in the orbits even when tACS was applied over visual cortex (Laakso and Hirata 2013). Nevertheless, retinal phosphenes can themselves entrain oscillations in visual cortex (e.g., steady state visually evoked potentials), and may therefore influence perceptual and cognitive performance (Spaak et al. 2014; Schutter 2016). In this manner, tACS may induce a frequency-specific effect on endogenous oscillations in visual cortex (e.g., alpha entrainment), but indirectly through sensory stimulation.

Peripheral nerve stimulation

During tES, the electric fields observed in the skin can be 20–100 times stronger than in cortex (see Fig. 1), easily surpassing the 4–6 V/m threshold for peripheral nerve stimulation (Asamoah et al. 2019a; see also Alekseichuk et al. 2019b). Previous research has shown that tACS can entrain pathological tremor (e.g., Brittain et al. 2015) and physiological tremor in healthy participants (e.g., Mehta et al. 2014)—as indicated by increased coherence between the hand electromyographic tremor signal and the tACS waveform. However, hand tremor has also been shown to entrain to photic (flashing light) stimulation (Mehta et al. 2015), and therefore current spread through the orbits—evoking phosphenes—may also contribute to tremor entrainment (Khatoun et al. 2018). Across a series of experiments, Asamoah et al. (2019a) demonstrated that both pathological (~ 3 Hz) and physiological (~ 10 Hz) tremor entrains to tACS, but that this effect does not originate from direct cortical stimulation. In one experiment, a topical anaesthetic was used to reduce the transcutaneous mechanism of tACS: the tremor entrainment effect was either dampened (physiological tremor) or disappeared entirely (pathological tremor). In another experiment, tACS was instead applied to the contralateral arm to block its transcranial mechanism, yet tremor entrainment

was still observed. When applied over motor cortex, transcutaneous effects were observed at intensities as low as 0.5 mA (no anaesthetic), yet no effect was observed at intensities as high as 5 mA with anaesthetic, suggesting no cortical contribution to tremor entrainment even with ~ 0.6 V/m in motor cortex. Interestingly, transcutaneous stimulation of the arm by tES was also shown to entrain electroencephalographic (EEG) activity in the beta band (16–30 Hz), suggesting any kind of peripheral sensation from tACS has the potential to indirectly influence neural oscillations.

Concurrent neuroimaging

Pairing tES with neuroimaging is scientifically valuable (i.e., to directly observe its effects on ongoing brain activity; Bergmann et al. 2016; Soekadar et al. 2016), but the resultant artefacts of stimulation often preclude online analysis. This is especially true for tACS since it is applied continuously and its artefacts are orders of magnitude larger than the endogenous activity observed in the magneto- and electro-encephalogram (M/EEG; see Kasten and Herrmann 2019). Effects of tACS are presumed to occur through neural entrainment and spike-timing dependent plasticity (e.g., Zaehle et al. 2010; Vossen et al. 2015; Alagapan et al. 2016). However, since these mechanisms necessarily take place online (i.e., during stimulation), good methods for removing artefacts of tACS are needed in order to capture these direct effects on neural activity (e.g., with spectral analysis). This is a complicated problem for two reasons: (a) artefacts of tACS behave nonlinearly, complicating their removal from the M/EEG (Noury et al. 2016); and (b) the endogenous activity we wish to observe typically shares its frequency with that of tACS (i.e., contaminating the spectrum of interest). Much of our understanding of the electrophysiological effects of tACS therefore comes from periods free from stimulation (i.e., aftereffects, see Veniero et al. 2015)—which necessitate that any effect of tACS survives beyond the period of stimulation (see "Online entrainment and offline aftereffects").

The nonlinear problem

Recently, there has been much commentary on the characterisation of tACS artefacts (e.g., Noury et al. 2016; Mäkelä et al. 2017; Neuling et al. 2017; Noury and Siegel 2017, 2018). It has been demonstrated that heartbeat and respiratory effort rhythmically modulate body impedance and head position, in turn modulating the amplitude of tACS artefacts in the M/EEG (Noury et al. 2016; see Fig. 2). These effects are complicated further by small deflections in the ongoing phase of tACS within and across sensors (Noury and Siegel 2017). These physiological perturbations result in

nonlinear artefact behaviour that is difficult to disentangle from meaningful M/EEG activity. There exist many published approaches to remove artefacts of tACS from concurrent M/EEG, with varying degrees of complexity and success. Universally, these methods assume that artefacts of tACS remain either (a) linearly consistent over time (i.e., an artefact is a scaled version of itself from cycle to cycle) or (b) linearly consistent over space (i.e., artefacts are scaled versions of one another from sensor to sensor). However, neither of these assumptions are true. The first violation (a) renders temporal filtering and template subtraction approaches (e.g., with moving averages; Noury et al. 2016) imperfect; the second violation (b) renders spatial filtering (e.g., beamforming; Noury et al. 2016) and other decompositional approaches (e.g., principal component analysis) imperfect. Worryingly, the enormity of tACS artefacts relative to endogenous oscillations make even these small modulations appear on the scale of genuine neural activity (Noury and Siegel 2017)—and may thus be easily mistaken for genuine neural entrainment (i.e., frequency-specific, phase-aligned, and with biologically plausible amplitudes).

