Trends in Neurosciences

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Review

Personalizing transcranial electrical stimulation

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Transcranial electrical stimulation (tES) encompasses non-invasive neuromodulation techniques, such as transcranial direct and alternating current stimulation, which modulate the central nervous system to probe causal links between the brain and behavior and treat disorders. Unfortunately, fixed stimulation paradigms induce variable effects due to intra- and interindividual factors. Consequently, personalized approaches to tES are increasingly used. In this review, we highlight this emerging domain of human brain stimulation, examining strategies for the personalization of stimulation parameters and their underlying rationales. Multiparameter personalization and the identification of markers indicating tES efficacy represent promising directions. Personalization is not a panacea for all the challenges of tES, but marks an essential step toward reducing the variability of this technique.

Highlights

Transcranial electrical stimulation (tES) is a promising non-invasive brain stimulation modality for fundamental and clinical human brain research.

The efficacy and reproducibility of tES are limited due to substantial intra- and interindividual variability, warranting parameter personalization.

Personalized tES protocols aim to reduce variability by tailoring stimulation parameters to both temporally stable and dynamic features of an individual, using metrics, such as brain structure and activity, to guide personalization.

Current personalization efforts are promising but remain fragmented, with limited integration across features reducing the potential gains of the approach.

Personalization is not a universal remedy, but represents a step toward more consistent stimulation effects, reduced unexplained variance, and the development of optimized protocols.

Beyond one-size-fits-all stimulation: the case for personalized transcranial electrical stimulation

Neurostimulation techniques are essential to investigate causal neural mechanisms and develop therapeutic interventions. Human neuroscience research is mostly constrained to non-invasive techniques with minimal side effects, among which **transcranial electrical stimulation (tES)** (see Glossary) is rapidly growing. tES encompasses a family of techniques that modulate neural activity by delivering weak electric currents through the scalp [1,2]. It allows causal study of brain functions, and has been applied across species [3]. From a translational perspective, tES modalities show promise in treating neurological and psychiatric disorders and enhancing motor and cognitive performance [4,5]. The appeal of tES also lies in its affordability, accessibility, and versatility [6,7]. Several medically approved tES devices offer a variety of stimulation paradigms for a relatively affordable price.

One major challenge for tES is heterogeneity in effects. Intra- and interindividual differences exist across multiple domains. Their cumulative impact can lead to markedly different responses to the same tES paradigm, both across individuals and over time [8,9]. In fact, the heterogeneity observed following some tES protocols is of such magnitude that their efficacy remains under scrutiny, even after decades of research and many thorough replication efforts (e.g., [9,10]). At the same time, robust effects of tES have been observed in both human and animal studies conducted under highly controlled conditions [10–15]. Together, these findings underscore the potential of tES to modulate brain function, while highlighting the need to better understand and reduce its variability in real-world applications. Researchers are increasingly adopting personalized protocols in response to the observed variability where tES parameters are tailored to an individual's features at a given moment.

In this review, we synthesize current strategies to personalize tES in humans. First, we map out the tES parameter space and the known variability sources. We then discuss the different personalization strategies per variability domain. We examine the merits of personalized tES and its challenges given the contemporary body of knowledge. Finally, we outline future directions and outstanding questions.

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The parameter space of tES

tES comprises a range of modalities, each of which involves multiple stimulation parameters that can be configured in various ways (Box 1 and Figure 1). This broad parameter space introduces substantial complexity when studying tES. This complexity is further amplified by the nonlinear dose–response relationships observed for some stimulation parameters [16–20]. For instance, 2 mA tDCS was shown to increase corticospinal excitability after 20 min, but not after 10 or 30 min, while 1 and 3 mA had no effect irrespective of duration [18].

If tES yielded robust effects, characterizing its dose–response relationships would be both feasible and clinically valuable, given the promise of this technique. However, the large variability in tES efficacy complicates interpretation, raising questions about whether some effects are genuine or simply reflect a large variability in efficacy. Therefore, a first priority is to tailor tES to achieve more robust effects.

Domains of variability in tES outcomes and their related personalization approaches

Effective personalization hinges on a thorough understanding of the myriad sources of variability in stimulation outcomes (Figure 2). The persistence of variability, even under tightly controlled application of tES, implies that variability arises, for a large part, from the recipient, rather than from the source. Personalized tES acknowledges this recipient-driven variability, but is no cure-all; it cannot substitute rigorous study design or ensure universally effective interventions. However, personalization can be a part of rigorous study design, with the tailoring of certain tES parameters

Box 1. Transcranial electrical stimulation paradigms

tES comprises many paradigms, applying either a direct or alternating current (see Figure 1 in the main text). Here, we describe several modalities, of which transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) are the most popular.

Direct current modalities

tDCS applies a constant, low-intense, direct current. While its working mechanisms are complex, according to the traditional dogma, stimulation of a cortical region with the anode increases excitability via currents entering the cortex. Conversely, stimulating a region with the cathode decreases excitability. The effects of tDCS outlast the length of stimulation, indicating the presence of neuroplasticity-like changes.

Oscillating transcranial direct current stimulation (otDCS) combines features of tDCS and tACS. It applies a direct current that oscillates in amplitude, and aims to elicit both tDCS- and tACS-associated effects.

Transcranial pulsed current stimulation (tPCS) applies electrical pulses rather than continuous or alternating currents. This allows for transient modulation of neural activity in a pulse-like pattern.

Alternating current modalities

tACS applies a sinusoidal, alternating electric current at a specific frequency. A central working mechanism is that of entrainment: the synchronization of endogenous neural oscillations to the externally imposed tACS frequency. The effects of tACS depend on the stimulation intensity and frequency in relation to the brain function and region. Various tACS subtypes exist, including in- and antiphase tACS, where multiple tACS montages are combined to alter inter-regional functional connectivity.

