

Transcranial Electrical Stimulation: What We Know and Do Not Know About Mechanisms

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Abstract

In recent years, there has been remarkable progress in the understanding and practical use of transcranial electrical stimulation (tES) techniques. Nevertheless, to date, this experimental effort has not been accompanied by substantial reflections on the models and mechanisms that could explain the stimulation effects. Given these premises, the aim of this article is to provide an updated picture of what we know about the theoretical models of tES that have been proposed to date, contextualized in a more specific and unitary framework. We demonstrate that these models can explain the tES behavioral effects as distributed along a continuum from stimulation dependent to network activity dependent. In this framework, we also propose that stochastic resonance is a useful mechanism to explain the general online neuromodulation effects of tES. Moreover, we highlight the aspects that should be considered in future research. We emphasize that tES is not an “easy-to-use” technique; however, it may represent a very fruitful approach if applied within rigorous protocols, with deep knowledge of both the behavioral and cognitive aspects and the more recent advances in the application of stimulation.

Keywords

neuromodulation, noninvasive brain stimulation, neuroenhancement, cognition, models, stochastic resonance, NIBS, tDCS, tACS, tRNS, tES

tES Good for All, or tES Not Good at All?

Reading recent publications on transcranial electrical stimulation (tES), one of the noninvasive brain stimulation methods, one can be impressed by the potentiality of this technique (Dubljević and others 2014). We can enhance cognitive performance in healthy people and ameliorate the clinical condition of almost all types of patients. It appears that humankind can greatly benefit from this simple and easy-to-apply technique! In general, there is extensive optimism within the scientific community regarding the validity of these methods (Riggall and others 2015), which is mainly driven by the urgent need of applied research. Such interest is also widely amplified by media and social opinion (Dubljević and others 2014) given that electrical stimulation of the brain is a scientific approach that is relatively easy to understand and that has a long scientific and literary history (see Zaghi and others 2010 for an exhaustive historical perspective).

tES affects neuronal states through different current waveforms applied transcranially, the most used forms are direct (tDCS), alternating (tACS) and random noise

(tRNS) stimulation (see Boxes 1 and 2). We know that these forms of current are able to induce changes in electrical activity both inside and outside the neurons, causing alterations of resting membrane potential and consequently modifying neuronal synaptic efficiency (Liebetanz and others 2002; Nitsche and others 2003). These modifications are insufficient to induce action potentials but adequate to introduce variation in the response threshold of stimulated neurons (Bindman and others 1964; Creutzfeldt and others 1962).

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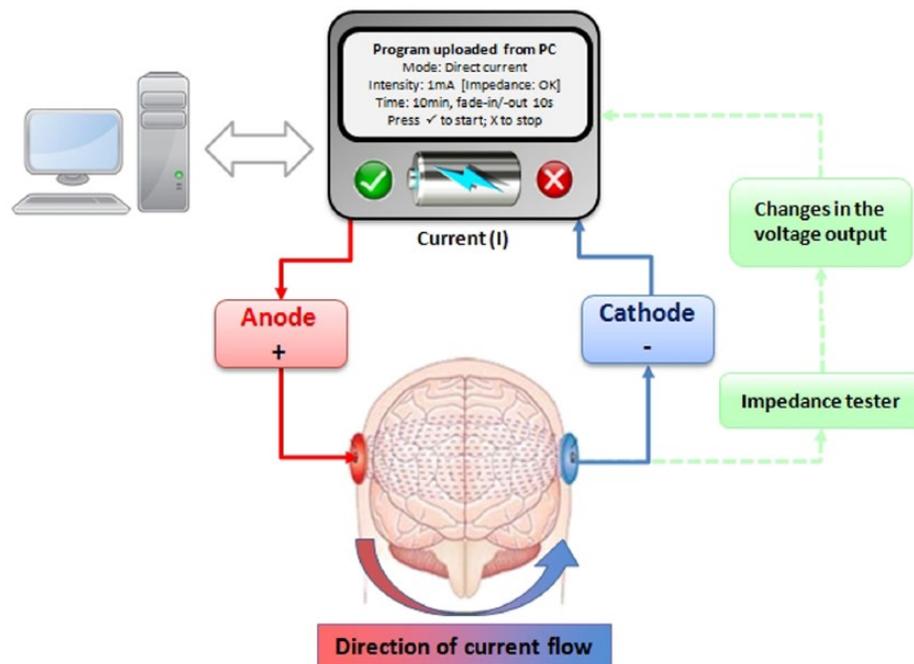
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Box 1.