A model for tACS artefacts

Recently, Noury and Siegel (2017) provided a model for the tACS artefact observed in a given M/EEG sensor (3), accounting for the known amplitude (1) and phase (2) modulations.

$$\alpha(t) = \alpha_{\text{average}} + \alpha_{\text{slow}}(t) + \text{Heart}(t) * h_{\alpha h} + \text{Resp}(t) * h_{\alpha r} \tag{1}$$

$$\phi(t) = \phi_{\text{average}} + \phi_{\text{jitter}}(t) + \text{Heart}(t) * h_{\phi h} + \text{Resp}(t) * h_{\phi r} \tag{2}$$

$$A(t) = \text{Re}\{\alpha(t) \times e^{i\phi(t)}\} \tag{3}$$

The amplitude α and phase ϕ are defined on a per-sensor basis, with constants reflecting the average artefact amplitude (e.g., increasing with proximity to the site of stimulation; α_{average}) and phase (i.e., relative to the injected current; ϕ_{average}). Critically, $\alpha(t)$ and $\phi(t)$ are time-continuous, with slow amplitude modulations (e.g., impedance changes over time; α_{slow}) and phase jitter (ϕ_{jitter}), and with modulations time-locked to heartbeats and inspiration (e.g., with known timing from the electrocardiogram, Heart; and a belt transducer, Resp). The mean-removed average time-locked modulation by heartbeat (amplitude: $h_{\alpha h}$ and phase: $h_{\phi h}$) and respiration (amplitude: $h_{\alpha r}$ and phase: $h_{\phi r}$) occur at the moments indicated by their impulse trains (i.e., Heart and Resp, respectively). In (1) and (2), * denotes temporal convolution. The artefact A can then be reconstructed from its (time-continuous) instantaneous amplitude and phase, where Re{} takes the real part of the analytic signal. In the case
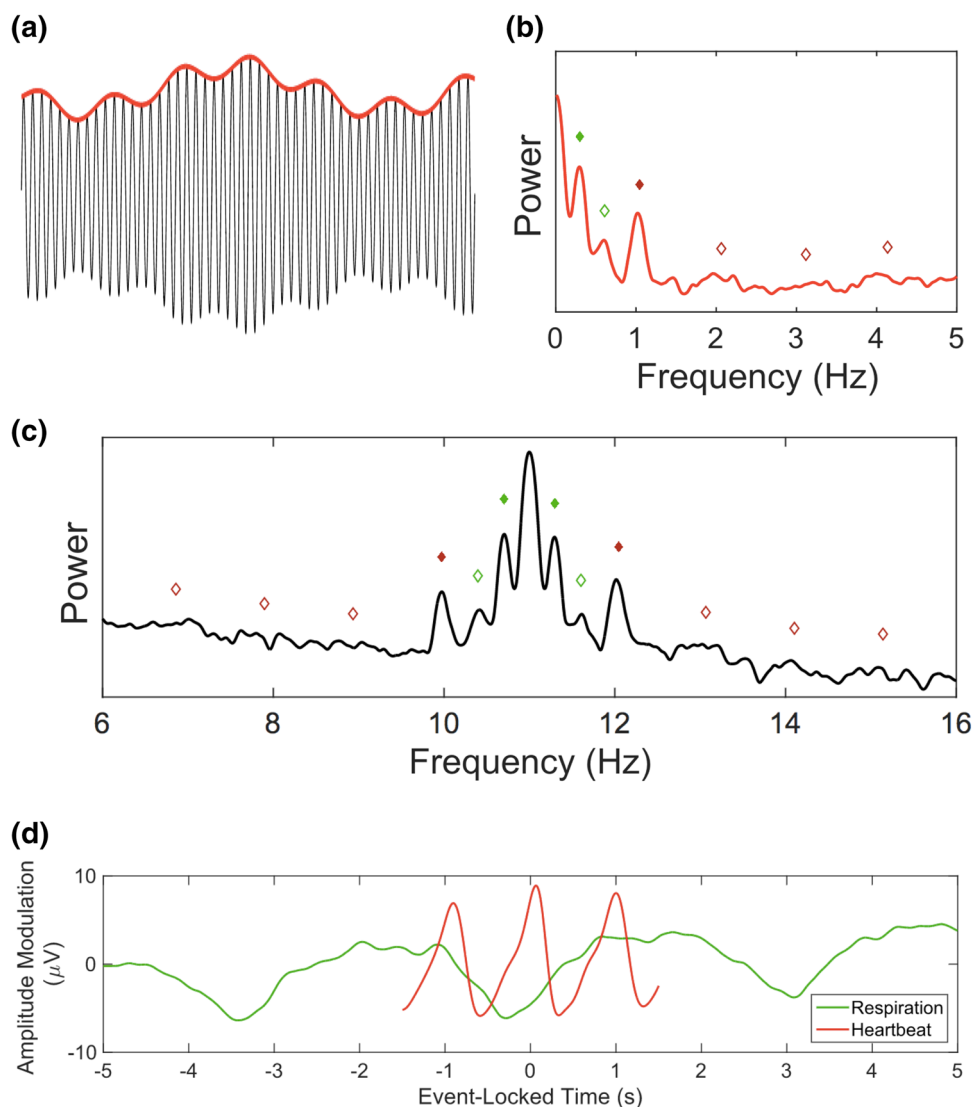
Fig. 2 Amplitude modulations of tACS by heartbeat and respiratory effort. **a** A fabricated example of a fixed-frequency sinusoid (black) with large modulations to its envelope (instantaneous amplitude; red). **b** The envelope power of an EEG sensor recorded during 10 Hz tACS. Amplitude modulations are evident at the frequencies of the participant's breathrate (0.3 Hz; green diamond; filled) and heartrate (1 Hz; red diamond; filled), confirmed by concurrently recording a respiratory belt transducer and an electrocardiogram. Multiples of these rhythms (harmonics) are indicated with unfilled diamonds. **c** The power of an EEG sensor recorded during 10 Hz tACS after subtracting an optimal sinusoidal model of the tACS artefact. The symmetry observed around the fundamental frequency of tACS is consistent with amplitude modulations by heartbeat and respiration. Note that the peak at 10 Hz does not reflect entrainment, but instead the very slow (< 0.2 Hz) amplitude modulations to the artefact over time (e.g., EEG or tES electrode impedance settling). **d** The event-locked instantaneous amplitude of an EEG sensor recorded during 10 Hz tACS. Based on the known timing of each breath and heartbeat (i.e., from the belt and electrocardiogram), the average mean-removed amplitude modulation observed over approximately three respiratory (green) and cardiac (red) cycles is displayed. Panels **b**–**d** were created using data published and provided by Noury et al. (2016), and detailed descriptions of the data and analytic methods can be found therein