Transcranial random noise stimulation (tRNS) delivers an alternating electric current at randomly varying amplitudes and frequencies. It is assumed to alter cortical excitability by injecting noise into the neural circuits. This enhances the ability of the neural circuits to detect and/or transmit weak signals via the phenomenon of stochastic resonance.

Transcranial temporal interference stimulation (tTIS) uses two or more slightly different high-frequency currents. These penetrate the head more easily compared with currents applied at lower frequencies. At the intersection of both currents, an electric field is generated that is amplitude modulated at the envelope beat frequency (i.e., the frequency difference between both currents). tTIS is assumed to enable stimulation of deeper brain regions.

Glossary

Amplitude-modulated tACS: form of tACS in which the amplitude of the applied current varies over time, typically by modulating a high-frequency carrier signal with a slower envelope frequency.
Closed-loop system: in the context of neurostimulation systems, including tES, refers to approaches that use real-time monitoring of brain activity to adapt stimulation parameters dynamically, with the aim of improving the precision and effectiveness of interventions.
Current flow modeling: computational technique used to predict the distribution and intensity of electric fields in the brain during tES, typically informed by individual anatomical information obtained via structural MRI, and reliant on assumptions about tissue conductivity values, which can introduce a source of uncontrolled variability.
Electroencephalography (EEG): non-invasive method to record electrical activity of the brain using scalp electrodes; commonly used to study neural oscillations and brain dynamics.
Electromyography (EMG): technique to record electrical activity produced by muscles; commonly used in non-invasive brain stimulation to assess electrophysiological responses to sTES and TMS.
Functional magnetic resonance imaging (fMRI): MRI-based technique that indirectly measures neural activity by detecting changes in blood oxygenation levels, which are coupled to local neural activity via neurovascular responses.
Functional near-infrared spectroscopy (fNIRS): non-invasive brain imaging technique that measures the hemodynamic response associated with brain activity, by detecting changes in the concentration of oxygenated and deoxygenated hemoglobin using near-infrared light.
Magnetic resonance current density imaging (MRCDI): MRI-based technique that maps the distribution of electric currents in biological tissues by detecting the magnetic fields they induce; enables non-invasive visualization of current flow, informing on externally applied stimulation. such as tES.
Magnetic resonance imaging (MRI): non-invasive imaging technique that uses strong magnetic fields and radio waves to produce detailed images of issues, including brain structures.

