Primer

Transcranial electrical stimulation

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Transcranial electrical stimulation (tES) is a neuromodulatory technique in which low voltage direct constant or alternating currents are applied to the human brain via scalp electrodes. The basic idea of tES is that the application of weak currents can interact with neural processing, modify plasticity and entrain brain networks, and that this in turn can modify behaviour. The technique is now widely employed in basic and translational medical research, and increasingly is also used privately in sport, the military and recreation. The proposed capacity to augment recovery of brain function, by promoting learning and facilitating plasticity, has motivated a burgeoning number of clinical trials in a wide range of disorders of the nervous system.

The mechanisms through which tES exerts its behavioural effects in the human brain, however, remain poorly understood. Recent debate has also focussed on the reliability and reproducibility of tES, including debate about its overall utility. This primer highlights important concepts, but also misconceptions surrounding the technique, and outlines possible avenues through which to advance the current state of the art.

Transcranial electrical stimulation in health and disease

At present, the field of tES presents a rather mixed state of affairs. Foundational *in vitro* and *in vivo* animal and human electrophysiological studies have inspired elegant applications of tES in the decomposition of behavioural processes, in the study of brain networks by causal perturbation, and in the targeted treatment of a small set of neurological disorders. Waves of

excitement about this body of work have encouraged ride wide-ranging proposals for its use, including attempts to enhance cognitive functions, motor skills and sporting abilities, and applications in the treatment of a bedazzling range of conditions including depression, autism, dyslexia, stroke, learning difficulties, dyscalculculia, pain, Parkinson's disease, migraine, schizophrenia, epilepsy, aphasia, dystonia, addiction, cognitive decline and memory defects. These proposals have generally not been supported by substantive evidence, nor have they involved valid mechanistic rationales. The outright hype around the multi-faceted use of tES, in turn, has recently led to questions about its general utility, including concerns about its reliability, reproducibility and effect sizes.

Despite the increasing excitement about tES, critical issues pertaining to our understanding of its effects on the brain therefore remain, along with questions about the rationales for its application, and its reliability and reproducibility. We shall consider some of the key issues in this debate, and discuss avenues that may help in devising more reliable and grounded applications of tES.

Mechanism of action in animals and humans

The notion that transcranial electrical stimulation of the human brain would work in the same way as in animal studies remains problematic. The rationales for the application of tES largely rest on *in vivo* and *in vitro* animal studies in which current is applied directly to cortex. One commonly made assumption is that the effects observed in animal experiments can explain the physiological and behavioural changes observed in humans when current is applied via surface electrodes attached to the scalp. In animals, however, tES is delivered in a well-controlled way, with precise knowledge about the strength and direction of current to which neural elements are exposed. With low electrical currents, the primary effect of direct current stimulation is through changes in the membrane potentials of neurons, such as the pyramidal neurons

orientated orthogonal to the cortical surface. The consequences of the cell membrane polarization trigger the changes commonly observed: for direct current stimulation, these include polarity-dependent long-term potentiation (LTP)-like and long-term depression (LTD)-like changes that outlast the stimulation. While stimulation modulates ongoing LTP, it does not itself generate synaptic plasticity. Consequently, tES requires ongoing learning in order to promote or modify plasticity. The specific effects, however, will depend further on the type of plasticity (dendrite-dependent or soma-dependent), which in humans remains unknown.

Another form of tES, transcranial alternating current stimulation (tACS), applies oscillating current within the standard electroencephalogram (EEG) frequency ranges and, similar to direct currents, this leads to sinusoidal subthreshold modulation of neuronal membrane potentials. While the direct effects of tACS are likely subthreshold, ongoing network activity and the coherent stimulation of entire brain regions amplify this effect, leading to changes in spike timing and ongoing neuronal firing rates. The effects of periodic stimulation are not necessarily a straightforward scaling of power in the applied stimulation frequency, but can be expressed through complex non-linear dynamics; tACS can also elicit cross-frequency coupling between endogenous and exogenous activity, and collectively these effects may be used for targeted stimulation in patient groups characterized by abnormal oscillatory activity.

