A Future of Current Flow Modelling for Transcranial Electrical Stimulation?

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Abstract

Purpose of Review Transcranial electrical stimulation (tES) is used to non-invasively modulate brain activity in health and disease. Current flow modeling (CFM) provides estimates of where and how much electrical current is delivered to in the brain during tES. It therefore holds promise as a method to reduce commonplace variability in tES delivery and, in turn, the outcomes of stimulation. However, the adoption of CFM has not yet been widespread and its impact on tES outcome variability is unclear. Here, we discuss the potential barriers to effective, practical CFM-informed tES use.

Recent Findings CFM has progressed from models based on concentric spheres to gyri-precise head models derived from individual MRI scans. Users can now estimate the intensity of electrical fields (E-fields), their spatial extent, and the direction of current flow in a target brain region during tES. Here. we consider the multi-dimensional challenge of implementing CFM to optimise stimulation dose: this requires informed decisions to prioritise E-field characteristics most likely to result in desired stimulation outcomes, though the physiological consequences of the modelled current flow are often unknown. Second, we address the issue of a disconnect between predictions of E-field characteristics provided by CFMs and predictions of the physiological consequences of stimulation which CFMs are not designed to address. Third, we discuss how ongoing development of CFM in conjunction with other modelling approaches could overcome these challenges while maintaining accessibility for widespread use.

Summary The increasing complexity and sophistication of CFM is a mandatory step towards dose control and precise, individualised delivery of tES. However, it also risks counteracting the appeal of tES as a straightforward, cost-effective tool for neuromodulation, particularly in clinical settings.

Keywords Transcranial electrical stimulation (tES) · Current flow modelling (CFM) · Neurophysiology · Therapeutic tES · Non-invasive brain stimulation (NIBS)

Modulation of brain activity via surface electrodes attached to the scalp holds great appeal as a non-invasive, inexpensive, safe, and, prima facie, easy to use method of brain stimulation [1–3]. Unsurprisingly, transcranial electrical stimulation (tES) has attracted enormous interest over the past two decades and holds potential for therapeutic use across a wide range of neurological and psychiatric disorders, including but not limited to Parkinson's disease [4], stroke [5–7], depression [8–10], addiction [11, 12], and Alzheime's disease [13]. However, tES outcomes are dogged by inter- and intra-individual variability, often small effect sizes, and limited efficacy [14–17], which impede its widespread and effective adoption into clinical practice.

The advent of current flow modelling (CFM), and increased efforts open-access, user-friendly application, boost the reliability, reproducibility, and efficacy of tES. CFM provides estimates of the distribution and intensity of electric fields (E-fields) in the brain during stimulation, allowing users to design model-based tES protocols to target specific brain areas or networks. Consequently, CFM has been heralded as a way for controlling tES delivery both within and across subjects and as a means to curb the variable outcomes that currently bedevil the field.

Yet, decades since the introduction of MRI-derived models [18–20], has CFM improved tES outcomes? The short answer to this question is likely that it has not; CFM has not yet been

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adopted into wider practice and has not become part of the routine for targeted tES delivery, nor for informing rationales for research and clinical application of tES.

We here discuss three determinant issues for the future of CFM in tES research and clinical use. First, we consider the multi-dimensional problem of optimisation of tES delivery. Second, we discuss how likely it is that CFMs will help us to predict target engagement and behavioural stimulation effects, given that CFMs are not designed for predicting the physiological impact of tES. Third, the technological demands and mandatory expertise required for the application of CFM (in combination with other models and approaches) are rapidly growing. We ask if the advancing sophistication of CFMs, potentially in conjunction with models that can predict physiological consequences of tES with high precision, will render the technique inaccessible for widespread clinical use?

Functionality of Current Flow Models

Current flow models simulate tES application and provide estimates of the magnitude, distribution, and direction of current that a given protocol will deliver to the brain. This is achieved through classification of different tissue types, based on MRI scans [21], and the assignment of conductivity values to the segmented tissue compartments (e.g. skin, scalp, CSF, grey matter, white matter). This allows for predicting the properties of current flow throughout the head [22, 23]. Previously modelled on concentric spheres [20, 24, 25] or standard model heads [26], CFMs today use individual structural MRI to inform researchers of where and how much current is likely to reach different parts

of the brain, given a specific electrode montage and stimulation intensity applied to an individual [27–34].