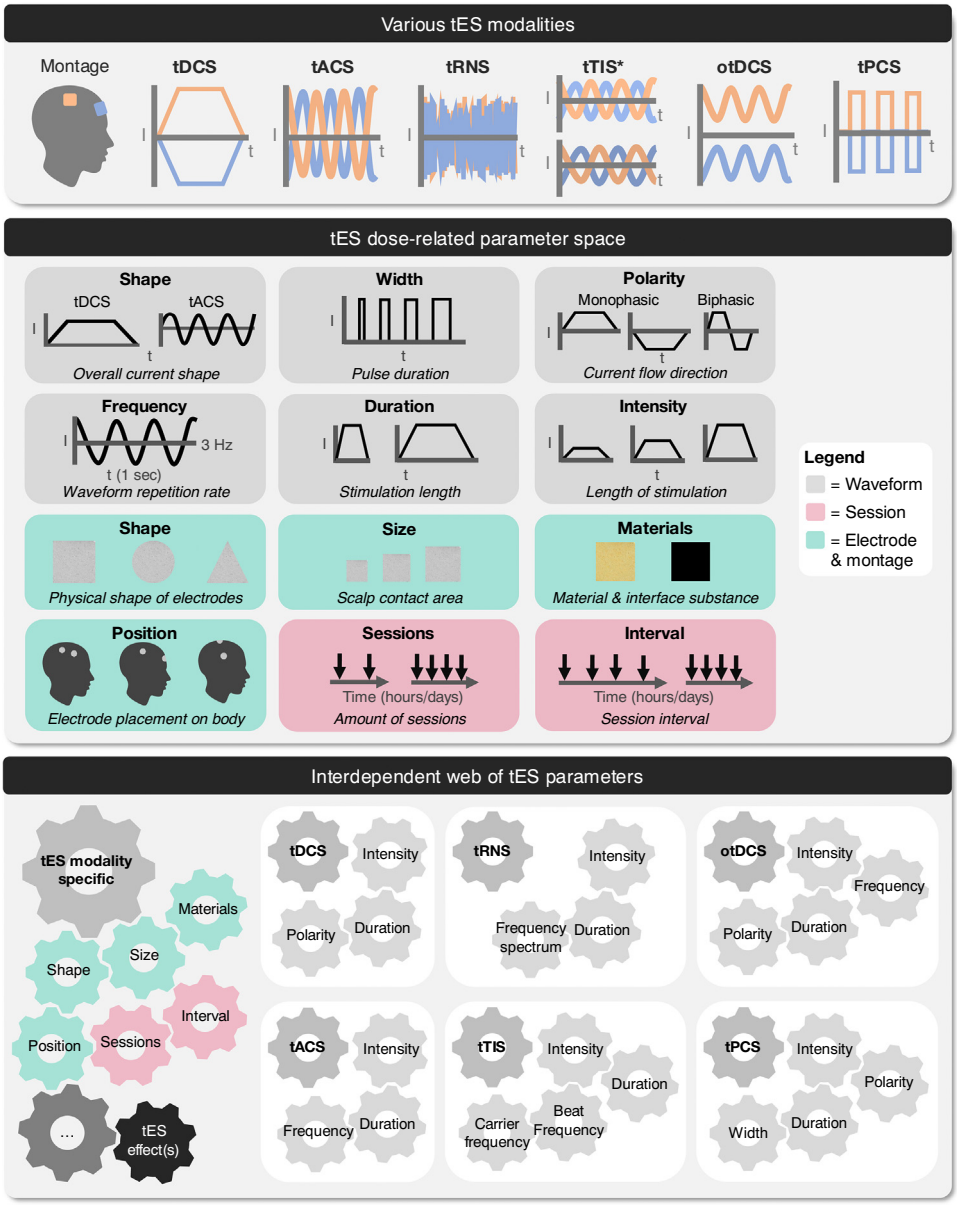

Figure 1. Overview of different transcranial electrical stimulation (tES) modalities and the interdependent tES parameter space. The upper panel displays the current waveforms of six tES modalities (see also Box 1 in the main text). Each modality is illustrated with a montage involving two electrodes (orange and blue), except for transcranial temporal interferential stimulation (tTIS, indicated by an asterisk), where at least two montages are required. The middle panel shows The nine parameters of tES. For multiple-site- and/or closed-loop oscillating tES, phase (difference) may be considered as a tenth parameter. The lower panel indicates the different parameters per tES modality. Adjusting one parameter can inadvertently influence the effect of other parameters on the brain. This, combined with the intricate relationship of each parameter with tES effects, results in a broad tES parameter space. Abbreviations: otDCS, oscillating transcranial direct current stimulation; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; tPCS, transcranial pulsed current stimulation; tRNS, transcranial random noise stimulation; tTIS, transcranial temporal interference stimulation.

Magnetoencephalography (MEG): non-invasive method to record magnetic activity generated by the brain at the scalp, commonly used to study neural oscillations and brain dynamics.

Suprathreshold transcranial electrical stimulation (sTES): non-invasive brain stimulation method that uses suprathreshold electrical pulses to influence neural activity, resembling tPCS to some extent.

Transcranial electrical stimulation (tES): category of non-invasive techniques that use low-intensity electrical currents to modulate brain activity, including tDCS, tACS, otDCS, and tPCS (see Box 1 in the main text).

Transcranial magnetic stimulation (TMS): non-invasive brain stimulation method that uses electromagnetic fields to influence neural activity. Unlike tES, TMS is suprathreshold and capable of directly eliciting action potentials, making it a valuable tool for researching the effects of tES on the central nervous system.

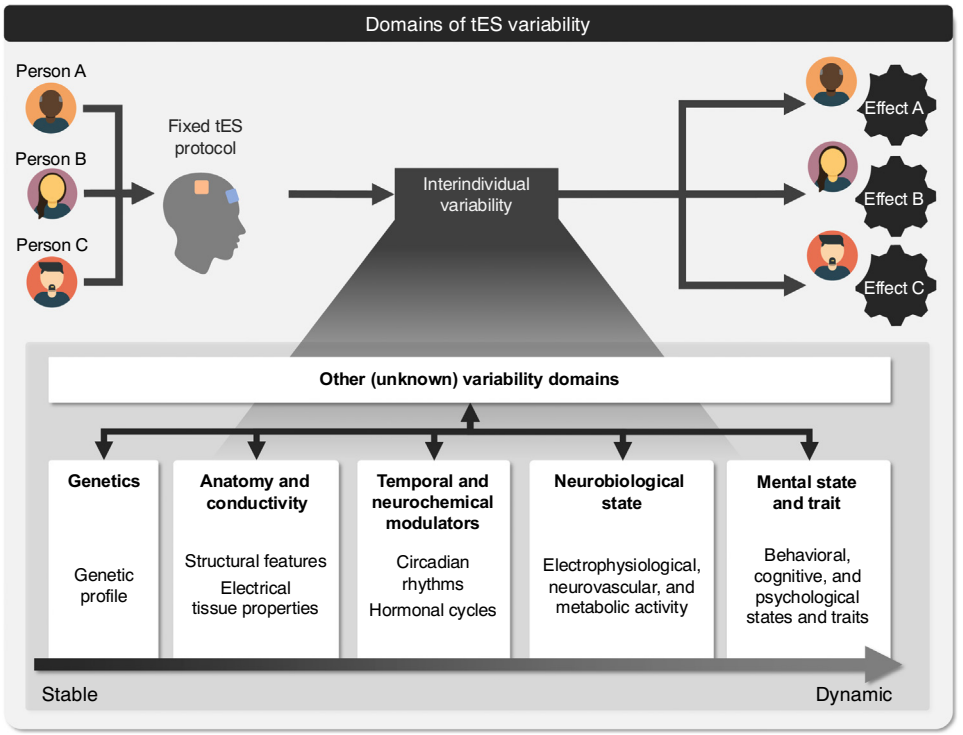

Figure 2. Domains of transcranial electrical stimulation (tES) variability. This schematic illustrates how the effects of a fixed tES protocol can vary across individuals due to several variability domains. Factors contributing to variability in tES efficacy are listed at the bottom of the figure, spanning multiple domains that range from being stable over time to dynamically changing. The different domains may interact with each other and overlap, encompassing shared influences, among which are age, sex, and clinical status. Other unknown domains could also exist, potentially influencing the interactions between known domains. The existence of such unknowns suggests that even full personalization of all known domains, a feat still far from reach, will not fully eliminate variability. However, it is unclear to what extent this residual variability will meaningfully impact clinical outcomes.

representing an informed experimental design choice. Importantly, personalization does not inherently compromise generalizability, because both can coexist depending on how generalizability is operationalized (Box 2).

Variability domains in tES outcomes span temporally stable domains, such as genetics, anatomy, and conductivity, as well as more dynamic domains, such as temporal and neurochemical factors, neurobiological state, and what we term ‘mental state and trait’; behavioral, cognitive, and psychological factors that influence tES efficacy.

Below, we discuss each of these domains, and highlight strategies to tailor tES parameters accordingly. While we discuss the domains separately, they are intertwined. For instance, genetic differences shape brain structure and influence neurobiological states. In turn, neurobiology influences gene expression, and can be constrained by brain structure [21]. This interconnectedness has implications for the personalization of tES parameters: personalizing tES based on one domain may inadvertently also control for other domains, and the benefits of advanced personalization may diminish when there is large overlap between personalized domains. Of note, several factors, including age, disease, and sex, are not explicitly tackled in this article, despite their importance, partly because they span many, if not all, of the domains being discussed.