In human applications, however, the sizes and montages of scalp electrodes will often span dozens or more square centimetres (a standard tES electrode is 7 x 5 cm). Because the electrodes are large and current flows between them, large areas of the brain are stimulated (Figure 1). Moreover, little consideration is given about how the underlying gyral and sulcal anatomy influences current flow. While the currents applied to the scalp are generally of low-intensity (0.5–2 mA), it is relevant to note that the electrical fields in the brain have been estimated to be at the lower end (~0.4 V/m for a 2 mA scalp current) of the intensity required to modify neuronal activity in animals experiments. It is therefore possible that the effects seen

in humans arise from different mechanisms of action than those observed in animal preparations, something to which we shall return.

In human applications of tDCS, it is commonly assumed that there is uniform anodal and cathodal stimulation under the electrode. With this assumption comes the idea that neural activity can be dialled-up or down depending on the polarity of the electrode placed over a target brain region. But several points render the concept of 'anodal' or 'cathodal' stimulation fraught with oversimplification. First, we know that, even at the level of individual neurons, the assumption of uniform polarization is incorrect: for example, the soma and apical dendrites may experience opposite polarization.

Second, at the macroscopic level, we also know that cortical folding results in an alternating pattern of inward (excitatory) and outward (inhibitory) current flow with respect to the cortical surface. So even underneath an electrode placed on the scalp, opposing patterns of polarization are likely to occur. With conventional surface electrodes, for example, cortex underneath an electrode is exposed to a mixture of inward and outward directed current (with respect to the cortical surface; see Figure 1). The consequences of this are not clear, but recent work suggests that control of current flow direction in a cortical target region may help to improve the consistency of outcomes. But even then, the idea of uniform polarization at the level of functional specialization in humans is overly simplistic.

Applications of tACS may be less affected by such considerations because the currents are periodic. In humans, tACS is thought to entrain rhythmic cortical activity in a frequency-specific way, and to exogenously modulate phase coupling among distinct cortical regions in healthy human: tACS thus influences the amplitude, phase or frequency of ongoing oscillatory activity, within and between cortical regions. This can provide powerful means to study cortical network interactions and their role for behaviour. But the mechanistic basis of the interaction between the exogenous stimulation and the endogenous activity remain unclear. To what

degree the low currents of tACS induce phase synchronization and entrain ongoing activity in the human similarly awaits clarification. Such question may be usefully addressed using modelling approaches.

Towards models for the behavioural selectivity of tES

Given these considerations of the complex nature of current direction, specificity and homogeneity in gyrified cortex, how could polarity-specific behavioural effects then arise? One answer is that it does not matter. If used to study behaviour, one can view tES as a perturbation to a neural system. If this perturbation leads to a clear decomposition of behaviour, we have learned something valuable about behavioural processes. It is tempting to attribute, almost always in a *post hoc* fashion, an observed behavioural change to an underlying neural mechanism, such as an increase in excitability, and to consult reductionist approaches from disparate levels of observation to explain the observed behavioural change. We think that this is unlikely to yield valid answers, and given the lack of knowledge about the physiological effects of tES in humans, has proven to be misleading to date.

If attempting to understand mechanistically how tES works, complementary computational neurostimulation approaches are needed to merge physiological experimentation with current flow models and biophysical models, and bridge between disparate levels of observation (Figure 2). The latter encompass the physiological consequences of stimulation in neural networks. The question then is not so much whether tES can effectively stimulate the human brain, but how it does so, how it can do so reliably and reproducibly, and how its effects differ from those in animal experiments. Because of the potentially very different ways through which tES interacts with neuronal processing in *in vitro* and *in vivo* animal studies, and human applications, analogies between the two model systems should be approached more cautiously than hitherto (Figure 2).