of tDCS artefacts (e.g., Marshall et al. 2016), (2) can be discarded, with ϕ in (3) equal to zero.

This model captures all known physiological perturbations to tACS artefacts to date, though further work is needed to demonstrate whether these parameters can be validly reconstructed from artefactual M/EEG. While estimating most of the parameters in (1) and (2) may be straightforward, estimating phase jitter is not (Noury and Siegel 2017): its strength is comparable to sham for most sensors (i.e., it predominantly reflects brain activity). The successful removal of simulated artefacts embedded in sham recordings would therefore help validate the utility of such approaches for real data. It should be noted, however, that additional complexities likely exist beyond the amplitude

and phase modulations described in (1) and (2). Firstly, the heartbeat- and respiration-locked modulations to amplitude and phase might slightly vary across heartbeats and respiratory efforts (Noury and Siegel 2017). By using the average event-locked modulation, any differences between events will be neglected (e.g., a shallow versus deep breath). Recent work suggests variable timing between events in the electrocardiogram and resultant ballistocardiographic artefacts (Marino et al. 2018a), suggesting a better approach to model these 'event-locked' modulations is to use the artefactual recordings themselves (Marino et al. 2018b).

Furthermore, Noury and Siegel (2017) described additive contributions in (1) for slow changes to amplitude (α_{slow}) and those related to ongoing physiological rhythms (e.g., the cardiac cycle). However, the sizes of $h_{\alpha h}$ and $h_{\alpha r}$ are likely to scale proportionately with the size of the tES artefacts. Since tES is current-controlled, Ohm's law dictates compensatory changes in the delivered voltage with any changes in impedance. At the start of stimulation—where impedance (and therefore voltage) is typically higher—the amplitude modulations by heartbeat and respiration may well be numerically larger, decreasing over time as the impedance settles (e.g., Hahn et al. 2013; Chhatbar et al. 2016). The opposite may plausibly be observed too: evaporation/drying of conductive gels may lead to increased impedance over time, and thus greater modulations to tES artefacts may be observed toward the end of the stimulation protocol. This may be sufficiently accounted for by including an interaction in (2) that scales $h_{\alpha h}$ and $h_{\alpha r}$ with changes in α_{slow}, though no published work to date has verified the presence of such an interaction in real recordings of artefactual M/EEG. The presence of hardware-related non-linearities will also inevitably complicate modelling artefacts of tACS (e.g., Minami and Amano 2017; Kasten et al. 2018), even in the absence of physiological perturbations (e.g., Neuling et al. 2017).