Box 2. Implications of personalized tES for generalizability

Reducing variability in tES effects through personalization implies tailoring parameters to an individual's characteristics at a given time. A common critique is that this reduces generalizability by limiting replicability and introducing ambiguity. This assumes an expression-based operationalization of generalizability, where fixed parameters are needed for replication. Here, we propose a principle-based operationalization, where generalizability is achieved through consistent engagement of targeted mechanisms.

From this perspective, personalized tES is more generalizable. An example is the application of tACS 1 Hz below an individual's endogenous theta peak. This enhances visual working memory because slower theta waves relate to greater memory capacity [85,95,96]. Conversely, applying tACS at the peak frequency does not alter memory, instead increasing theta power [85]. Thus, a tES paradigm that is fixed in expression will increase working memory in some individuals and theta power in others, depending on the relationship between the endogenous theta peak and the tACS frequency.

Challenges and risks of personalization for generalizability

Personalization introduces potential pitfalls that must be managed to maintain replicability. Small methodological variations can inadvertently alter the mechanisms targeted by tES. For instance, measuring endogenous theta peak frequency with eyes open versus closed yields different results [131]. To mitigate these risks, it is imperative that personalization strategies are rigorously standardized and transparently reported. We propose to report the following details to ensure that personalized paradigms can be properly evaluated, reproduced and compared:

(i) Personalization basis: define the features that were used to tailor stimulation. Examples include the individual peak theta frequency or the mean electric field magnitude in a specific gray matter volume.

(ii) Parameter mapping procedure: describe how these features were translated into tES parameters. For instance, stimulation frequency might be computed as the individual theta peak frequency minus 1 Hz, while current intensity might be scaled using Equation I:

$$\textit{Current intensity} = \frac{1\ \text{mA target electric field magnitude}}{\textit{Individual electric field magnitude at a 1 mA tES}} \quad [\text{I}].$$

(iii) Parameter mapping implementation: share analysis pipelines or code used to translate individual features into stimulation parameters. This ensures replicability and is particularly relevant in light of future more complex personalization strategies where, for example, mental constructs may be mapped onto tES parameters.

(iv) Stimulation parameters: provide a full description of the tES parameter space. For fixed parameters, reporting group-level values suffices, while personalized parameters should be reported on a per-subject basis or via adequate summary statistics.

Genetic polymorphisms may shape tES efficacy, but have yet to yield personalization strategies

Genetic polymorphisms (common variations in DNA sequences) shape how individuals respond to tES. They may do so directly, when affecting factors closely related to tES working mechanisms, such as neuroplasticity, neurotransmitters (e.g., GABA, glutamate, and dopamine), and neurotrophic factors (e.g., brain-derived neurotrophic factor; BDNF) [22–24]. For example, tES efficacy has been linked to the BDNF Val66Met polymorphism, which reduces activity-dependent BDNF secretion and alters neuroplasticity, and GABRA3 polymorphisms, which modulate GABAergic inhibition [25,26]. Indirectly, genetic variations shape tES effects by influencing other variability domains. For example, altered BDNF release relates to differences in (sub)cortical anatomy and neurobiological and mental state [27–30].

Despite these associations, efforts to predict tES responses through genotyping have yielded limited success [25,26,31–33]. This may be due to genetic variability having a secondary role to more established variability domains. Alternatively, it could be due to the complex impact of genetics, the currently limited assessment of genetic factors, or the complex interplay between genes and other variability domains. Future advances in epigenetics and functional genomics, which capture dynamic gene–environment interactions and gene expression patterns, may offer more insights.

For genotyping to become a viable personalization approach, stronger links between specific genotypes and tES efficacy need to be established. While the personalization of tES parameters

through other domains could help isolate the indirect contributions of genetics, this may imply that some secondary genetic effects are overlooked. Nevertheless, such a trade-off may ultimately be justified by the goal of achieving accessible and consistent tES protocols.

If a robust genotype–tES relationship is identified, a next step is determining which tES parameters should be tailored to individual genotypes. For example, tES intensity and/or duration could be personalized to control for altered BDNF release in individuals with a BDNF Val66Met polymorphism, because both parameters relate to the neuroplasticity-like effects of tES modalities, such as transcranial direct current stimulation (tDCS) [34,35].

Anatomy and conductivity shape tES-induced electric fields and provide avenues for tES personalization

Anatomical idiosyncrasies are arguably the most understood source of variability in individual responses to tES. Electric fields induced in the brain depend on the thickness, distribution, and conductivity of the head tissues [3,11,20,36–43]. In terms of extracranial tissues, the skull and cerebrospinal fluid layers are particularly important given their pronounced conductivity profiles [44]. Gyral and sulcal anatomy further shape the effects of tES. Together with the orientation of the induced electric fields, they determine which neuronal structures are polarized and how [45,46]. Finally, both gray and white matter features, including cortical integrity, structural connectivity, cell type, and cellular density, relate to stimulation efficacy [47–51].

Efforts to control for anatomical variability almost exclusively rely on structural, **magnetic resonance imaging (MRI)**-driven, macrolevel **current flow models** [52]. Such endeavors simulate electric fields based on individual anatomy [52–56]. One straightforward approach involves scaling current intensity to equalize electric field magnitude within a region of interest (ROI) across individuals [40,57,58]. In its simplicity, this method overlooks critical factors, such as electric field orientation and off-target effects [46]. The optimal target magnitude also remains unclear, and likely depends on factors including neurobiological state and mental state. Head circumference-based adjustments offer a more accessible alternative, but only capture a fraction of the variability explained by MRI-derived models [59].

More advanced strategies tailor current intensity and/or electrode placement to control electric fields across multiple ROIs while minimizing unintended stimulation of other regions [60,61]. Yet, even incorporating such advanced electrode placement personalization does not always show significant advantages over fixed tES protocols [36]. In this study [36], links were found between tES effects and nonpersonalized factors, such as inward electric field strength, field focality, and the spatial relationship between the electric field and the **functional MRI (fMRI)**-identified ROI. This points to the potential of multiparameter tES personalization.