CFMs have now been validated in a range of studies, including comparison with in vivo human and non-human primate recordings during application of tES [18, 35–38]. While nuanced differences distinguish between different CFM approaches, they generally provide, gyri-precise estimates of E-fields in the brain.

We here focus on two attributes of CFM. First, CFMs can provide estimates of where and how much current is delivered to in the brain given a user-defined tES protocol—information that cannot be obtained non-invasively by other means. Alternatively, CFMs can guide tES protocol selection given a set of criteria, such as desired magnitude or direction of E-field in a cortical region of interest (Fig. 1).

What Are the Optimisation Criteria for Effective tES Delivery?

The inter- and intra-individual effects of tES remain variable [14, 16, 17, 39, 40], as do the protocols used between different studies. CFMs can be used to minimise inter-individual variability in the magnitude, focality, or direction of current at a cortical target, though they are agnostic to the effects associated with current applied to the brain. By exploiting Ohm's law, for example, one can use the predictions of CFM to adjust stimulator output for each subject such that dose in a cortical target area is matched across all individuals [41]. However, the CFM would not provide predictions of the physiological outcome of the simulated protocol.

The importance of critical decision-making by the CFM user is apparent; tES optimisation might only be achieved where a user is able to rationally prescribe tES parameters
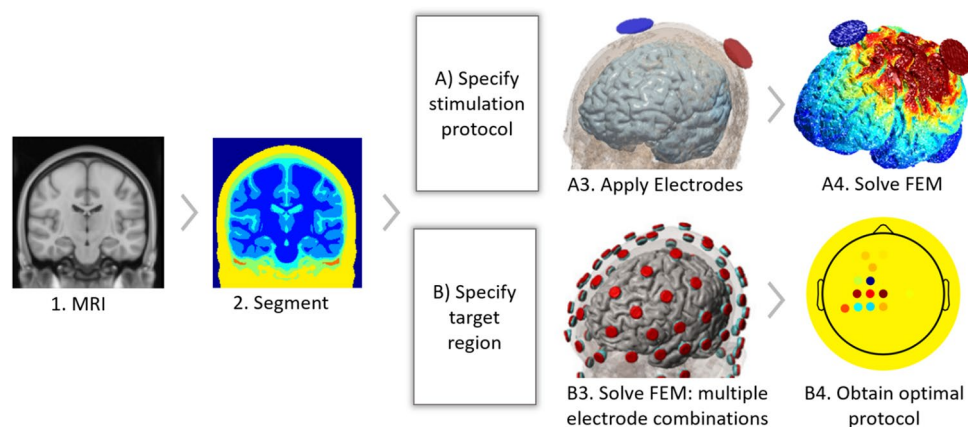

Fig. 1 Current flow modelling. An individual MRI (1) is segmented into different tissue types (2). If a stimulation protocol is specified (A3), the finite element model (FEM) for this specific electrode montage is solved (A4). If target E-field properties are specified, the FEM is solved for multiple electrode combinations (B3), to identify a stimulation protocol that optimises tES application to achieve the desired criterion (for example a montage that delivers focal stimulation to a cortical target region) (B4). Image B3 modified from Huang et al. 2019 [31]

likely to achieve a desired effect. This may be possible when sufficient precedence exists in the literature for the expected effects of a given tES protocol. However, it is though often unclear which E-field characteristics should be prioritised to target a given brain region (is the direction or intensity of current in the brain more predictive of tES outcome?), or what the optimal parameters for CFM application might be (what intensity of stimulation should be applied to the scalp?). While CFMs are useful for post hoc assessment of brain regions which have likely been exposed to currents above a given threshold [42], for novel questions and applications, the parameters likely to yield the strongest and most reliable effects are often unknown.