Online entrainment and offline aftereffects

The primary goal of tACS is to target ongoing brain activity, whereby the frequency of the applied field is typically matched to the intrinsic frequency of the target activity ("frequency tuning"; Veniero et al. 2015). By definition, any entrainment to tACS can only occur during stimulation (i.e., online)—since the internal oscillation needs to couple with the external oscillator. While online analyses may capture genuine neural entrainment—for example, individuals' peak alpha activity was reported to shift toward 10 Hz (the tACS frequency; Helfrich et al. 2014b)—these effects may spuriously reflect residual artefact instead (Noury et al. 2016), especially when entrainment is observed in response to implausibly low current intensities (e.g., 0.05 mA; Ruhnau et al. 2016). To avoid having to deal with artefacts in the M/EEG, many researchers instead restrict spectral analyses

to post-stimulation periods. While echoes of entrainment are observable only for a few cycles after stimulation offset (e.g., Marshall et al. 2006; Hanslmayr et al. 2014), longer-lasting aftereffects of tACS are almost always reported (Veniero et al. 2015). These longer-lasting effects therefore likely reflect plasticity-related network changes rather than entrainment per se (Zaehle et al. 2010; Vossen et al. 2015; Wischnewski and Schutter 2017).

Any entrainment effect is likely related to subsequent aftereffects (Vosskuhl et al. 2018). For example, entrainment is likely responsible for increased regularity in spike timing during tACS (i.e., online), and this synchronised spike timing may have plasticity-related effects on the targeted networks (Vossen et al. 2015), resulting in prolonged amplitude increases beyond stimulation (i.e., offline; Zaehle et al. 2010). Indeed, if online and offline effects are associated, then this should be detectable across participants (e.g., Helfrich et al. 2014a, b)—and may provide a good validation for online spectral analyses. For example, Helfrich et al. (2014b) showed that alpha power during 10 Hz tACS predicted alpha power outlasting tACS. This suggests that the online measure of entrainment captured something meaningful about the effect of tACS on the brain. However, alpha power was also more peaked during stimulation (i.e., the peak frequency was 'tuned' toward 10 Hz). This suggests that the two effects, while related, do not simply reflect the same effect of tACS on endogenous activity: the online effect may reflect entrainment (and thus high frequency-specificity), and the aftereffect may reflect some plasticity-related network effect (i.e., with a more broadly affected—native—power spectrum). Of course, a less interesting explanation for observing a frequency-tuning effect online is that the 10 Hz artefact was not completely removed (see Noury et al. 2016). Understanding the extent to which tACS modulates endogenous activity online—and thus the extent to which entrainment mediates any aftereffect—clearly depends on the validity of these artefact-cleaning procedures.

The efficacy of tACS appears to increase with stimulation intensity and by tuning its frequency to the targeted oscillation (Schutter and Wischnewski 2016), findings that are expected given an entrainment-mediated effect of tACS (see also Thut et al. 2017). However, there is no clear pattern of frequency-specificity across the few studies that have assessed tACS-dependent spectral aftereffects in the M/EEG. Veniero et al. (2015) identified 22 reports (33 experiments) that assessed tACS aftereffects in the M/EEG, with only mixed evidence for frequency-specific effects. While some of these findings may reflect genuine cross-frequency interactions (e.g., gamma tACS may suppress endogenous alpha activity; Helfrich et al. 2016), frequency-nonspecific aftereffects may also reflect effects through alternative mechanisms or false positives (which are expected to be uniformly distributed across frequency bands). Similarly, evidence for

frequency-specificity may spuriously arise from the analysed bands themselves (e.g., assessing only alpha activity after alpha tACS, and thus excluding possible evidence to the contrary). At best, our understanding of how—and to what extent—tACS affects neural activity beyond stimulation is poor.

Future directions

While this review so far has focused predominantly on the ongoing challenges in the field, it is a testament to tES researchers that all of these issues are being acknowledged, debated, and—in many cases—creatively ameliorated to improve the ways both tACS is delivered and its effects measured. Below, we outline some of the exciting ways in which tACS may be improved, and the likely future directions of the field. We describe some ways in which artefacts of tACS may be better managed using high-frequency protocols, and describe innovative methods for current interactions within the brain that offer either dynamic or more focal current distributions while also minimising transcutaneous effects.