Schematization of the transcranial electrical stimulation (tES) stimulating device.

The technique involves the delivery of a low-level intensity (~1-2 mA) current by a battery-driven stimulator between two electrodes (anode and cathode) that are placed on the scalp. The electrodes are typically large, conductive-rubber sheets inserted in saline-soaked sponges (20-35 cm²). The current passes through the scalp and crosses the extracortical layers to reach the cortex, which modulates the membrane polarity of the neurons within a region of underlying neural tissue. In the case of direct current delivery, the current flow direction is from the anode to cathode. This current induces changes in the electrical activity of the neurons, and it consequently modifies the neurons' synaptic efficiencies. This modification is insufficient to induce action potentials; however, it is adequate to introduce variation in the response threshold of the stimulated neurons (Bindman and others 1964; Brunoni and others 2011; Creutzfeldt and others 1962) (Fig. 2). To maintain a constant current, the impedance is regularly verified by an impedance tester to establish whether it is necessary to vary the voltage delivered from the stimulator.



Oversimplifying, the idea is that whereas anodal tDCS and tRNS increase neuronal excitability and may consequently enhance behavioral performance, cathodal tDCS decreases neuronal excitability and subsequently worsens behavioral performance, tACS can increase neuronal excitability via entrainment of the desired neuronal firing frequency and consequently modulate performance (Paulus 2011). However, if you have ever used tES, you are certainly aware that applying this simplistic, sliding-scale reasoning (from excitation to inhibition or vice versa) does not always lead to the desired results at either the neurophysiological or the behavioral level.

One of the first studies to clearly demonstrate that tDCS does not function in such a linear manner was Jacobson and colleagues (2012; but see also, e.g., Nitsche and others, 2009). With their meta-analysis, the authors confirmed the impression that many factors, most of which are likely as yet unknown, determine the outcomes

of tES and often induce unpredicted effects, especially in the cognitive field.

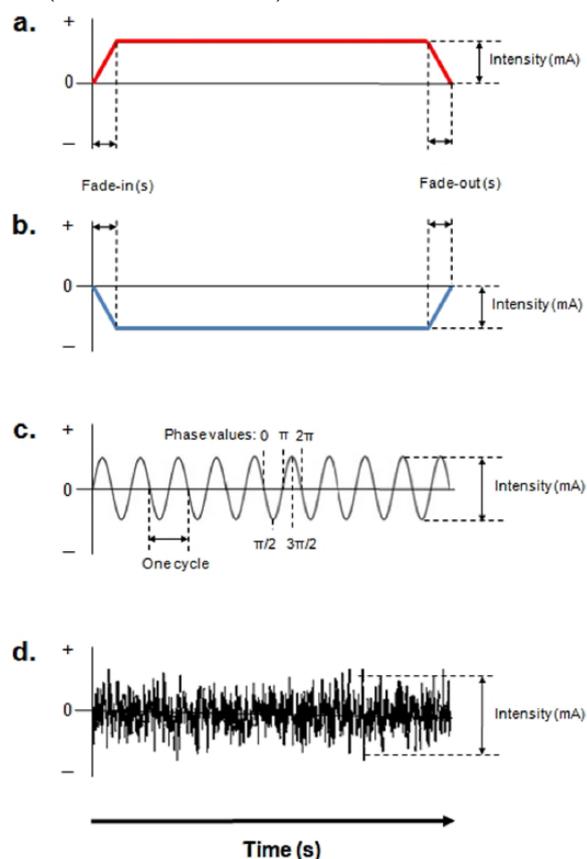
Indeed, in recent years, several studies have revealed the complexity of the technique and the non-linearity of the induced effects (Batsikadze and others 2013; Fricke and others 2011; Moliadze and others 2012; Nitsche and others 2009; Pirulli and others 2013; Pirulli and others 2014). One aspect to consider is that there are several technical parameters from which we can choose to run an experiment and of which little is known about the consequences of their use. For example, only a few authors have considered the importance of task engagement or performance level during stimulation (e.g., Bortoletto and others 2015a; Dockery and others 2009; Hsu and others 2014; Learmonth and others 2015; Tseng and others 2012), intrasubject variability (e.g., Krause and Cohen Kadosh 2014; Li and others 2015; Wiethoff and others 2014), and the factors that influence the diffusion of the

Box 2.