Let us assume, for example, that a given tES montage applied at 1 mA was to create, on average, an E-field magnitude of 0.2 V/m (and consequently 2 mA would deliver, on average, 0.4 V/m) to a primary region of interest (ROI) in the brain. Across individuals, the E-field magnitude in the ROI would likely vary substantially, by over 100% or more [18, 35, 38, 41, 43]. Assuming that the E-field magnitude in the ROI is the determining factor for the effect on neural processing, tES optimisation could be achieved by a simple adjustment of the stimulator intensity in each person, based on their individual CFM, such that the dose (e.g. 0.2 V/m) is the same for all individuals. This would remove the inter-individual variance originating from differences in the applied dose. It appeals to intuition that doing so should also remove (some of) the variance in the effects of stimulation. However, whether this is indeed the case and, consistently so, remains to be shown.

Similarly, one may be tempted to increase stimulator output with the goal of maximising E-field magnitude in an ROI (while staying within safety limits). Conceptually, there is little merit in this approach because the dose–response relationship of human in vivo tES is likely non-monotonic [44, 45], and the optimal E-field magnitude for target engagement is generally not known. Simply maximising current for everyone, up to an acceptable stimulator output intensity, is unlikely to result in predictable or reliable effects. Drawing rationales from animal studies may have limited value because the intensities used in animal models are often much higher [44, 46] and current delivery more tightly controlled [47] than is possible in human applications. While technically, therefore, CFMs can now be used to adjust stimulator output to specific values for each individual, it remains unclear *how* one should adjust stimulation protocols. Simply assuming that larger stimulation intensities will lead to larger effect sizes is likely to be incorrect.

To add complexity, the E-field magnitude is not the only variable that determines the impact of stimulation on physiology. Increasing stimulator output will inevitably also increase the number of brain regions exposed to E-field magnitudes equal or above values expected in a targeted region.

It would seem judicious to assume that inter-individual variability in both the magnitude *and* spatial distribution of current contributes to variability in the physiological outcomes of tES. Controlling for both variables at once poses a more significant optimisation problem for CFM than optimising for the magnitude of the electrical field alone.

The vexed issue of spatial distribution of current is grounded in the idea that focal stimulation is generally desirable, but that tES, by delivering diffuse current, is inevitably not focal. We point out that it is by no means established that focal stimulation is indeed necessary, or even important, for efficacious stimulation, but for simplicity, we will here assume that focal delivery can at least simplify optimisation of tES delivery.

Two approaches can be used to limit the spatial extent of E-field throughout the brain. First, one can simply reduce stimulator output intensity. This results in exposure of fewer brain regions to current above a certain threshold. Second, the use of multi-electrode tES montages can constrain diffuse current [18, 28, 48, 49]. An example of this approach is the so-called 4 × 1 montage where an electrode (e.g. an anode) placed on the scalp over a cortical region of interest is encircled by a ring of electrodes (e.g. cathodes). Such a montage constrains the spread of current radiating from the central electrode [18, 24]. This exemplifies the contribution of CFMs which have provided suggestions for montages that minimise spatial spread of E-fields, both within and between subjects.

However, the increased focality that can be achieved with multi-electrode montages must be balanced against reduced E-field magnitude (given the same stimulator output) resulting from increased shunting between proximal electrodes on the scalp [19, 28], and increased E-field variability [50] (Fig. 2). In principle, this trade-off can be mitigated by adjusting the stimulator output, though matching E-field magnitudes achieved by bipolar tES may require stimulation intensities that exceed what is commonly tolerated or within recommended safety limits.

Finally, the direction of current relative to the orientation of targeted neural structures is a critical though seldom-discussed determinant of tES effects. In single neurons, the direction of applied current with respect to the somato-dendritic axis of a target neuron dictates polarisation effects [46, 51–53]: as an approximation, current flowing radial-inward from dendrite to soma causes somatic depolarisation and is associated with excitation of the cell, whereas current flowing radial-outward from soma to dendrite causes hyperpolarisation and is associated with inhibition. Tangential current flow does not induce somatic polarisation (Fig. 3).