Emerging machine learning approaches offer promise by identifying responder-specific electric field patterns without predefined ROIs [62]. However, their additional value remains to be tested, and they further increase the technical threshold of personalization.

Conductivity has received much less consideration compared with anatomy. However, accurate electric field simulations require correct conductivity assumptions. Techniques such as **magnetic resonance current density imaging (MRCDI)** could advance this field. By enabling current flow models to use personalized conductivity values, they may relieve the reliance on fixed conductivity assumptions [63,64]. However, this method is still relatively new and requires further advances and validation before implementation.

Overall, current flow models are important for tES personalization. However, they are no standalone solution to variability, as highlighted by the poor reliability of tES effects across repeated sessions in the same individuals. Goals for future work include the exploration of dose–response relationships, investigating which electric field features are suitable to guide personalization, personalization of conductivity parameters, and further model improvement by, for instance, incorporating vascular structures and cranial nerves. Furthermore, integrating microscale neuronal models holds promise. These capture the microstructural inhomogeneity of the brain, and inform on how parameters, such as tES frequency and current direction, influence neural populations [52,65–67].

Temporal and neurochemical modulators are relevant yet largely uncharted tES personalization avenues

Beyond static determinants, time-dependent and biochemical factors cause tES to yield varying effects. The circadian rhythm and sleep–wake cycles cause fluctuations in neural excitability over time, which modulate tES responses. At least for tDCS, optimal effects appear to occur when stimulation aligns with an individual's preferred circadian phase [68–72]. Similarly, neurochemical factors, such as hormonal fluctuations (e.g., estradiol and cortisol) and neurotransmitter levels (e.g., GABA) influence synaptic plasticity and are affected by tES [73–76]. Psychoactive substances also have a role, altering hormonal and neurochemical states [77,78].

Despite the evident roles of temporal and neurochemical modulators in tES responsiveness, these factors remain a largely uncharted territory. Methodological progress should be made in the retrieval of reliable and accessible measures of hormones and/or neurotransmitters before these factors can become directly integrated in tES personalization pipelines.

Timing tES to a specific circadian phase or endocrine status is a practical way to mitigate variability, but its predictive value beyond established neurobiological state markers remains uncertain [71,75]. Future work should assess whether more direct quantification of hormones or neurotransmitters meaningfully improves predictive power to warrant the added complexity. In some cases, standardized questionnaires about, for example, circadian preference, alongside neurobiological markers may already capture these factors sufficiently.

Personalizing tES by accounting for neurobiological metrics before and during stimulation

The efficacy of tES hinges on the neurobiological state before and during stimulation, which offers personalization opportunities. The post-tES neurobiological state, while potentially relevant for efficacy and outcomes, does not offer a straightforward avenue for personalization and, therefore, is not discussed here.

In terms of personalizing tES parameters based on electrophysiological signatures preceding stimulation, the most common relevant measurement modalities are **electroencephalography (EEG)** and **magnetoencephalography (MEG)**. While phenomena, such as the phase lag between different brain regions, have been related to tES efficacy (e.g., [79]), the main focus of MEG/EEG research has been on the Arnold Tongue Principle [80,81]. This principle states that the effectiveness of oscillating tES modalities at a fixed amount of energy depends on the relationship between the frequency of ongoing neural activity and the tES frequency. When both are close, entrainment (i.e., synchronization) is more likely to occur [81]. The relevance of the Arnold Tongue Principle for oscillating tES has been shown in humans, primates, and computational models, causing tES frequencies to be increasingly matched to endogenous rhythms [16,80–82]. While a few studies report null effects [83,84], most research reports positive effects of this personalization approach, including studies comparing fixed with personalized paradigms [83–93]. However, while stimulating at the peak endogenous frequency appears to be best for

electrophysiological entrainment, the resultant synchronized neural activity is not beneficial per se in terms of behavior. For example, Parkinson's disease is characterized by hypersynchronization of beta-band activity, and beta-band transcranial alternating current stimulation (tACS) aimed at enhancing this synchronization through entrainment worsens motor symptoms [94]. Thus, the preferability of stimulating at the endogenous frequency may depend on the function of the targeted oscillatory activity. To illustrate further, longer theta cycles have long been related to better working memory capacity, by allowing the circuits oscillating at theta frequency to interact with more gamma cycles [95,96]. This cross-frequency theta–gamma coupling implies that slowing down theta may be the most desirable approach in this context, as demonstrated by research that applied tACS at a frequency below the theta peak frequency to enhance working memory [85]. Furthermore, many brain processes are event related, a feature not readily captured by approaches based on peak frequency over time.

Electrophysiological signals that allow for personalization do not need to stem directly from the brain. Several studies have used **electromyography (EMG)** or related measures to tailor stimulation parameters, typically with the goal of enhancing brain–body communication. For example, corticospinal excitability, as quantified by motor evoked potentials (MEPs) elicited via **suprathreshold transcranial electrical stimulation (sTES)**, can be used for personalization [97–99]. Specifically, the sTES threshold required to produce MEPs correlates to the personalized tES current intensity obtained via **current flow modeling** [100]. By contrast, efforts to personalize intensity based on **transcranial magnetic stimulation (TMS)** in a similar context did not appear to be effective, likely reflecting the fundamental difference in mechanism of action between TMS compared with tES and sTES [100,101]. While TMS does not inform on tES intensity, it can guide tES electrode placement by mapping the cortical representation of targeted muscles. This has resulted in promising effects of tDCS on corticospinal excitability [10], although no comparison was made in that study against nonpersonalized electrode locations. Furthermore, this strategy only applies when stimulating primary motor regions.

