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Understanding the behavioural consequences of noninvasive brain stimulation

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Transcranial electrical stimulation (tES) influences neural activity in a way that can elicit behavioural change but may also improve high-level cognition or ameliorate symptoms in neuropsychiatric disorders. However, the current fervour for tES contrasts with the paucity of mechanistically detailed models of how stimulation causes behavioural change. Here we challenge the plausibility of several common assumptions and interpretations of tES and discuss how to bridge the ravines separating our understanding of the behavioural and neural consequences of tES. We argue that rational application of tES should occur in tandem with computational neurostimulation and appropriate physiological and behavioural assays. This will aid appreciation of the limitations of tES and generate testable predictions of how tES expresses its effects on behaviour.

Noninvasive brain stimulation: promise and reality

tES is a promising tool for noninvasive stimulation of the brain in basic and translational neuroscience. Mounting evidence suggests that tES can have a role in altering brain activity in a way that could be beneficial in health and disease [1–3]. Reports of such improvements, or neuroenhancement, span a surprisingly wide range of cognitive processes [1–8] and a perplexing variety of neuropsychiatric disorders [4,9–14].

The overall promise of tES is not matched by our mechanistic understanding of its influence on brain activity and how this influence might alter behaviour. Similarly, there is insufficient understanding of the potentially detrimental effects of tES. The use of tES has thus outpaced the mechanistic rationales for its application. This is no trivial matter, because these gaps in our knowledge delay the development of more effective and ever-safer stimulation protocols, lead to wastefulness when applications are based on spurious rationales, and promote the proliferation of implausible mechanistic inferences.

Here we address two key questions regarding tES. First, what are the theoretical foundations for the use of tES, and second, where these foundations are built on soft ground, how can such foundations be strengthened? Applying an electrical field to a dynamic electrochemical system like the brain seems likely to have myriad nontrivial effects that preclude simple extrapolation onto behaviour. A key issue is therefore the distinction between understanding the physiological effects of tES and understanding its effects on behaviour. Making untenable links between these two levels of description spreads misunderstanding, as recently highlighted by the discrepancy between the role of tES in the media and the evidence supporting it [15,16].

There is thus a necessity for finessed ways to interrogate the effects of tES. We argue that this will require appropriate explanatory models of the consequences tES has on neural activity, through the continued development and

Glossary

Computational neurostimulation: biologically plausible models and/or neural networks that simulate the consequences of neurostimulation. One can thereby generate physiological or behavioural predictions that in turn can be used to adjudicate between competing mechanistic hypotheses about the regional and inter-regional impact of tES.

Functional improvement: a behavioural improvement that may occur in concert with impairment in another behaviour, but which outweighs this impairment from the perspective of the subject.

Genuine improvement: truly beneficial changes that do not affect other behaviours detrimentally and transfer to behaviours underpinned by the same or similar processes.

Paradoxical improvement: behavioural improvements occurring as a consequence of altered competitive opponent processing, so-called compensatory augmentation [58] arising from tES-induced changes.

Selective improvement: a behavioural improvement in a single task, or single dependent variable, without further assessment of transfer, or simultaneously occurring costs in other tasks. This could also simply reflect a dependent variable insufficient to describe the impact of tES (e.g., a focus on reaction times while ignoring parallel changes in accuracy).

Simulation of current flow/current modelling: mathematical models of current flow induced by tES, based on segmented individual high-resolution structural MRI and knowledge of the conductivity of different tissues types. These models provide spatial estimates of current distribution but make no prediction about the physiological consequence of current–tissue interactions and are therefore distinct from computational modelling approaches.

Transcranial electrical stimulation (tES): we here use tES as shorthand for the various types of battery-driven stimulator delivering weak (~1–2 mA) currents between pairs of or multiple electrodes attached to the scalp, including protocols such as tACS [80,83–87] and transcranial random noise stimulation (tRNS) [88,89]; we also include pulsed techniques such as TMS, given that it is the induced current that acts on brain activity. These tES approaches are generally well tolerated, easy to apply, and inexpensive [90,91] – features that now make them the methods of choice for noninvasively shaping activity in neural circuits, cortical entrainment, functional localisation, widespread translational application, and, increasingly, home use [92].