Amplitude-modulated tACS

Removing artefacts of tACS from the M/EEG is made difficult by modulations to amplitude and phase by heartbeat and respiratory effort (see "The nonlinear problem"). Modifying the waveform of tACS may not only change how readily neural activity is influenced, it may also make it easier to break the nexus between meaningfully entrained activity and the resultant artefacts of stimulation. For example, sawtooth tACS is piecewise linear (Dowsett and Herrmann 2016), and its artefacts may therefore be easier to remove. However, it too (and indeed any current-controlled waveform, including tDCS) will be modulated by impedance changes due to Ohm's law. Unfortunately, non-sinusoidal waveforms almost always make these nonlinear modulations less traceable than conventional (mono-sinusoidal) tACS. One promising alternative, however, is to purposely modulate the amplitude of tACS at the frequency of interest (amplitude-modulated, AM–tACS; Witkowski et al. 2016). By introducing the critical frequency (e.g., 10 Hz) as the envelope of a higher-frequency carrier wave (e.g., 220 Hz; itself not of physiological importance), the M/EEG spectrum in principle becomes contaminated over a range of frequencies that are not of interest to the researcher [220 Hz ± 10 Hz]—disentangling the endogenous spectrum of interest from the artefactual tACS spectrum (Fig. 3a versus Fig. 3b). There is growing evidence that AM–tACS can entrain oscillations at the frequency of its envelope (Chander et al. 2016; Witkowski et al. 2016; Minami and Amano 2017), though

may require greater stimulation intensities (Negahbani et al. 2018) compared to mono-sinusoidal tACS. Unfortunately, recent work suggests that some artefact remains near the envelope frequency (Minami and Amano 2017; Kasten et al. 2018). In principle, AM–tACS should well tolerate heart-beat- and respiration-related modulations, since these too will symmetrically contaminate the spectrum near the high-frequency carrier.

Targeting network connectivity

While there are many methods to rhythmically induce oscillations in the brain (Herrmann et al. 2016), tACS is one of the only techniques that allows for the manipulation of phase coherence between distant brain regions—one exception being bifocal rTMS (e.g., Plewnia et al. 2008). This makes it a great tool for causally studying communication through coherence (Fries 2015) across brain networks (Saturnino et al. 2017; Tan et al. 2018). Basic two-electrode tACS montages always have opposite polarities (i.e., oscillate in anti-phase; 180°-lag). However, the tACS current output can be split into many sites of stimulation, resulting in both 0°- and 180°-lags between electrodes (e.g., Bland et al. 2018). Broadly, anti-phase relationships are thought to decouple network nodes (e.g., down-regulating functional cooperation, Helfrich et al. 2014a; Polanía et al. 2015), whereas in-phase relationships are thought to couple the targeted structures (e.g., up-regulating functional cooperation, Polanía et al. 2012; Reinhart and Nguyen 2019). Given neural transmission delays, however, perfectly in-phase relationships may not always lead to increased functional cooperation (e.g., Tseng et al. 2016; Miyaguchi et al. 2019).

With growing interest in the use of tACS to target oscillating neural networks (Saturnino et al. 2017; Tan et al. 2018), greater control over ongoing phase relationships may be desirable. Using a single tACS device, any stimulating electrodes (even within a high-density montage) must either have an in-phase or anti-phase relationship—and any electrode with an in-phase relationship must have some other anti-phase relationship with an electrode elsewhere on the body. This restricts the coupling of network nodes to a zero-lag relationship (though often a small delay is hypothesised to be beneficial; see Bastos et al. 2015). Using two independent current sources, the induced phase relationship can be set to any angle (e.g., Polanía et al. 2015). An example of a 90° phase relationship is contrasted with 180° and 0° montages in Fig. 4. Implanted electrodes during dual-source tACS capture interesting properties of the induced electric fields with different phase relationships between the current sources (Alekseichuk et al. 2019a). At offsets other than 0° and 180°, the location of the maximum voltage gradient is not consistent throughout the tACS cycle (Fig. 4): the interacting current sources instead generate a "travelling wave"
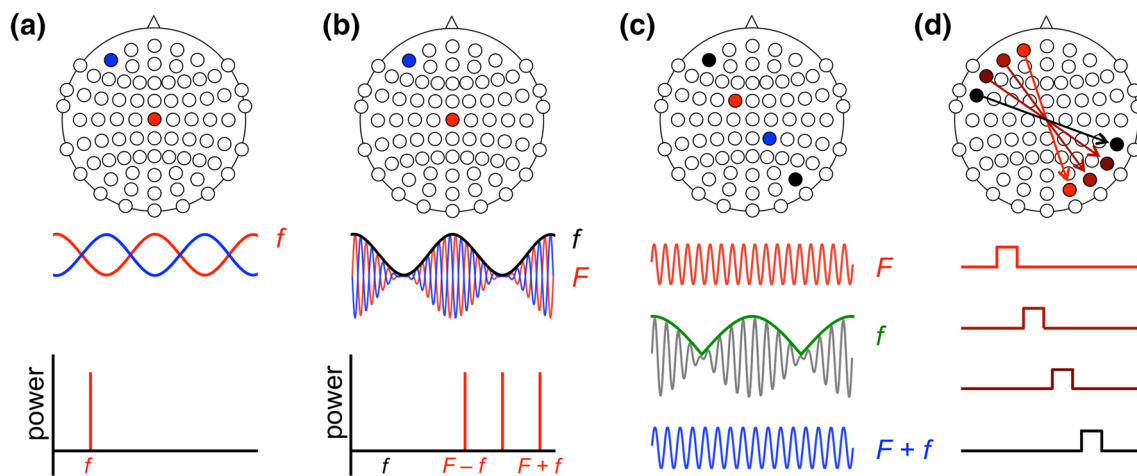
Fig. 3 Variants of rhythmic tES. **a** Conventional mono-sinusoidal tACS, where a fixed-frequency sinusoidal current is delivered through two electrodes on the scalp. The power spectrum of any electrophysiological recordings will be contaminated at this frequency. **b** Amplitude-modulated tACS, where the amplitude of a high-frequency carrier wave (F) is purposely modulated at another frequency of physiological relevance (f). Now, the power spectrum is contaminated at the carrier frequency (and above and below it by the envelope frequency). This preserves the lower power spectrum (i.e., endogenous activity near the envelope frequency), provided $F \gg f$ (e.g., 220 Hz carrier with a 10 Hz envelope). **c** Two independent high-frequency alternating current sources with different frequencies (F and $F + f$) temporally interfere with each, resulting in an amplitude-modulated waveform with 'beats' at the frequency of their difference (i.e., f).