While there is currently a paucity of quantitative models that seek to link the dose of stimulation with the resultant changes in neurophysiology, and critically, their consequences on behaviour, advances have recently been made to explain how externally applied weak currents could exert their behavioural effects. One hypothesis is tDCS alters the input/output function of neurons in response to synaptic input. Recent work combining recordings from rat hippocampal slices and computational modelling lends credence to this idea: for anodal stimulation, the inevitable opposing polarization of the cell soma and apical dendrites may increase the likelihood for synaptic plasticity whilst also increasing the probability of spiking at the soma. With these effects being absent for cathodal stimulation, the occurrence of inward/outward directed current flow in cortex thus determines whether input/output function changes or remains unaffected. This may explain how specific cortical regions are effectively stimulated while nearby regions are not. In addition to these effects, spatially distributed and diffuse weak polarization may promote connectivity and interactions between interconnected and interacting brain regions. The use of biophysical models that simulate the physiological and behavioural effects of tES can indeed successfully predict the resultant consequences of stimulation, but further efforts are needed to develop working models on how widespread polarization of cortex could express its effects.

Dose-control and dose-response

It would be merely surprising that currently there is no established dose–response relationship for tES in humans, if it were not that the literature appears to have invented one. Put simply, we generally do not know how much current is applied to a brain region in an individual, nor do we know which brain regions are being stimulated. Yet not knowing how much current is applied, nor how a certain dose of current would physiologically exert its effects, is relevant

because it may contribute to variable outcomes across studies, and complicates the decision about the intensity of current that should be applied.

The physics of tDCS postulate that the intensity of current flow inside the brain relates linearly to the intensity of the externally applied current. There is therefore an assumption in many studies that more current directly translates into more stimulation. Whether the physiological consequences of tES in humans behave in a linear or even a monotonic way remains unclear, however, with recent evidence pointing to the contrary. One reason for a potentially complex dose–response relationship in tES is that not only brain regions underneath a scalp electrode will be targeted, but current flows between electrodes and can be widely distributed, including subcortical structures. The net behavioural consequence of tES are therefore difficult to attribute to a single brain region (Figure 1), and likely arise through complex network interactions that differ from most *in vitro* and *in vivo* studies.

For a given current applied, the electric field (V/m) that each brain region experiences is therefore generally unknown, yet identifying the dose-response of tES requires accurate targeting and control of applied effective dose across individuals. Recent work comparing intracranial currents recorded in patients with implanted electrodes and current flow models in the same patients suggests that individualized dose-control can now be accomplished. The question now is whether this will lead to larger effects sizes and better reproducibility, which so far has not been established.

The above is the state of play in physiology, then: scalp-applied electrical currents do have physiological effects on the brain, but the effects are uniform in neither polarity, magnitude nor anatomy, and these effects remain to be modelled seriously. There are some indications that polarity of stimulation may have different effects on GABA and glutamate neurotransmitter regulation, which can be quantified in humans using magnetic resonance spectroscopy. While these changes can provide biomarkers for behavioural change, such as

tES effects on motor learning, a mechanistic account of how such effects cause the behavioural changes seen with tES remains to be established.

Cognitive enhancement

Given the uncertainties in our knowledge regarding the physiology of tES, it is remarkable that some sections of the literature display a high degree of uniformity in reporting the positive effects of tES, particularly tDCS. Perceptual, performance and cognitive enhancements have been reported in visual detection, memory, priming, reading, creativity, mathematical cognition, morality, decision making, sports performance, endurance, dieting behaviours, addictive behaviours, intelligence and several other cognitive functions. There are three important features of these reports to address: the presumption of physiological effects; the nature of the stimulated and the control sites; the presumption of dosage.

Presumption of physiological effects:

The primary logic of tDCS stimulation in cognition is as follows: anodal/cathodal stimulation over the motor cortex (M1) produces excitation/inhibition; therefore, anodal/cathodal stimulation effects observed in this region extend to other areas of cortex. There is scant evidence for this assumption. Given the limitations of our knowledge about the primary effects of M1 stimulation, it is a stretch to assume effects elsewhere. A further, deep difficulty is that of cortical state: when the excitability of the motor cortex is measured, it is so when the muscle is relaxed; simply activating the muscle will alter the effects of stimulation. Now consider the initial state of the prefrontal cortex. How does one begin to equate a relaxed muscle with a relaxed cognitive state? And if activating the muscle alters the effects of tDCS, how — if the logic of what is good for M1 is good for all cortex holds — do the effects survive the activation of prefrontal areas during cognitive tasks?