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Box 1. Polarisation of cortex through transcranial currents

Broadly speaking, anodal surface polarisation causes time- and intensity-dependent increases in neuronal excitability and spontaneous firing rates by depolarising membrane potentials, whereas the opposite effect occurs for cathodal stimulation. As noted by Fritsch and Hitzig [93], positive currents have amplifying effects, whereas negative currents have suppressing effects on firing rates. A large body of evidence from animal studies confirms that polarising, externally applied currents can lead to polarity-dependent net activity changes [94–99] (for a historical overview, see [100]), on which the immediate effects of tES are thought to depend.

This rebalancing of inhibition and facilitation, however, influences ongoing plasticity; for example, tES applied to mouse M1 slices potentiates long-lasting synaptic potentiation (tES-LTP) induced by repetitive low-frequency synaptic activation [33]. Activity-dependent polarisation effects thus have the capacity to accelerate or slow plastic changes and a reasonable inference is that lasting influences of tES on cortical processing are mediated through augmentation of processes required for synaptic plasticity [33].

At a cellular level, the acute effects of externally applied direct currents depend on cell morphology, the (layer-specific) orientation of excitable neural elements in the induced electrical field [32,101], stimulation intensity and duration, and the degree of spontaneous dendritic and somatic activity [32,33,102–104]. Early studies in animals [95] demonstrated that current orientation *per se* does not predict the after-effects of polarisation. Instead, a distinction is necessary between the effects that external currents have on different types of neuron and polarisation-induced changes in cells participating in ongoing responses [96]. However, the relatively uniform and homogeneous currents applied in *in vitro* or animal studies are unlikely to occur in humans. A key factor in the net outcome of stimulation is individual morphology, with cortical folding rendering it rare that functionally cogent regions are exposed to homogenous currents. Factors such as these may contribute to the nonlinearities in the physiological response to different tES protocols [67]. More generally, the effects observed in well-controlled *in vitro* or *in vivo* animal recordings may be difficult to apply in a straightforward way to human studies and complicate straightforward, reliable and generalisable tES rationales.

A hallmark rationale for 'increasing' or 'decreasing' activity in specific cortical structures, and thereby 'enhancing' or 'reducing' behaviour, rests on polarity-dependent changes in neural activity. The concept of a sliding scale [105], derived from the neural effects outlined above, permeates molecular, cellular, electrophysiological, and behavioural levels of description (Box 2). How these different levels ought to be related to one another, however, is more often than not unknown.

improvement of computational neurostimulation (see Glossary). This will provide models of neural and behavioural data that bridge between, and formulate novel predictions about, the physiological and behavioural impact of tES.

On the concept of uniform polarisation with tES

We here largely focus on transcranial direct current stimulation (tDCS) [17,18], which has become neurostimulation's *modus operandi* across many fields of cognitive and translational research, but we acknowledge that sophistication is required regarding discussion of other forms of tES.

Despite its apparent simplicity, the physiology of tES is complex [19] (Box 1). Moreover, evidence from *in vivo* recording [20,21] and human neuroimaging [22–27] studies suggests that tES effects are not constrained to the cortex underneath an electrode. Simulations of current flow in the brain suggest a widespread and complex distribution of induced currents [28–30] that can expose both cortical and subcortical regions to currents of sufficient intensity to affect neural activity. Furthermore, profound reversals in polarity can occur across sulcal and gyral elements within the vicinity of the same electrode [29,31,32], so electrode montage alone does not dictate current flow.

The concept of uniform and localised polarisation underneath an electrode thus becomes difficult to defend. In the same vein, straightforward mechanistic rationales for employing one type of stimulation over another can be problematic, because in many cases we do not know the transfer functions between different levels of description (Figure 1). For example, there is a substantial body of evidence detailing how tES-induced changes in membrane excitability alter firing rates in neural populations and how these in turn affect processes related to long-term potentiation and depression [33]. How these will affect the type of recording of neural activity used in humans is likely to be complicated. Motor-evoked potentials (MEPs) [17,18] elicited by transcranial magnetic stimulation (TMS) are another specific example: the MEP is a complex signal with transcortical, intracortical, and spinal contributions [34,35]. Drawing analogies between polarisation effects on MEPs and behaviour likely faces limitations.