Transcranial electrical stimulation (tES) waveforms and mechanisms of action.

Anodal (a) and cathodal (b) transcranial direct current stimulation (tDCS), which is conventionally represented in red and blue, respectively. The delivered current is direct and monopolar. At the start and end of the stimulation, the current is gradually increased/decreased until the desired level of intensity (fade-in/fade-out periods). Because of single neuron registrations, we know that the application of a direct current can depolarize (anodal stimulation) or hyperpolarize (cathodal stimulation) the neuronal membrane potential, which enhances or diminishes the neuronal firing rate (Gartside 1968) (Fig. 2). Thus, we are reasonably certain that at a cellular level, the direct current impacts the membrane excitability in the opposite way depending on the stimulation polarity. Furthermore, these polarization effects persist beyond the tDCS period (Bindman and others 1964), and the after-effects involve the participation of glutamatergic *N*-methyl-D-aspartate receptors (Liebetanz and others 2002) and therefore long-term potentiation-like mechanisms. The amount of neuronal Ca^{2+} influx caused by the stimulation protocol has been proposed as a crucial factor in explaining nonlinear tDCS effects (Batsikadze and others 2013; Nitsche and others 2003; Nitsche and others 2009). A modest and prolonged postsynaptic increase of Ca^{2+} levels leads to long-term depression, and a moderate increase induces no synaptic modulation (the so-called no man's land, Lisman 2001) whereas a brief but large increase of Ca^{2+} triggers long-term potentiation-like effects (Lisman 2001). The no man's land explanation suggests that both the intensity and duration of tES carry significant biological information.

Transcranial alternating current stimulation (tACS) (c) delivers an alternated sinusoidal current at a specific frequency. Based on several studies in ex-vivo and in-vivo animal models (for a review, see Reato and others 2013), tACS can entrain oscillations, and neuronal networks can amplify the effects of the stimulation (Francis and others 2003). In this respect, tACS could serve as an instrument for interacting with ongoing cortical oscillations, inducing entrainment (Thut and Miniussi 2009) and thereby contributing to a better understanding of cortical binding in cognitive processes. Transcranial random noise stimulation (tRNS) (d) comprises the application of alternating currents in a range of frequencies, typically between 0 and 1000 Hz, but a narrower range of frequencies can be used (e.g., from 100 to 600 Hz). In tRNS, the alternating current is no longer sensitive to the current flow direction. It has been proposed that this type of repeated random subthreshold stimulation could induce an increase in the sodium inflow and a consequent prolonged depolarization and induction of long term potentiation-like phenomena (Fertonani and others 2011; Schoen and Fromherz 2008; Terney and others 2008). Another hypothesis is based on the temporal summation of neural activity, which may occur if the time constant of a neuron is sufficiently long to permit the summation of two stimuli that are presented in close sequence (Pirulli and others 2013).