CFM suggests that conventional tES application, where electrodes are positioned on the scalp directly over a cortical target site, likely produces varied and predominantly tangential current in targets positioned in gyral banks of the brain (such as the primary motor cortex (M1), a common target for tES) [52, 53]. CFMs offer some remedy to the issue as

Fig. 2 E-field when modelling bipolar and HD (4 × 1) electrode montages. (**A**) higher intensities achieved with bipolar montage at the cost of focality. (**B**) improved focality at the cost of intensity. **C**) E-field direction plotted around the central sulcus (image **C** taken from Saturnino et al., 2019) [34]
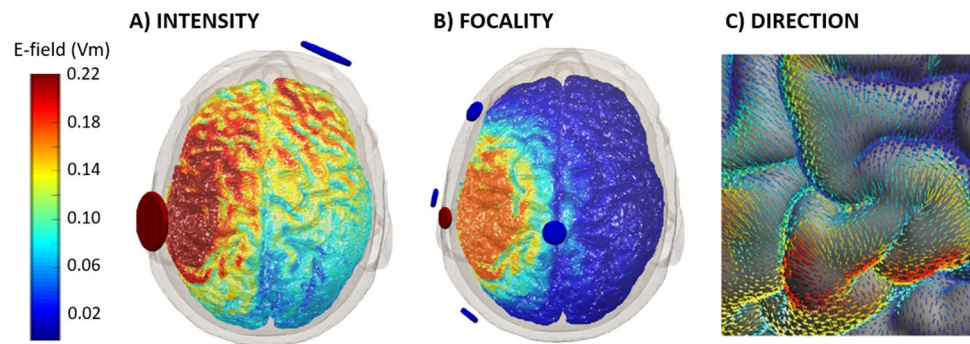

Fig. 3 Polarisation effect of applied current depending on neuron orientation. Current applied radial-inward along the somato-dendritic axis from dendrite to soma causes depolarisation (D), current applied radial-outward from soma to dendrite causes hyperpolarisation (H), and current applied tangentially across the somato-dendritic axis causes little to no polarisation effect
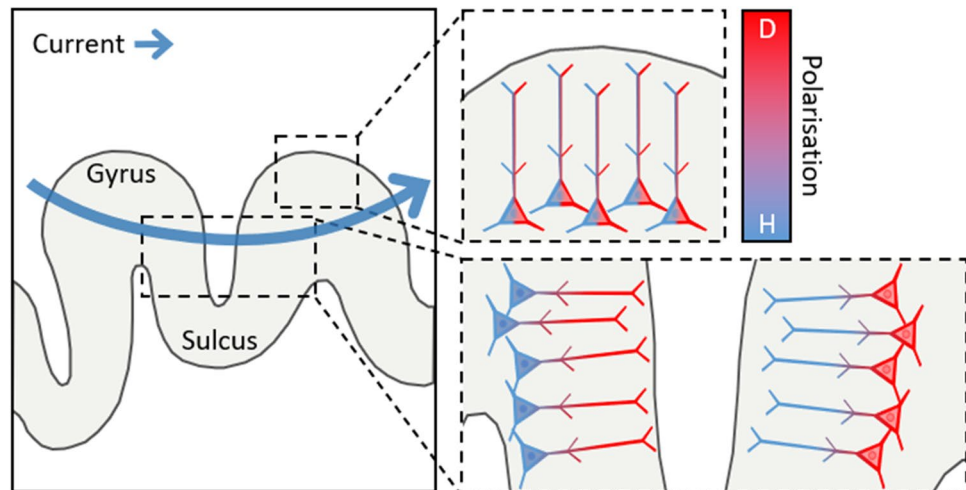
they can be used to estimate the direction of current in relation to the somato-dendritic axes of pyramidal neurons, for example, by using the cortical surface at a given location as proxy for the predominant orientation of pyramidal neurons at a target site. Application of tES can then be optimised to achieve more consistent E-field direction in an ROI across a group of individuals. This can indeed lead to greater consistency in tES effects [54, 55]. Such optimisation can be done in combination with adjustment of the stimulation intensity, though simultaneously controlling for a third parameter, the spatial distribution of current, is a much harder optimisation problem (Fig. 2).

Nevertheless, the strength of CFMs lies in their ability to generate novel predictions about where and how much current is delivered to in the brain with a given montage, and to thereby control the dosing of tES intervention. This, in turn, has spawned further development and more recent incarnations of CFM software can, for example, deal with multiple ROIs at once [32]. This is relevant as the diffuse nature of tES means many brain regions are inevitably exposed to current. Without CFMs, one would be reduced to guessing which regions are targeted by a given tES protocol.