Predictions of how physiological change at a microscopic, macroscopic, or mesoscopic level will lead to behavioural

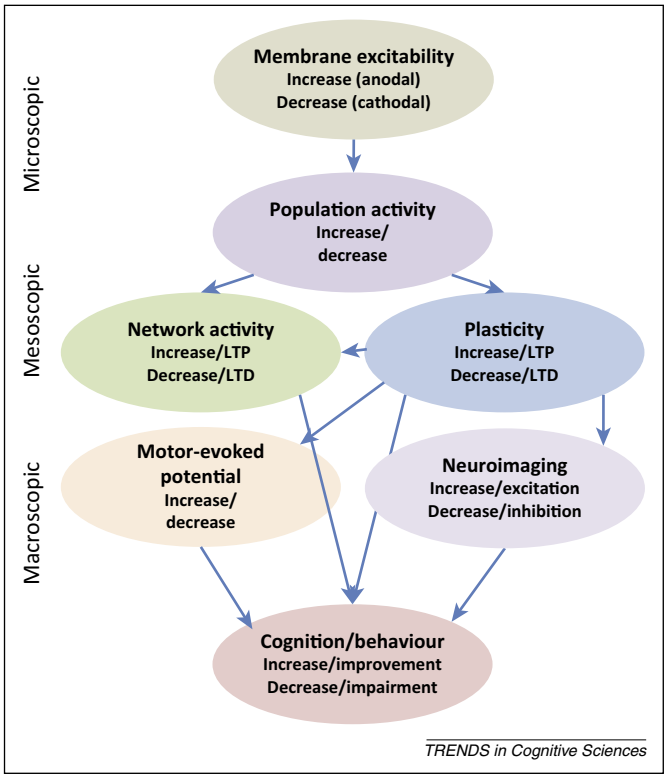

Figure 1. The various levels of description of the effects of transcranial Electrical Stimulation (tES). tES has the capacity to change membrane excitability and membrane potentials. However, the transfer functions between these different levels of description are largely unknown. This is most strikingly illustrated by the known effects of tES on membrane excitability at one end of the spectrum and the often-observed behavioural change elicited by tES at the other. How the two ought to be related remains unclear and involves a complex cascade of processes across the different levels of description.

Box 2. Conceptual models of tES

The most prevalent concepts of the effects of tES (Figure I) include sliding-scale [105], inhibition–excitation balance [106], efficiency [17,106], zero-sum gain [52], stochastic resonance [31,107], and activity- and input-selectivity [105] models.

The broad majority of these concepts falls under the category of sliding-scale models. These assume that tES can dial-up or -down neural activity, but they make no prediction of how this change affects the computations in an area. Related excitation–inhibition balance [106] and efficiency [106] models propose that tES adjusts the inhibition and excitation balance. Stimulation thus ought to improve behaviour when this balance is optimised, although shifts in the inhibition–excitation balance alter speed–accuracy trade-offs rather than causing genuine improvements [108]. Models citing improved efficiency lack mechanistic insight; improved efficiency is not an explanation but rather a *post hoc* re-description of data [109]. For example, metabolic savings may occur due to sparser neural codes or reduced costs of transmitting information across networks. Thermodynamic and computational (statistical) imperatives for self-organisation of neurobiological systems [110] can also lead to manifestations of efficiency gains. However, these concepts have not been transferred to models of tES.

Zero-sum models [52] borrow concepts from game theory whereby computational gains elicited by neurostimulation must be met by losses such that the total sum is zero. Put simply, they apply a sliding-scale rationale antagonistically to different regions. The neurobiological plausibility of this idea has been challenged [111], but the conceptualisation of potential losses caused by tES is relevant.

Activity-selectivity models conceptualise tES effects as state dependent: subthreshold effects too weak to affect inactive networks but are able to boost or suppress activity in already active ones. This is used to explain why spatially nonspecific stimulation may produce spatially specific effects.

Input-selectivity models propose that tES switches the affected network state, either by modulating input-gating mechanisms or by biasing networks with bistable states.

Finally, stochastic resonance accounts conceptualise tES as an injection of noise, which can be beneficial in small amounts when the signal is low but detrimental in larger doses [107]. This counter-intuitive situation arises when the relevant signals are below some threshold for propagation. Added noise allows some percentage of signal to pass this threshold, resulting in increased propagation [112].

Collectively, these models provide helpful heuristics and *post hoc* explanations by which to linguistically conceptualise the impact of tES. Their psychological or physiological validity is questionable and they do not explain the transfer from physiology to behaviour or make reference to the cortical computations underlying behaviour.