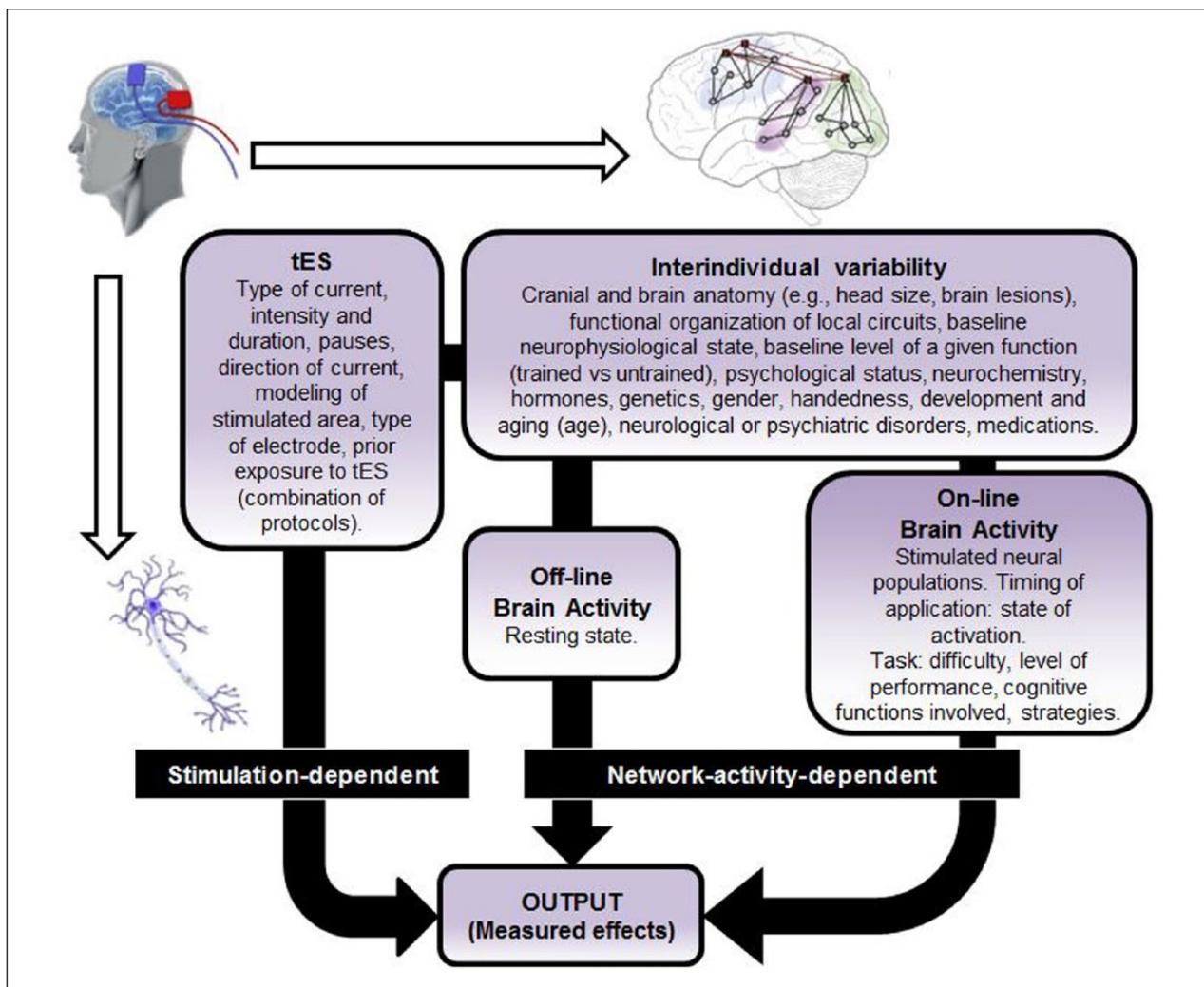


Figure 1. According to the stimulation-dependent model (left black arrow), the measured effect of transcranial electrical stimulation (tES) may be fully explained by considering the effects induced by the different tES protocols at the neuronal level. According to the network-dependent model (central and right black arrows), the final effect of a tES protocol in terms of excitability modulation depends on the interaction of several factors related to not only tES but also the subjects (Li and others 2015) and tasks. The inter-individual variability in the tES effect is associated with several factors known to influence cortical excitability. The excitability state of the stimulated area is another important aspect, that is, the presence or absence of its involvement in the execution of a task.

currents in the brain (Opitz and others 2015) in relation to different neuronal populations and orientations (see also Box 2 “no man’s land” hypothesis to explain nonlinear effects). Undoubtedly, the interactions of all of these important, basic elements are relevant to the final result (Li and others 2015) as outlined in Figure 1.

Additionally, the human brain is exquisitely complex and a self-organizing, highly dynamic system that can react to different situations based on environmental demands such that if it has the power to respond to an external driving force, it will certainly do so. In a situation where the driving force is weak, such as in tES; the type of stimulation is constant; and there is sufficient time

to react (e.g., several minutes of unvarying stimulation, such as in tDCS); we can predict that the central nervous system will produce a homeostatic reaction to ensure that the activity in the cortical network remains within a functional dynamic range. Considering all of these factors along with the neuromodulatory nature of tES, we can conclude that the final response that the tES method induces will be due to the integration of several stimulation parameters and system features.