Other nonbrain-derived signals can also be informative. For example, accelerometry measures of tremor in Parkinson's disease have shown that tACS reduces tremor the most when applied at a frequency matching the fundamental tremor frequency [102].

Heart-rate variability, a measure of the autonomic nervous system and cardiovascular health that has been receiving increasing attention, is prone to changes following tES (e.g., [103]). However, its use as a personalization metric remains underexplored, and further research is needed to establish its relationship with tES efficacy.

Differences in neurovascular activity preceding tES, as quantified by fMRI, relate to stimulation efficacy [104,105]. Neurovascular signals are not only a proxy of neural activity through neurovascular coupling, but are also directly affected by tES, in turn affecting neural activity (reviewed in [106]) [106–110]. Specifically, medium-to-large arteries dilate following electrical stimulation in a dose- and frequency-dependent manner, as demonstrated in both humans and rodents. In smaller vascular structures, work in rodents showed that tES can increase the permeability of the blood–brain barrier [111].

Through fMRI, activity in brain regions, estimated through blood-oxygenated level-dependent (BOLD) signals, and functional connectivity patterns relevant to a brain state of interest can be identified. Combined with current flow modeling, this allows for focal induction of electric fields in the target regions [36,112–114]. For instance, task-based fMRI has been used to personalize tDCS in stroke survivors, targeting motor hotspots to enhance recovery over a 6-month period

[112]. While this suggests that neurovascular signals are effective for tES personalization, a comparison to a fixed tDCS group was lacking. In the related domain of TMS, an fMRI-based personalized repetitive-TMS protocol, referred to as SAINT, showed high efficacy in treatment-resistant depression, although its effectiveness may also be due to its high dose [115].

The relevance of **functional near-infrared spectroscopy (fNIRS)** for tES personalization remains to be explored. In principle, fNIRS is a compelling method for personalization, because it is less prone to tES artefacts compared with other mobile recording techniques, such as EEG [116,117]. For example, the potential of combining fNIRS and tES is illustrated in a study where fNIRS was used to show that short-range connectivity in the prefrontal cortex after tDCS plateaued after ~6 min [118], suggesting that fNIRS-derived network metrics could guide stimulation length.

Conventional personalization strategies are limited by the need to configure parameters before tES administration. This implies that the parameter space may already be outdated upon tES application due to the dynamic nature of some variability domains. While still in their infancy, **closed-loop systems** (reviewed in [119]) overcome this limitation by enabling dynamic adjustments of the tES parameter space based on real-time neurobiological signals. This holds promise not only for tES personalization, but also for the rapid assessment of multiple tES parameters. However, major challenges remain, including the need for online cleaning procedures of tES-induced artefacts at a nearly immediate computational throughput. In particular, low-latency processing of nonlinear tES artefacts in MEG/EEG data remains a problem. This is especially true for oscillating tES modalities, where the neurobiological activity of interest often overlaps with the stimulation frequency. Phase-dependent stimulation adds further complexity, because it requires algorithms with subcycle precision. Conversely, paradigms based on features such as oscillatory band power may be more easily achievable.

Some closed-loop protocols have already been used. For instance, **amplitude-modulated tACS** synchronized to online EEG-registered alpha oscillations was used to probe the link between oscillatory alpha phases and working memory [120]. In- and antiphase tACS with respect to endogenous alpha band activity has been used to examine the role of alpha band activity in memory retention [121]. Finally, real-time fMRI-guided dual-site tACS has been used to target the frontoparietal network through continuous adjustments of the stimulation frequencies and phase alignment between both tACS montages [122].

Mental state and trait as an overlooked domain in the personalization of tES parameters

A large body of literature links tES efficacy to behavioral, cognitive, and psychological state and trait factors (e.g., [123–127]). For instance, the effects of tDCS on performance in an emotional working memory task are enhanced when preceded by stress priming [124]. In addition, tDCS reduces mathematics-related anxiety and cortisol levels only in anxious individuals and yields the strongest working memory improvements when baseline performance is low [128,129]. Likewise, tACS effects on corticospinal excitability are state dependent [130]. Beta-tACS nonselectively increases excitability at rest, while alpha-tACS selectively enhances excitability of only the prime-mover muscle during action observation of a pinch-grip movement, and gamma-tACS increases excitability in both prime-mover and control muscles [130].

Despite the well-established role of mental state and trait in shaping tES effects, these factors have been largely overlooked with respect to the personalization of stimulation parameters. In cases where they have been incorporated into task design, this has typically been indirectly, via neurobiological state measures (e.g., perform task X during fMRI to guide electrode placement).

This lack of translation of mental state and trait factors into tES parameters likely arises from the challenge of mapping such broad constructs onto concrete stimulation parameters. By contrast, approaches such as current flow modeling and EEG-based endogenous frequency derivations offer more directly actionable links to stimulation parameters, including intensity and frequency.

Expanding mental state and trait-driven personalization strategies may enhance the efficacy of personalized tES. To this end, future work should associate differences in tES efficacy with variations in baseline and/or online mental states and traits. Meeting this goal will require a coordinated effort. Studies should use validated psychometric tools and behavioral markers to assess psychological and cognitive states, such as anxiety levels, cognitive fatigue, or attentional strategies. By combining harmonized data sets, large-scale machine learning or multivariate analyses can be used to account for the many degrees of freedom these domains entail. In parallel, research examining associations between neurobiological and mental states can help determine the extent to which neurobiological signals can serve as proxies for mental state and trait.

Building on these insights, future frameworks could adapt tES parameters based on individual prestimulation profiles. For example, profiling a person's cognitive strategy might guide the selection of montages or waveforms, aligning stimulation modalities with task-relevant cortical networks. While such applications remain speculative, they illustrate how mental trait and state information could be leveraged to inform the tES parameter space.