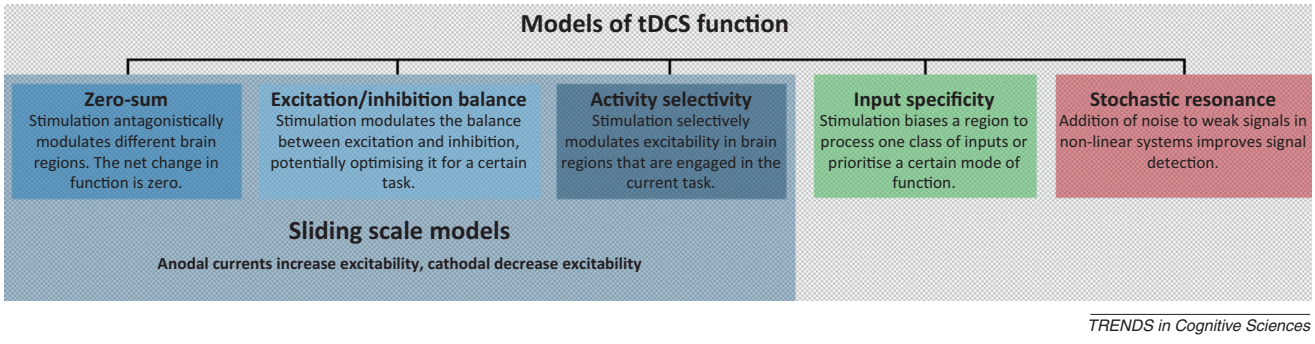

Figure I. Categories of conceptual models of transcranial Electrical Stimulation (tES).

change should thus be corroborated by models that incorporate the transfer function between these levels of observation. Bleed-over between these levels (Figure 1), such as the idea that an increase in excitability means an increase in processing efficacy (Box 2), must therefore be avoided. The appeal and strength of many tES applications is their simple utilisation, but the conclusions thus drawn should be constrained to the level of description in which the experiments are conducted.

On the rationales for changing behaviour with tES

This raises an important issue: how can one formulate rationales for changing, or even improving, behaviour? The short answer is that in many cases currently one cannot. The simple distinction between anodal and cathodal currents seems descriptively useful but is fraught with potential for oversimplification. For example, both modelling [36] and Magnetic Resonance (MR) spectroscopy [23,37] studies indirectly indicate that anodal polarisation may also affect excitability in inhibitory interneurons. This immediately suggests a complex influence of stimulation on excitation–inhibition balance in which the emergent properties of stimulated networks, and thus the resulting behavioural consequences, become difficult to predict.

There is an additional worrying counterpart to the myriad reports of enhanced function with tES. If cathodal stimulation indeed leads to neural (and behavioural) effects opposite to those of anodal stimulation, *a priori* beneficial and detrimental effects should occur in parallel on the processes and behaviours supported by brain regions under both the anode and cathode. The fact that potential behavioural effects induced by the 'return' electrode are rarely measured does not alleviate the conceptual problem inherent in the idea of selectively influencing the function of a single brain region. This problem may be alleviated by the use of inert (e.g., extracephalic) return electrodes [38,39], asymmetrical electrode sizes [40], or more complex multi-electrode, high-definition (HD) tDCS montages [41].

Removing the simplistic scientific scaffolding surrounding the concept of anodal and cathodal stimulation can lead to only two conclusions. It is either logically impossible to target a single behaviour or even elicit genuine improvements as long as electrodes with both polarities are placed over active brain regions, or the sliding-scale concept on which many studies rest (Box 2) requires modification. The latter would impact both the conception of tES studies and their interpretation.

Box 3. Computational neurostimulation

Computational models span multiple spatial and temporal scales from neural circuits to behaviour. The realistic biophysical architecture of such models allows interrogation of the neural consequences of simulated currents and, critically, how these change the behaviour of the model [32,34,36,75,76,78,79]. The key challenge is to develop computational neurostimulation approaches that adjudicate between explanations for the physiological and behavioural effects of tES.

Biophysical and network-level models can be distinguished by the level of description in which they are cast (microscopic, mesoscopic, macroscopic). Biophysical simulations seek to describe the complex interactions in biological systems and can provide useful predictions of, for example, the impact of tES on the membrane properties or firing rates of different neural populations. Such models may include both excitatory and inhibitory populations and can be instantiated utilising spiking neurons with conductance-based synapses, with simpler models using extensions of the Wilson–Cowan model, or by mean field approximations such as dynamic neural fields. Currently, elegant examples using modelling approaches have explored the effects of tACS on neural activity [75,79] and the effects of pulsed tES on neural circuits in M1 [34,35,76].