Here, each current source has its own return electrode (black). This technique (temporal interference stimulation) is described in Grossman et al. (2017). **d** An array of stimulating electrode pairs induce staggered current pulses in quick succession. This technique exploits the relatively slow integration time of the neural membrane, allowing the short pulses (all with similar electric field orientations) to sum near their intersection. The pulse width (e.g., 2.5–10 μs) and inter-pulse interval (e.g., 5–50 μs) are chosen as desired. Rhythmicity can be achieved by cycling through the pairs of electrodes for different durations across time (e.g., 1 s on; 1 s off). This technique (inter-sectional short-pulse stimulation) is described in Vöröslakos et al. (2018). Panels **c**, **d** are also described in greater detail in "Interfering currents"

within the brain. In future, dual-source tACS may enable the design of novel stimulation protocols not achievable with a single device (e.g., purposely inducing an oscillation that propagates dynamically from parietal to frontal areas). However, the application of two independent current sources will likely make artefact removal even more difficult, since both will be vulnerable to nonlinear modulations.

Interfering currents

At its core, tES is a blunt instrument for neuromodulation: its application is typically unfocused, with the low proportion of current that does reach the brain inducing highly distributed and diffused effects (Wagner et al. 2013; Opitz et al. 2015). The use of multi-electrode montages can better focalise these effects, but often at the cost of dramatically decreasing intracranial electric field strengths at the target (see "Shunting"). For many clinical and research applications, it is desirable to apply tACS in a focal manner—at intensities sufficient to influence brain activity—without causing undue discomfort to the recipient. In essence, we wish to increase the electric field strengths in the brain while decreasing those at the scalp (i.e., reducing the peripheral effects, Liu et al. 2018; Alekseichuk et al. 2019b). Multi-electrode tES montages are one potential method to reduce

sensations at the scalp, since the injected current is divided proportionally across the electrodes. However, because the scalp, skull, and brain conduct current in a near-homogenous manner, an arrangement of multiple electrodes that deliver current simultaneously offer limited control for inducing a spatially confined effect (Vöröslakos et al. 2018; but see Huang and Parra 2019). Instead, high-frequency alternating currents and short pulses of direct currents (i.e., faster than the neuronal membrane time constant, ~30 ms; Liu et al. 2018) may induce spatially confined effects while reducing unwanted peripheral nerve stimulation. When these currents interact within the brain, they may offer the ability to induce strong electric fields with comparably weaker scalp sensations.