Stimulation and Control Sites:

The presumption that the effects of tES in M1 can be applied as rationales for stimulating other cortical regions remains problematic because it is not clear how changing excitability of a large brain region may be something useful. The intellectual terrain gets rougher for the idea of cognitive enhancement when one considers how most enhancement stimulation is carried out. The assumption is that one electrode behaves as an anode, one as a cathode, with little consideration about any between-electrode modulation. It is difficult to reconcile the distributed current flow with the idea of uniform effects, and no interactions between the two stimulated sites. Comparison of active control montages may help to address this, as is the comparison with control processes that are thought to be supported by the same or similar cortical architecture than the process of interest.

The effects of 'dosage'

A third major difficulty in understanding the effects of tDCS in cognitive enhancement is that of dosage. Again, even if there were reasons to accept the M1/rest-of-cortex equivalence assumption, the findings from M1 contradict the post hoc mechanistic assumptions of many enhancement papers. Put simply, the enhancement literature logic is that M1 is a model for the rest of the cortex, that anodal/cathodal is excitatory/inhibitory and that more current means greater polarity-specific effects. As intimated above, the M1 literature suggests a non-linear, or even non-monotonic dose–response relationship, in which the effects of stimulation at higher intensities (such as 2 mA) null or even reverse, compared to stimulation at lower intensities.

It seems, then, that the physiological assumptions upon which the majority of enhancement designs and mechanistic explanations are based are simplistic. How have so many reports appeared? There are a number of reasons, including publication bias, small sample and

effect sizes, and insufficient replication. The main problem could be conceptual, however. It is unclear why widespread, non-uniform polarization of distinct brain regions should be beneficial to the computations carried out by these regions. With this comes the problem of defining what enhancement actually means. Behavioural tasks of often ill-equipped to detect a genuine and desirable improvement of cognitive function that would translate into real world benefits, as opposed to an insular change in a laboratory performance score. Unfortunately, many salient commercial and therapeutic uses of tES in cognitive and performance enhancement are offered to people unable to critique claims about the beneficial effects of tES.

Translation

Following on from this, the persistent notion that tES might be beneficial in a large number of disorders remains similarly puzzling. One may argue that medicine is full of examples where application has preceded knowledge. However, several problems seem specific to tES. First, it is often ignored that the physiological consequences of tES in animals and healthy humans, which in essence provide the rationale for its application in disease, may not translate to patients in a straightforward way. For example, many psychiatric disorders are characterized by changes in neuromodulatory systems. These very same systems are known to determine the physiological effects of tES, so applying the same stimulation protocol in two populations with distinct neuromodulatory states may not yield the same effects. Similarly, the rationales for applying specific protocols of tES patients with brain damage neglect that this damage can profoundly influence the distribution of current flow, and also changes the state of any peri-lesional tissue. How this affects the impact of tES is unclear but it is likely to be a critical factor.

There is thus the worrying possibility that the effects of tES in the healthy human brain do not translate to patient groups in a straightforward way, simply because the brain of these patients is likely to react differently to stimulation. Informing the clinical use of tES with

insights from healthy human participants and animal studies may therefore not adequately consider disease specific changes that determine the effects of tES. It is thus of paramount importance to move towards disease specific models for the application of tES, such as the possibility for considering the impact of brain lesions on current flow, and the possibility to model the interactions between stimulation and neuromodulation.

Outlook

We have been here before. In the early days of transcranial magnetic stimulation (TMS) there were many claims about the illnesses it could help, and after a quarter of a century of research these have been pared down to less than a handful — depression, migraine, pain, and anxiety. We are now at the beginning of the paring process for tES, and the risk is that the field holds the tiger by its tail. The appeal of tES is its capacity for non-invasively modulating plasticity and neural circuits, paired with an ease of application and high tolerability. There are exciting and promising examples for the capacity of tES to influence cortical networks and the behaviour they control. The challenge is now to exploit this progress optimally — a point that seems relevant in light of the negative hype, including questions about its general usefulness, that currently engulfs the wave of enthusiasm about tES. Much of this debate is fuelled by an increasing number of meta-analyses, but these can only be as good as the methods they employ and the data they use. Ironically, there is also no agreement among meta-analyses about the same applications of tES. We think that as long as large sources of variance, such as the current lack of dose-control, or lack of individualized targeting remain, discussion about the general utility of tES seems premature.