Presently, large-scale models that also generate behavioural predictions about the same tasks tested in humans undergoing tES are notably absent. Their development requires amalgamation of physiological with network-level models that describe the unobservable computations performed by a simulated network. This can provide explicit hypotheses about the 'hidden processes' through which physiological change elicited by tES transfers to behavioural output.

For example, decision-making models based on recurrently connected populations of spiking pyramidal cells and inhibitory interneurons [113] could be used to estimate the effects of tES by simulating injected current of differing magnitude and direction in populations of excitatory pyramidal cells and inhibitory interneurons (Figure I). The simulated behaviour of such models could then be compared with the effects of tES in participants performing the same tasks. This can provide mechanistic explanations and explicit behavioural predictions for how the cellular and network effects of different tES regimens determine their behavioural effects.

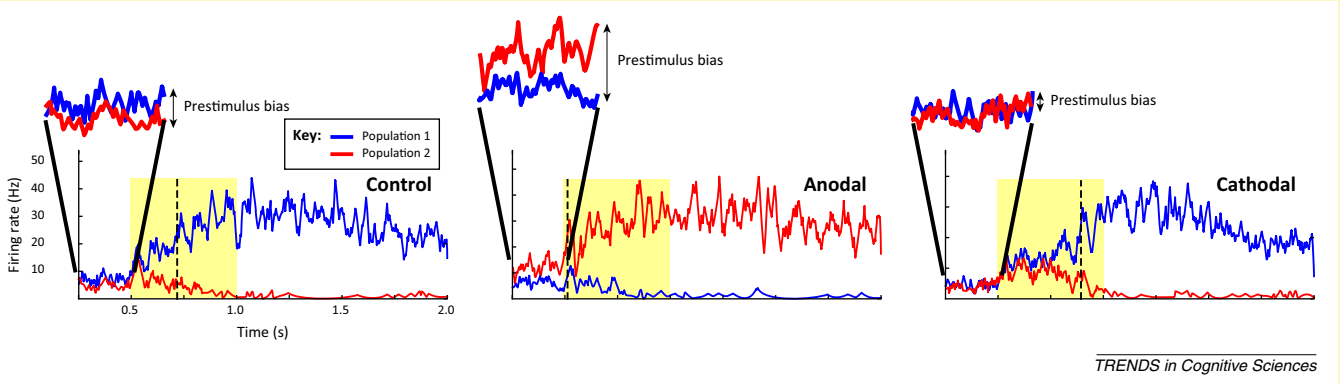

Figure I. Simulated neural polarisation effects in a decision network. Hypothetical firing rates of simulated pyramidal populations encoding response options in a simple decision-making task. Synthetic data without simulated stimulation (control) or with simulated depolarisation (anodal) and hyperpolarisation (cathodal) are shown. The shaded box indicates choice-stimulus presentation. The vertical broken line indicates the time at which the decision threshold is reached. Here, random differences in baseline firing rates bias the network to choose one option over another. Depolarisation increases these biases, which would lead to decreased accuracy but faster reaction times, while hyperpolarisation reduces baseline firing rate differences, which would result in increased accuracy but longer reaction times.

On the concept of eliciting behavioural improvement with tES

What type of inference can then be drawn from tES? One powerful appeal of tES is as an interventional approach for the decomposition of different cognitive processes involved in a task [42]. For example, tDCS with the anode over M1 during motor skill learning has been used to provide support for the idea that motor skill consolidation processes contribute to offline (between-days) effects but not to online (within-day) effects or the retention of newly acquired motor skills [43]. In such examples, tES is used to decompose the processes underlying a behaviour such as motor learning (see [44] for a recent overview) in the absence of strong claims about the precise physiological mechanism mediating these specific effects on behaviour. Used in this way, tES can be a powerful tool for dissecting the cognitive architecture of specific behaviours without committing to unwarranted mechanistic interpretations [45,46]. We emphasise our view that declining to speculate on the precise mechanism of tES in this case does not detract from the inferential power of this approach.