The first method that offers this ability is 'temporal interference' stimulation (Grossman et al. 2017; see Fig. 3c), whereby two independent high-frequency currents of slightly different frequencies (e.g., 2000 Hz and 2010 Hz) are delivered to the brain at the same time. Where these fields overlap in the brain, the resultant envelope has a frequency equal to the difference between the frequencies of the two waveforms (i.e., 10 Hz 'beats'), offering a means to entrain oscillations with this slower amplitude modulation. A second method is 'intersectional short pulse' stimulation (Vöröslakos et al. 2018; see Fig. 3d), whereby sets of
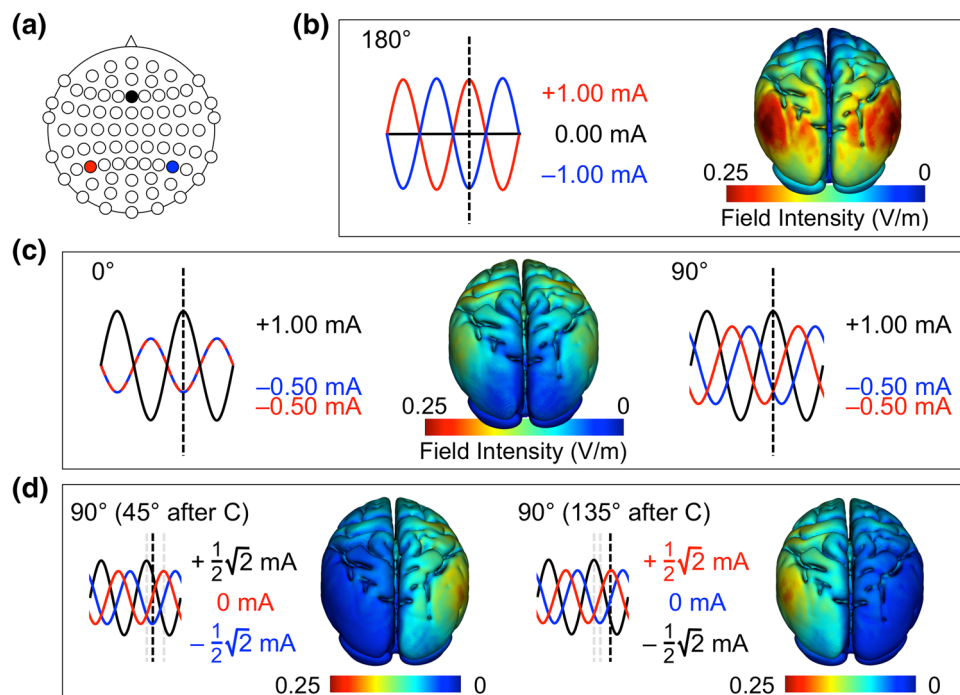
Fig. 4 Multi-electrode and multi-source tACS for targeting ongoing phase relationships. **a** A toy example of a three-electrode montage, with the phase relationship between the left and right parietal electrodes (red and blue) of interest to the researcher. **b** A classic tACS application where two electrodes oscillate in anti-phase (180°-lag). Here, the return (black electrode) remains inactive, since the red and blue electrodes mirror each other exactly. Delivering a single current source through two electrodes will always induce an anti-phase relationship (i.e., there is no need for the third electrode). The field spread was computed at the extremum of 2 mA peak-to-peak tACS (1 mA entry, red; 1 mA exit, blue). **c** Left, a simple example of splitting the current source between two electrodes (red and blue) so that they oscillate in-phase (0°-lag). Since the current is halved between them, they each have a maximum value of 0.5 mA, while the return (black) retains its maximum value of 1 mA. Right, the red and blue electrodes have separate current sources, and an offset of 90° has been chosen. At this instant in time (dashed line), this montage induces the same electric field in the brain as the in-phase montage. **d** Because the return (black) electrode must equal the sum of the red and blue electrodes (though with the opposite polarity) at each point in time, the field distribution changes dramatically across the tACS cycle. The 90°-lag between red and blue electrodes results in each equaling 0 mA exactly when the other reaches an extremum (~ 0.7 mA). For example, 45° forwards in time (indicated by dashed line), the left parietal electrode (red) becomes inactive. Another 90° forwards in time (135° total), the right parietal electrode (blue) becomes inactive. The ongoing 90°-lag between red and blue electrodes therefore creates a "travelling wave" throughout the brain. Indeed, any phase relationship other than 0° and 180° induces a non-static maximum absolute field across time. Field spread was computed for a composite scan (MNI 152) using Soterix Medical HD–Explore software. Note: For the in-phase and anti-phase montages, the point of absolute maximum field intensity remains constant across the tACS cycle (i.e., the value of the maximum electric field magnitude scales with the current intensity, but the position of this maximum remains static). For example, the red and blue electrodes in **a** always have equal but opposite values (180°-lag; i.e., current is always strongest under the two stimulating electrodes); similarly, the return (black) electrode in **b** is always twice the absolute value of the other electrodes (0°-lag; i.e., current is always strongest under the return electrode). At all other phase relationships, the electrode delivering the maximum absolute current changes over time. This phenomenon is described in Alekseichuk et al. (2019a)

electrode pairs each deliver a brief current pulse in quick succession (e.g., 10 µs pulse width with a 50 µs inter-pulse interval). Near the intersection of these electrode pairs, neurons can temporally integrate the multiple staggered electrical gradients—exploiting the (relatively slow) neuronal membrane time constant (temporal multiplexing). While these techniques are still very new, they show promise for offering better focality and depth of stimulation (Widge 2018; Karabanov et al. 2019), since the area of intersection can be arbitrarily chosen within the brain. The application of high-frequency alternating currents (Grossman et al. 2017)

or short pulses of direct current (Vöröslakos et al. 2018) may also make it easier to deal with the resultant artefacts of stimulation.