Going forward, we identify at least three key developments that will benefit the field. First, efforts for targeting and dose-control should increasingly be employed, pending validation that doing so increases efficacy and reproducibility of tES. But simplistic concepts

such as ‘anodal stimulation of…’ are likely to keep delivering mixed results without these approaches. Second, it is remarkable that replication of behavioural effects between laboratories, in particular those of cognitive enhancement, are almost absent. More replication studies are needed, and may benefit from pre-registration and use of comparable protocols. And third, computational neurostimulation approaches will help bridging between the different levels of observation at which tES is studied and used, and help formulating mechanistically grounded protocols and applications.

Further reading

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Figure 1. Example electrode montage most commonly used for stimulation of primary motor cortex.

One electrode (anode) is placed over central sulcus, and the other electrode (cathode) placed over contralateral prefrontal cortex. As shown on the right, the distribution of current inside the brain with this montage is not focal. Instead, peaks of current can not just occur under both electrodes, but also in brain regions in between and remote from the stimulation electrodes.

Figure 2. Levels of observation of the effects of tES.

While the effects of tES in humans and animals are studied at various spatial scales, it is often unknown how an effect at one spatial scale relates to an effect observed at another spatial scale. This highlight a paucity of mechanistic understanding of how tES might alter behaviour. EEG, electroencephalography; fMRI, functional magnetic resonance imaging; LFP, local field potential; LTP/LTD, long-term potentiation/depression; MEG, magnetoencephalography; MRS, magnetic resonance spectroscopy; TMS, transcranial magnetic stimulation

In Brief

A Primer by Bestmann and Walsh explaining how weak transcranial electric currents affect the human brain, with a critical look at concepts, mechanisms, and future directions.