Transitioning toward a broader, yet principled, approach to personalized tES

Many domains relate to tES effectiveness, and the tES parameter space is broad. Yet to date, personalization has been conceptually and methodologically relatively narrow, focusing on tailoring stimulation intensity, frequency, and electrode placement to address anatomy or neurobiology (Figure 3). Although interest in personalized tES is growing, many sources of variability, such as mental state and genetics, remain largely overlooked. As a result, empirical support for personalization remains inconsistent despite its theoretical appeal and growing evidence linking individual differences to tES efficacy.

Addressing the remaining challenges, we would argue, requires two key developments. First, a more comprehensive framework is needed, one that evolves through an iterative cycle of increased mechanistic insights and advancing personalization. A pragmatic path forward involves a hierarchical approach to personalization, where foundational sources of variance, such as anatomy and baseline neurobiology, are controlled first, because they likely account for the largest variability. Only then can the more complex contributions of other factors be effectively isolated and addressed. This proposed path is not meant to be absolute (Figure 3, lower panel). Effective personalization must remain flexible, context dependent, and anchored in theoretical rationale. In the context of basic research, personalization should depend on the research questions at hand. In clinical settings, it should hinge on disorder characteristics. To illustrate the point, while anatomy may be paramount for stroke, neurobiology may be more relevant in domains such as sleep deprivation.

Second, identifying specific markers is a prerequisite for effectively guiding the tES parameter space and assessing the efficacy of personalized tES paradigms. Without markers that are known to represent tES efficacy, convincing evidence of target engagement remains elusive, and seamless navigation through the tES parameter space remains out of reach.

Is the juice worth the squeeze? Assessing the value of personalized tES

Personalized tES demands expertise, time, and resources, which, to some extent, undermines the aspects of simplicity and affordability that make tES attractive. Full personalization of all sources of

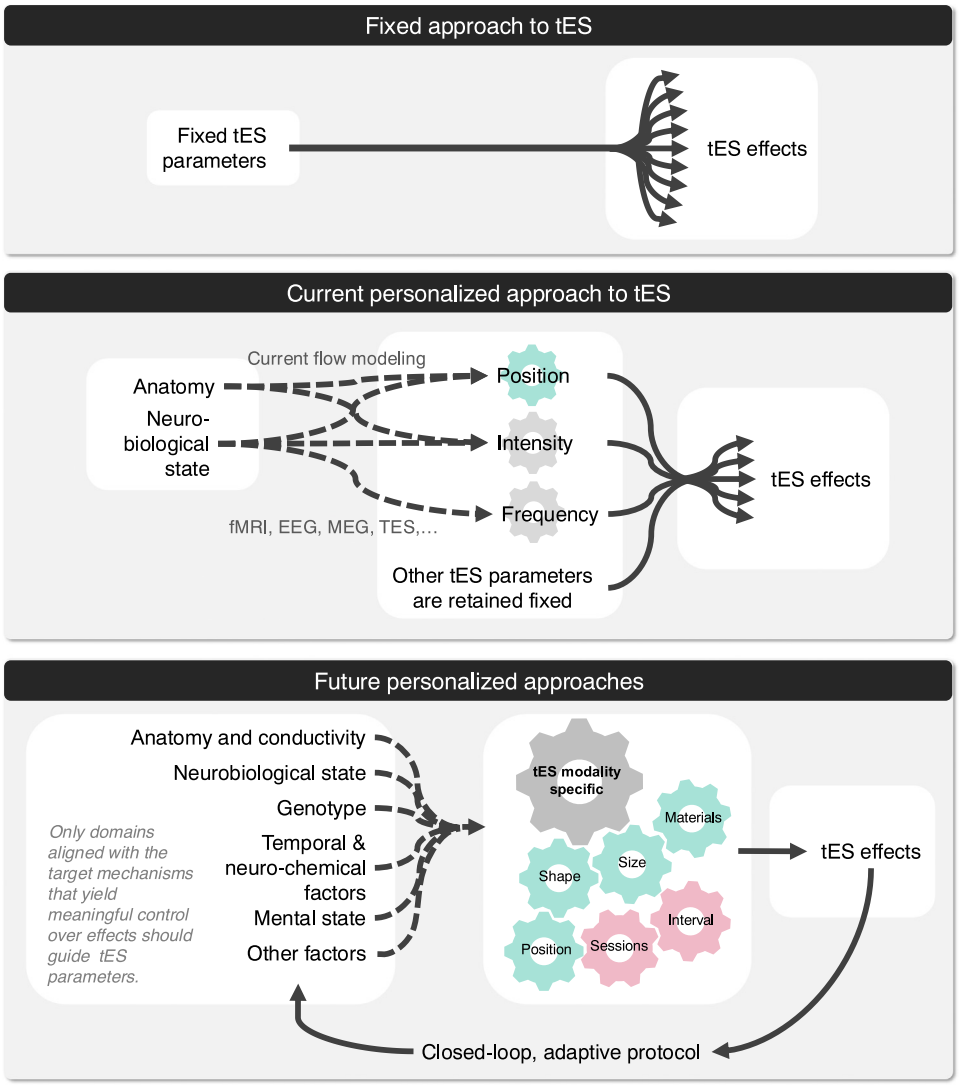

Figure 3. Schematic of different approaches to transcranial electrical stimulation (tES) personalization. The fixed approach to tES (upper panel) applies stimulation uniformly, regardless of intra- and interindividual variability. Current personalized approaches to tES (middle panel) account for anatomical and neurobiological variability by personalizing electrode position, intensity, and frequency, although these approaches do not typically adapt all of these parameters within a single protocol. For future personalized approaches (lower panel), we envision an adaptive tES framework, where multiple variability domains inform the tES parameter space, with some of these domains informing real-time adjustments. As with the current state of personalization, this future approach does not involve concurrent personalization of all parameters to account for all variability domains. Practical constraints necessitate users to define which variability domains are of most relevance given their specific tES application. Abbreviations: fMRI, functional magnetic resonance imaging; EEG, electroencephalography; MEG, magnetoencephalography.

variability is not only unrealistic, but also risks overfitting, potentially introducing new errors. Furthermore, given the interdependence of variability domains, returns may diminish as more (overlapping) factors are personalized. Empirical studies are needed to evaluate this trade-off.