Phase-dependent outcomes

Residual artefacts of tACS are extremely difficult to disentangle from genuine neural entrainment (Noury et al. 2016). An alternative method to probe an effect of tACS on functionally relevant brain oscillations is to model electrophysiological or behavioural outcomes dependent on

the ongoing phase of tACS. For example, auditory perception has been shown to depend on the ongoing phase of tACS (e.g., 4 Hz, Riecke et al. 2015a, b; 10 Hz, Neuling et al. 2012; but see Asamoah et al. 2019b). Similar phase-dependencies have been shown for both visual (Helfrich et al. 2014b) and somatosensory (Gundlach et al. 2016) perception during alpha tACS (but see de Graaf et al. 2019). Cross-frequency phase-amplitude coupling has also been shown for oscillatory activity outside the frequency of tACS (e.g., modulating gamma power by the phase of alpha tACS, Helfrich et al. 2016; Herring et al. 2019). Modelling such phase-dependent effects of tACS is rapidly gaining popularity, though the many ways these effects can be quantified may influence their detectability (see Zoefel et al. 2019). One common approach is to compare the outcome variable once it has been divided into discrete phase bins. However, individuals may differ in their preferred phase (i.e., the offset in their observed phase-dependency to tACS). Consequently, individuals are often aligned based on this offset (e.g., setting the 'best' phase bin for each participant as though it occurred at the same point in the tACS cycle). Unfortunately, this alignment procedure can easily result in observing a spurious phase-dependency if not correctly accounted for (Asamoah et al. 2019b). It may therefore be desirable to model such phase-dependencies continuously (i.e., no phase binning), with the amplitude, phase, and any bias left as free parameters when fitting these models. These sinusoidal models can be fit iteratively (e.g., Fiene et al. 2019). However, exact solutions can be found with least squares optimisation, making such approaches more computationally efficient (especially when this process needs to be performed thousands of times for non-parametric permutation analysis).

Knowing the instantaneous phase of tACS at the times of the relevant events (e.g., taken from the current output, or a recording of its artefact), the following can be used to find optimal sinusoidal models (either with or without phase-binning) for continuous outcome variables. Given some outcome y observed at phases x (both vectors of length n), compute a predictor matrix (4) with columns for the bias (all ones), and with unit sine and cosine components (used together for computing the model amplitude and phase offset). This predictor matrix is used to find the model parameters that minimise the squared cost. Solving the normal equations in (5) provides a unique solution to the minimisation problem. A desirable property of (5) is that the Gramian X^TX remains 3×3 irrespective of n (i.e., the number of datapoints), keeping computation time for its inverse low. In (5), T denotes the matrix transpose. The model values $\hat{y}$ can be reconstructed at the observed phases x (6). Equivalently, the optimal bias b (7), amplitude α (8), and phase ϕ (9) can complete the one-cycle sinusoidal model. In (9), atan2(y, x) computes the four-quadrant inverse tangent—the angle between the positive x-axis and the vector representing (x, y) in the Cartesian plane.

$$X_{n \times 3} = \begin{bmatrix} 1 & \sin(x_1) & \cos(x_1) \\ \vdots & \vdots & \vdots \\ 1 & \sin(x_n) & \cos(x_n) \end{bmatrix} \tag{4}$$

$$\theta_{3 \times 1} = \left(X^T X\right)^{-1} X^T y \tag{5}$$

$$\hat{y}_{n \times 1} = X\theta \tag{6}$$

$$b = \theta_1 \tag{7}$$

$$\alpha = \sqrt{\left(\theta_2\right)^2 + \left(\theta_3\right)^2} \tag{8}$$

$$\phi = \text{atan2}\left(\theta_3, \theta_2\right) \tag{9}$$

Conclusion

Neuromodulation by transcranial electrical stimulation (tES) remains a promising tool to engage or disrupt ongoing oscillatory activity within the brain, with the potential to provide causal perspectives on the roles of oscillations in neural processing and inter-regional brain communication. Nevertheless, there remain important challenges to and considerations for how best to induce intracranial electric fields with sufficient intensity to modulate endogenous brain activity without causing undue discomfort from transcutaneous effects of stimulation. In our view, the community of tACS researchers (and other forms of low-intensity tES) is already cognizant of the many issues outlined in this review. Indeed, even within the time of writing, many new articles warranted inclusion—itself a testament to the rapid progress within the wider field of non-invasive brain stimulation. Recently, there have been calls for (Bikson et al. 2018; Modolo et al. 2018) and significant strides in (Bikson et al. 2019) bettering our reporting standards (e.g., with systematic dosimetry and nomenclature for tES applications), and we remain optimistic for the continued use—and due criticism—of tES. Still, there remains an urgent need for well-powered replications, for the design and implementation of well-controlled experiments, for the preregistration of preprocessing and analytic procedures, and for open access to data (Héroux et al. 2017; Bikson et al. 2018). These are not issues unique to tES research, though we are hopeful that tES researchers are uniquely motivated to improve the quality of scientific inquiry within our field. While tACS has certainly had its ups and downs over the past decade, this by no means marks its rise and fall as a valuable tool for the study of brain–behaviour relationships.

Compliance with ethical standards

Conflict of interest The authors state that they have no conflict of interest.

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