Figure 1

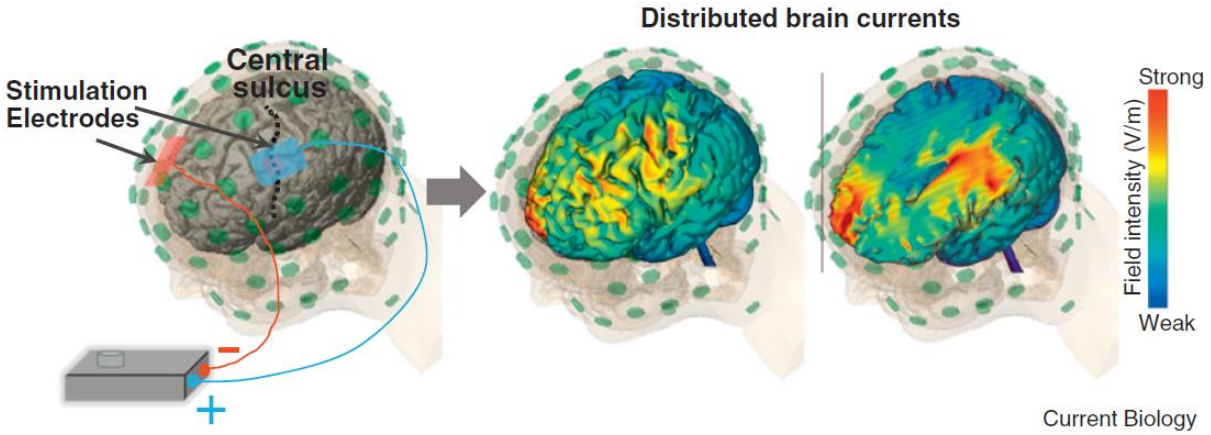
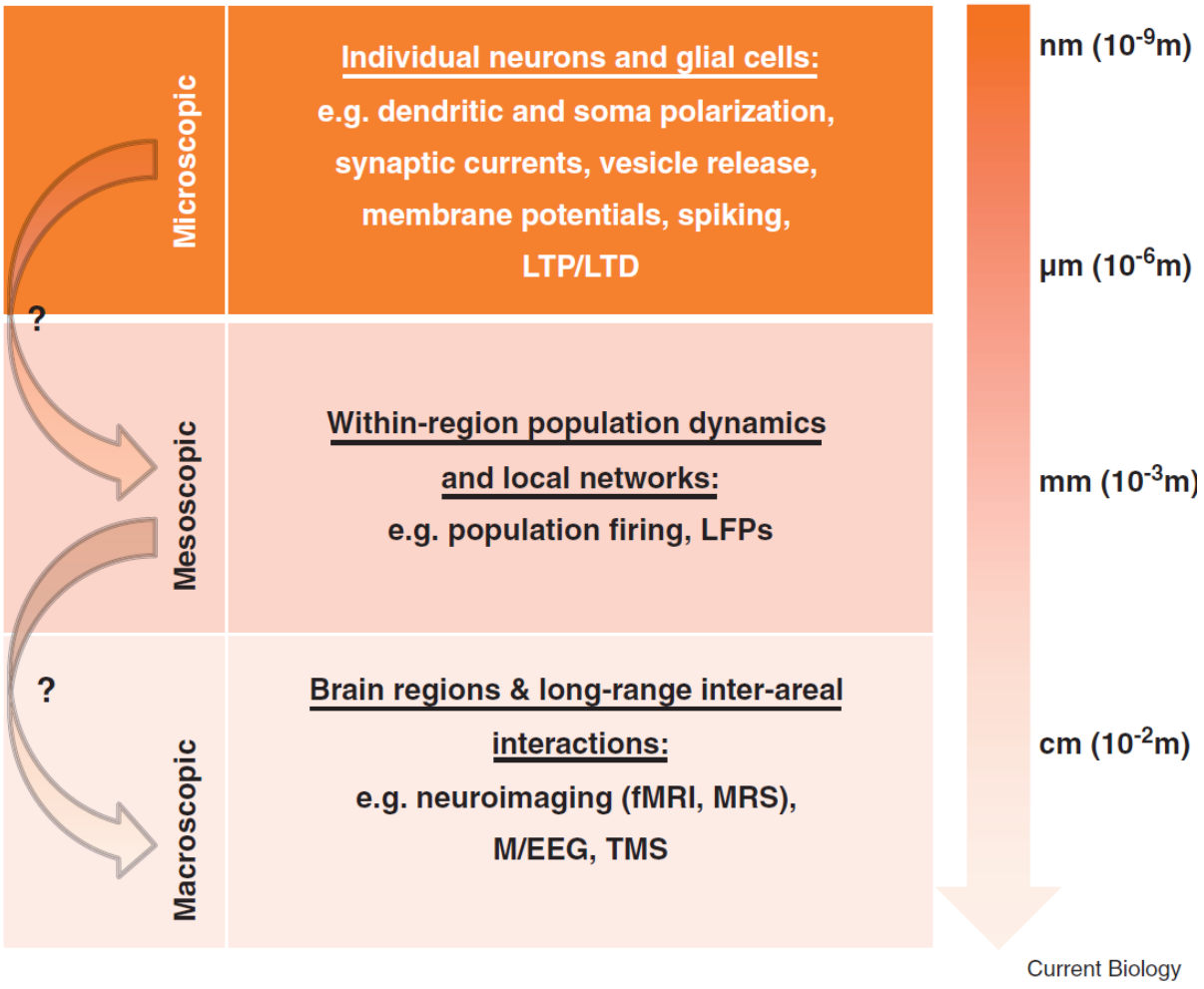

Distributed brain currents
Stimulation Electrodes
Central sulcus
Strong
Field intensity (V/m)
Weak
Current Biology

Figure 2


Microscopic
Individual neurons and glial cells:
e.g. dendritic and soma polarization, synaptic currents, vesicle release, membrane potentials, spiking, LTP/LTD
?
Mesoscopic
Within-region population dynamics and local networks:
e.g. population firing, LFPs
?
Macroscopic
Brain regions & long-range inter-areal interactions:
e.g. neuroimaging (fMRI, MRS), M/EEG, TMS
nm (10^{-9}m)
μm (10^{-6}m)
mm (10^{-3}m)
cm (10^{-2}m)
Current Biology