By contrast, we know of no account that generates behavioural predictions of the effect of gross polarisation of cortex (Box 3). In support of this, behavioural improvements have also been reported for so-called cathodal stimulation [6,47]. Moreover, suppression of function in one region may even improve behavioural outcomes ('paradoxical facilitation'). More generally, brain regions at a resolution targeted by tES are functionally pluripotent [48] and whether a single process in a region can selectively be changed while sparing other processes supported by that region remains an open question. Thus, statements such as 'we hypothesised that weak electric currents of opposite polarities over M1 differentially modulate learning' are valid. They exploit the capacity to influence cortical excitability and to explore how this alters behaviour and are agnostic about the selectivity of this effect. However, hypotheses of the kind that 'anodal stimulation increases excitability and thus improves cognition' are currently not defensible from a mechanistic perspective.

How then should one then conceptualise behavioural change through tES? This issue is most pressing for studies that seek to elicit behavioural improvements or neuroenhancement. One can distinguish different types of improvement and we suggest a taxonomy that centres on the distinction between genuine, selective, functional, and paradoxical improvements.

A strenuous definition of neuroenhancement would be one of genuine behavioural improvements. These will be

Box 4. Outstanding questions

- Efficient behavioural procedures are required to distinguish genuine, selective, functional, and paradoxical improvements, yet there is little consensus regarding the behavioural assays best suited to divorce different levels of behavioural improvement from each other.
- The hype surrounding tES can lead to toxic misunderstanding and even misuse. How then should the field of tES research deal with this hype, while acknowledging the unquestionable potential of the technique?
- How can models of current flow in the brain be combined with models of the physiological impact of these currents? How can models of current flow be validated and used to reduce the large variability in tES outcomes?
- The behavioural consequences of tES are often variable and the effect sizes small. True progress requires approaches that rest on mechanistic insight into how specific protocols affect brain function and behaviour. This is paramount in improving the efficacy of tES, rather than relying on trial-and-error variation of stimulation parameters. What are the key factors contributing to unexplained variance of stimulation outcomes and how can these sources be better controlled experimentally? Furthermore, how should we characterise meaningful variation between individuals in their response to different stimulation protocols?
- It remains largely unclear how the changes occurring in healthy ageing and various pathologies influences the physiological impact of tES. Structural brain damage affects current flow whereas disease-related changes in neurotransmission are likely to have significant consequences on activity-dependent interactions with tES compared with healthy brains. Devising successful translational strategies for tES hinges on a better understanding of changes in the brain's response to tES in disease.
- How can the effects of tES observed at a microscopic, cellular level be adequately summarised at a mesoscopic level and how do these in turn transfer to a macroscopic and regional level of description? What are appropriate models that capture this transfer with sufficient detail?
- How can models of synaptic plasticity be augmented to simulate the effects of tES over longer timescales? The online effects of tES are thought to largely occur through changes in membrane potentials. By contrast, longer-lasting effects following cessation of stimulation are more complex and likely to involve plastic changes over timescales of minutes and hours. This added complexity requires appropriate models that can capture these plastic changes and their effect on behaviour, complemented by *in vitro* and *in vivo* direct recordings that provide prior constraints on these models.

challenging to demonstrate, but caution would recommend the more conservative view that scrutiny of a single task can provide evidence for selective improvement only. At the very least, function related to brain regions under both electrodes (and more in the case of more complex montages) would have to be assessed if one wished to infer true neuroenhancement without cost. Recent elegant work on the impact of tES on performance monitoring and learning suggests that selective targeting of cognitive processes might be possible [49], but further discussion about the possible costs of tES interventions is warranted (see [49–52]).

The situation may be somewhat different for the application of tES in children or in ageing or patient populations [3,10,12,53–55]. Here similar (sliding-scale) rationales are commonly applied in the hope that tES can help development or normalise the dysfunction of a region or network to a level that alleviates impairment. That inference is troublesome: tES-evoked changes in healthy subjects may not transfer to such populations in a straightforward way, given the differences in brain structure and neurotransmission resulting from development, ageing, and pathology [4,9,17,56]. On the issue of costs, behavioural impairments in these populations can be acceptable if they are outweighed by the beneficial effects of stimulation. Labelling these as functional improvements would allow distinction from other types of behavioural change.