Going forward, CFM has the potential to drastically change the way we administer tES (it has cautiously done

so already). It can facilitate a move away from conventional fixed stimulation protocols based on historical norms, towards informed, individualised tES delivery. In practice, the optimisation problem is multi-variate in nature, with inter-dependencies between magnitude, spatial distribution, and direction of current delivered to the brain. Some constraints are inescapable, such as limits to the intensity of current that can be delivered, or the focality (or lack thereof) that can be accomplished with tES, but these can provide useful constraints to optimisation. While CFM can therefore be used to control the magnitude, focality, or direction of current at a cortical target, currently, there is no straightforward optimisation routine available to optimise for all three variables at once. Informed tES study design thus remains a balancing act, which relies as heavily on judgement calls by the researcher as it does on the information provided by CFMs.

The critical issue, however, is another: even if CFM users could optimise across the parameter space, we would remain naïve to the physiological consequences of the modelled tES protocol and the degree of target engagement. The question then is whether - even if we knew how to optimise tES delivery - the variability of outcomes could be reduced in a meaningful way? Will

the use of models that are agnostic to physiology ever be sufficient to develop effective and reliable rationales for stimulation protocols?

How Generalisable Are CFMs?

The utility of CFMs lies in generating predictions about the properties of tES currents flowing through the brain. However, there is currently no straightforward mapping between the diffuse currents delivered by tES, their physiological impact on the brain, and the resulting behavioural consequences of stimulation. Here, we will focus on two factors which require attention because they determine what stimulation effects will be but are rarely taken into account when designing stimulation protocols: the anatomical and physiological state or trait of the subject.

CFMs provide estimates of current flow based on assumptions about the 'anatomical state' of healthy individuals, for example, anatomical features and tissue properties of the healthy adult brain. That anatomical state can vary profoundly across different populations is not considered. Put simply, standard CFMs assign the same tissue conductivity values to all populations and are agnostic to changes which occur across the lifespan or in pathology. For example, the impact of morphological changes associated with healthy ageing [39, 56–59] on the distribution of current is not known.

Structural changes that occur in degenerative disease such as dementia or ALS, or in acquired brain injury such as stroke, are also likely to have an impact on the distribution of current such that optimisation criteria for tES derived from healthy populations may no longer apply [60, 61]. We know that changes in skull density, and in thickness of CSF and skull tissue [62, 63], or the presence of lesions [61, 64] will drastically alter E-field distribution. For example, the presence of a lesion can result in either an increase or decrease in E-field magnitude in a region of interest, depending on the lesion location and size relative to the path of the current [60]. To add to this complexity, the conductances of lesioned tissue also remain unknown [60; 81]. The likely impact of these brain differences on dose and target engagement poses a challenge to the efficacy of stimulation in clinical practice [62, 65].

The extent to which predictions of CFMs generalise to other populations remains untested, perhaps simply because accommodating for structural differences across different clinical populations is not straightforward and currently requires bespoke solutions with considerable modelling expertise. Even if CFMs accounted for anatomical state, however, they would not offer predictions of the physiological impact of target engagement.

A similar argument can be made for the 'functional state' of the brain, which we here simplistically equate with the state of the underlying activity, neurochemistry, or excitability in a targeted region or network at the time of stimulation. Consider the simple case of applying tES either during task performance or during rest. Clearly, brain activity in these two states differs, and tES application will result in a different response: applying tES either before or during movement can result in opposing effects [66–69], though CFMs would prescribe an identical stimulation protocol in either case.

Another example pertains to the influence of neurotransmitters on the impact of stimulation, and vice versa. On the one hand, we know that tES can alter GABA concentration, even in unstimulated brain regions [70, 71], and that this directly relates to performance in a behavioural task [72–74]. We also know that neurochemical 'state' determines the capacity to undergo tES-induced cortical plasticity [45, 75, 76]. For example, the relative concentrations of both GABA and glutamate in prefrontal cortex determine the impact of tES on performance in a response to a selection task [77]. Since CFMs are not designed to account for functional state and trait differences, they cannot be used in isolation to support a priori optimisation, especially in cases where the underlying state of the brain is likely to influence target engagement.