This raises a central question: even if personalization reduces variability, is it worth it? We argue that personalized tES is valuable not only as a clinical endpoint, but also as a tool for research.

Box 3. Personalized and optimized tES: two distinct but connected concepts

The ultimate goal of tES research is to develop protocols that reliably produce the desired behavioral and/or cognitive effects across individuals and over time. Personalization is a promising means toward this goal, but not a direct solution. Rather than guaranteeing optimal outcomes, personalized tES aims to enhance consistency. This is relevant, because it mitigates the risk that genuine effects are confounded and aids the investigation of underappreciated sources of variability.

Furthermore, personalization enables the formulation of clinically testable hypotheses by shifting the focus from physical parameters to neurobiological targets. For instance, rather than aiming for a consistent electric field magnitude of 0.5 V/m in the left dorsolateral prefrontal cortex, one could test whether achieving consistent entrainment of the individual's peak alpha frequency in this region, irrespective of the stimulation intensity required, leads to a greater reduction of depressive symptoms. This comparison addresses a critical question: is clinical efficacy better predicted by physical consistency (e.g., electric field magnitude) or by neurophysiological consistency (e.g., oscillatory entrainment)? Framing such hypotheses would clarify the therapeutic, clinically relevant, mechanisms underlying tES, while also informing on its working mechanisms.

Alternative paths to tES optimization

Personalization is not the only means toward optimized tES. Alternative strategies include group-based optimization and responder identification.

Group-based optimization

This approach involves defining tES parameters based on large-scale neuroimaging data, such as resting-state fMRI, to optimize electric field distributions [132]. This has the advantage of requiring fewer technical, time, and financial resources. However, it lacks personalization to individual characteristics. Future research should assess the extent to which this trade-off affects outcomes. While group-based optimization may suffice for modulating corticospinal excitability in the primary motor cortex [133], it is likely less effective for complex cognitive functions, where people can use different cognitive strategies or heterogeneous clinical populations.

Responder identification

Another strategy involves distinguishing responders from nonresponders, for instance based on neurobiological signals or mental state or trait factors. However, this comes with the ethical risk of potentially systematically excluding certain individuals from tES interventions. These nonresponders may then be prematurely excluded from tES while they might in fact benefit the most from a different, genuinely personalized tES intervention.

Importantly, none of these strategies are mutually exclusive to personalization. Effective personalization can enhance the current understanding of how tES interacts with the central nervous system, ultimately informing and refining group-based optimization approaches and/or responder identification.

Outstanding questions

Which markers best reflect and validate tES target engagement and efficacy? Currently, validated markers known to causally mediate the behavioral effects of tES are limited. Prioritizing the identification and validation of such markers is essential for the development of effective tES interventions.

What is the true impact of individualization on tES efficacy? Comparisons between individualized and fixed tES are scarce. To justify the added cost and complexity of individualized tES, its advantage should be demonstrated. Individualized tES should also be compared with other optimized applications, such as group-based optimization.

What other tES parameters and/or sources of variability are worth looking into? Most of the focus so far has been on current intensity, frequency, and electrode placement to overcome variability introduced by anatomical and neurobiological state differences. The relevance of other parameters and sources of variability remains to be examined.

Can multiple individualization strategies be synergistic? While some may be synergistic, other combinations may not justify the added costs because their overlap may result in diminished gains.

In basic research, it can reduce noise and reveal complex dose–response relationships, such as the nonlinear effect of stimulation intensity, by aiming for more uniformly induced electric field strengths. In clinical and translational research, where feasibility is important, personalized tES can support the goal of consistent, beneficial effects with minimal technical complexity by enabling simplified, optimized, approaches. Personalization also enables the development of clinically testable hypotheses, allowing to test directly whether tES efficacy is better predicted by physical or neurobiological consistency. This could help advance both the understanding of the pathophysiology of a disease and the ability to optimize treatments for it (Box 3).

It is important also to consider the potential scenario where personalization fails to meaningfully mitigate variability. While discouraging from a practical viewpoint, this scenario also be instructive, by signaling the limitations of current tES technologies. It could prompt exploration of alternative strategies, such as increasing dose or treatment frequency, or support a more realistic view of tES as an intervention with variable outcomes, yet low-costs.

Concluding remarks and future perspectives

As the field of tES continues to mature, there is growing interest in developing personalized stimulation protocols. While early efforts have provided valuable insights, they have often remained fragmented and yielded mixed outcomes. Future progress may benefit from a more integrative

approach to personalization that simultaneously accounts for multiple key sources of interindividual variability. Among these, anatomical and neurobiological factors represent logical starting points.

While personalized tES poses real challenges, it appears essential for achieving more effective, reproducible, and mechanistically grounded outcomes. Even if personalization falls short of its promise, the effort may still reshape how tES interventions are designed, dosed, and deployed. Crucially, personalization is not a substitute for methodological rigor; it should complement robust experimental designs by improving mechanistic precision and reducing unexplained variance. Adaptive and closed-loop methods hold promise, although technical barriers remain. Key challenges include identifying markers of tES target engagement, identifying underexplored variability sources, and developing scalable strategies for addressing well-characterized ones (see Outstanding questions).

When applied judiciously, personalization can enhance tES by increasing its utility for probing causal brain function and improving its translational reliability.

Acknowledgments

We thank Marten Nuyts and Raf L.J. Meesen for the helpful discussions leading up to this manuscript. S.V.H. is funded by an FWO fellowship fundamental research (G1129923N and G1129925N) and the BOF Incentive fund (BOF22INCENT19). C.J.S. holds a Senior Research Fellowship, funded by the Wellcome Trust (224430/Z/21/Z). M.W. has received a seed grant by the Research School for Behavioral and Cognitive Neurosciences.

Declaration of interests

The authors declare no competing interests.

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