Finally, tES may elicit paradoxical improvements [52,57,58] through restorative and enhancing effects resulting from disruption of a process that exerts a suppressive effect on the process of interest. For example, stimulation of the dorsolateral prefrontal cortex with TMS can impair declarative memory formation but simultaneously may remove the negative influence of this process on procedural memory formation. As a consequence, performance in tasks assessing procedural memory formation can improve [59], but importantly this arises through interference with another process and is clearly distinct from a genuine improvement in brain function. Crucially, without a broad array of behavioural assays, impairments produced by tES may go unnoticed and could create the impression that paradoxical improvements are genuine.

On bridging the explanatory gap between physiology and behaviour through computational neurostimulation

How then can one best devise approaches that further the quest to elicit controlled behavioural change and maybe even improvement with tES? Drawing simply on precedents from the literature can be complicated by diversity in the applied stimulation protocols, uncertainty about the effectively targeted structures [60–62], and the heterogeneity of stimulation outcomes [61,63–66]. The physiological consequences of tES are also potentially nonlinear with regard to current strength [67] or neurotransmitter activation state [68], further complicating the choice of stimulation protocol and formulation of *a priori* hypotheses regarding how a protocol will influence behaviour.

We suggest that approaches based on computational neurostimulation may pave the way for a deeper understanding and more efficacious application of tES (Box 4). Such approaches can provide intermediate (meso- or macroscopic) levels of description that map physiological change onto behaviour and, importantly, formalise how we think transcranial currents act on the brain. The use of models is now becoming standard in other fields of neuroscience and translational research [69,70], with computational psychiatry [71,72] a notable recent example that conceptualises mental illness in computational frameworks. Perhaps surprisingly, few attempts have been made to use such models with tES. However, recent advances provide promising examples of the potential contributions of computational neurostimulation approaches (see Figure I in Box 3) [32,34,36,73–79].

For example, one recent study addressed how simulated transcranial alternating current stimulation (tACS) affects

the transition of a cortical network from one state of rhythmic activity to another [75]. From the perspective of tES, this elegant work provides a model platform on which to interrogate how specific changes in cortical network dynamics impact the computations performed in these networks, including simulation of known network changes in neuropsychiatric illnesses such as schizophrenia. Such work can identify the parameters through which tES might produce changes in network oscillations, such as those recently observed using electroencephalography [80].

Another relevant study used neural mass modelling [81] to ask about the model parameters that reproduce the impact of tES on sensory evoked potentials (SEPs) [36], as observed *in vivo* in rabbit somatosensory cortex [82]. Using separate populations of pyramidal cells and different types of inhibitory interneuron, this work highlights the importance of feedforward inhibition in expressing the effects of tES. Externally applied currents may therefore also act on interneurons, despite their smaller size and orientation, with functionally significant consequences. This study also highlights the potential for refinement of computational neurostimulation techniques by applying this approach to investigate the effect of tES on physiological responses and on animal models. This allows direct comparison between internal model states and experimentally measured physiological signals and can help refine models that can then be tested against human data where only behavioural responses or large-scale neuroimaging signals are available.

The use of biophysically realistic simulations can therefore generate novel hypotheses and explanations for the physiological change elicited by tES. The further development of computational neurostimulation should focus on (at least) three criteria. First, models need to be grounded on realistic biophysical assumptions and neurobiology. Second, they must simultaneously provide predictions about both physiological and behavioural changes, which permit the scrutinising of these models with empirical data from human participants. Third, these models in turn must be validated, cross-fertilised, and iteratively improved through complementary techniques such as *in vitro* [32] and *in vivo* recordings [20,21,82], human electrophysiology, and neuroimaging.

Only recently have attempts started to leverage models for our understanding of tES. The conceptual challenge ahead may not lie in finessing the techniques at our disposal but in the models available to explain experimental data.

Concluding remarks

For the field of noninvasive brain stimulation to mature, rationales for its use must be built on appropriate explanatory models. The inferences drawn from studies using brain stimulation should not exceed the level of interpretation in which they were. The credulous reader might at this point ask what the pressing need for mechanistic insight is, given the apparent success of tES. Although the history of medicine is littered with examples of treatments that have proved effective despite ignorance regarding their mechanism of action, in general these treatments have rarely given us novel insights into biology, have not experienced the large parameter space for optimisation of tES, and, importantly, have not been employed as widely in healthy populations as is tES. The emerging field of computational neurostimulation will provide one of the cornerstones of a deeper understanding of tES, allowing tES to fulfil its rich scientific and therapeutic potential.

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