Target engagement to any tES intervention depends on functional state during stimulation. Yet we (almost exclusively) select our clinical stimulation protocols from studies conducted in healthy young adults. For example, many of the neurological or psychiatric disorders studied and treated with tES are characterised by abnormalities in one or several neurotransmitter systems. The expectation that the effects of stimulation in patients can be predicted from the effects observed in healthy individuals receiving the same intervention seems fraught with logical problems (see Fig. 4 for hypothetical dose–response relationships in health and pathology).

Indeed, even if clinical anatomical differences were successfully accounted for through CFMs, for example, by development of models which incorporate lesions and their effect on current flow, the missing link to target engagement will ultimately necessitate the addition of adjunct models and measurements. Biophysically and morphologically realistic models are now emerging [78], and biophysically grounded computational models that are able to predict some of physiological and behavioural tES outcomes are being developed [79, 80]. These can formulate mechanistically grounded predictions about the impact of stimulation. Similarly, neuroimaging is one way to demonstrate target engagement, though in isolation it will not inform about the efficacy of the intervention on behaviour.

CFMs have facilitated a recent critical jump in understanding of tES application, though when used in isolation, this may not be sufficient to increase reliability and
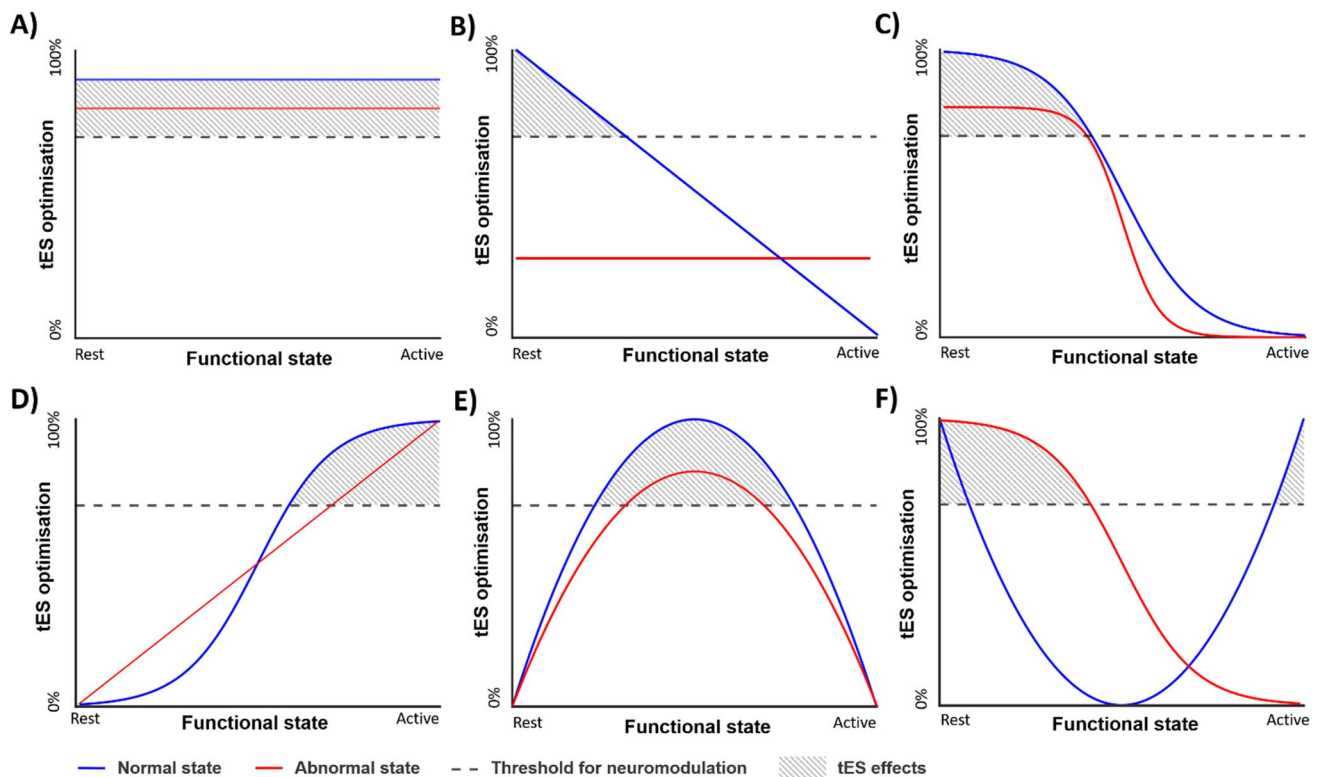
Fig. 4 Possible dose–response relationships between E-field and functional state of the brain. The effect of stimulation is determined by the magnitude, focality, and direction of E-field (tES optimisation: 0 to 100%), in interaction with the functional state of the brain (functional state: rest to active). The dashed line denotes a threshold for human neuromodulation (value unknown), above which a meaningful stimulation effect is expected (shaded grey area). In general, the function that maps the stimulation parameters onto tES outcomes in either health (blue lines) or disease (red lines) is unknown, with some but not all possible cases depicted in the figure. (A) The common assumption is that once a threshold for neuromodulation is reached, the effects are constant regardless of state. (B–D). The effects of stimulation are state-dependent, being largest either at rest (B, C) or in the active state (D). (E–F) The mapping between stimulation and its effects is non-monotonic or non-linear

reproducibility of tES. Investigating the degree to which CFM alone is sufficient to reduce the persistently variable outcomes of tES is of high priority in the field. We suggest that continued development of CFM and linkage with biophysically grounded models that can provide predictions about the nature of target engagement is needed for fruitful progress in tES application.

Outlook

Without knowing which neural structures are targeted by a given tES protocol, attempts to improve its efficacy would likely remain guesswork. CFMs have been hugely insightful in this regard, enabling researchers to quantify intra- (E-field across the cortex itself) and inter-individual variability in applied current. Through open-access, freely available CFM software, researchers can begin to control E-field magnitude in a region of interest by adjusting stimulation intensity, enhance focality by using multi-electrode montages,

and direct current in a desired orientation relative to a target structure. These parameters can be prescribed by the researcher or suggested by the model itself.

CFMs are thereby facilitating a move away from historical norms which prevent mechanistically informed study design, such as binary ideas of stimulation effects propagated by the language 'anodal' and 'cathodal' tES. They have enabled a shift from group-level design—applying a fixed intensity and electrode montage to everyone—to personalised tES application. Within-group variability, often masked by group-level analyses, can now be quantified and reduced.

That said, it is by no means clear that CFMs improve stimulation outcomes. Research showing a relationship between E-field magnitude in a cortical target and physiological outcomes hints that we are on the right track [42]. Yet it remains unclear which parameters should be prioritised by the CFM user for optimisation, and how these parameters differ across different populations with fundamental anatomical and functional differences. A greater number

of CFM-informed tES studies, which control for the multivariate characteristics of endogenous current (magnitude, spatial distribution, and direction), is necessary to determine the role of CFM in the future of tES. Though progress is limited without the inclusion of modelled functional state, CFM-informed studies will bring us closer to knowing whether CFMs improve tES application and by extension, tES efficacy.

As CFM improves and develops, it is likely that it will also become more complex. With this progress comes a risk that features which originally popularised tES, namely that it is inexpensive and easy to use, will be lost. For example, individualised CFM alone requires a high-resolution structural MRI of a subject's brain, specialist software, and user expertise. The increased control of E-field achieved in simulations will require complex multi-electrode tES and neuronavigation equipment for implementation in practical settings, which is not yet readily available. The evolving demands of informed CFM user decision-making, the need for quality MRI scans, accounting for patient-specific changes in neuroanatomy and underlying brain state, and a link between CFM and physiological models of stimulation outcomes, may render the widespread use of tES in clinical settings impractical.

If CFM in its current form is found to improve tES outcomes by allowing users to predict current flow and achieve targeted, individualised stimulation, the benefits of its use must outweigh the burden of additional equipment, expertise, and time required to implement it. Without these gains, the future of tES as an effective, practical, and financially viable therapeutic technique is uncertain.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

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