In a recently published work, Horvath and others (2015a) concluded that in the motor domain, tDCS appears able only to modulate motor-evoked potential amplitude and not any of the other indexes or motor performance.

Moreover, they state that tDCS appears ineffective in the cognitive domain (Horvath and others 2015b). Although their final assumptions are strong, the work presented is insufficient to justifiably draw such negative conclusions about the effectiveness of the technique. Indeed, there are important limitations in their meta-analysis, as suggested by several authors (Antal and others 2015; Chhatbar and Feng 2015); however, their work stimulated critical reflections on the use and efficacy of tDCS.

In general, the extreme views like “tES is good for all” and “tES is not good at all” are both incorrect and do not accurately consider the complexity of the mind. It would be very unexpected that the stimulation of a complex system (i.e., a self-organizing, non-linear and dynamic system) such as our brain resulted in simple, predictable behavioral outcomes, as was initially assumed.

To understand the use and potential applicability of tES, we must be aware of the level of the effect that we are considering/measuring with our testing/intervention, and explanation must then be provided at that level.

For example, if we measure motor-evoked potential or finger-movement acceleration after tES of the primary motor cortex, the inference of changes in excitability and an explanation at the primary motor cortex level (in addition to the excitability changes induced to the corticospinal tract) might be adequate. However, if we test the learning of complex movement sequences, changes in the excitability of the primary motor cortex might ultimately explain only one part of the final behavioral outcome.

The aim of this article is to provide an updated, unified picture of how these techniques can non-invasively interact with the human brain and how can we interpret their outcomes. Given the large number of published articles on the physiological, basic and clinical aspects of tES methods (e.g., Brunoni and others 2012; Stagg and Nitsche 2011; Woods and others 2016), we confine our discussion to the presentation of a unified framework that considers the present level of knowledge of tES effects and a behavioral perspective as the area of research.

tES can be delivered before (offline) or during (online) a task/assignment/condition as part of the experimental procedure. This review focuses mainly on the effects induced during online procedures (i.e., online effects). It does not include specific consideration of offline protocols, in which task performance or brain response before and after stimulation is compared. Offline stimulation involves additional neuronal activity changes that continue beyond stimulation (i.e., after effects); mechanisms including homeostasis of the system, long-term potentiation or depression, metaplasticity, and neuroplasticity in general are strongly involved in the offline approach (Müller-Dahlhaus and Ziemann 2015; Nitsche and others 2012). Therefore, the mechanisms that are discussed here are important but insufficient if we are aiming to clinical

applications; we emphasize that in the neurological and psychiatry fields, all of these aspects must also be considered (e.g., Brunoni and others 2012).

In the next section, we systematically analyze the theoretical tES models proposed to date and contextualize them in a specific, unitary framework. We first describe each of the proposed theoretical models in sections with headers that are based on the proposed mechanisms. We refer to the concepts as models even when they are primarily descriptions of the tES basic mechanisms of action. For each proposed mechanism, we discuss the implications. We then finish the manuscript by presenting a coherent view for explaining tES effects.

Models of tES Effects

Only recently have papers appeared that reflect on tES conceptual models (see, e.g., Bestmann and others 2015; de Berker and others 2013; Krause and others 2013). To date, most proposed mechanisms have been developed with a focus on tDCS functioning; however, nearly all mechanisms are equally valid for other modalities of current deliveries (e.g., tRNS, tACS). The only problem is that the mechanisms that have been proposed to date consider tES functioning at different brain hierarchical levels. Thus, we suggest that they are not mutually exclusive; rather, they merely adopt different levels of complexity in their explanations. Therefore, it is not possible to choose only one of these mechanisms because all of them are necessary to produce an emergent (i.e., global) view of tES effects to interpret specific outcomes. According to the process of emergence, the final behavior of a complex system arises via specific interactions among minor entities; nevertheless, the final response cannot be directly derived from the responses of these simpler units.

Stimulation-Dependent Model

The anodal excitation cathodal inhibition (AeCi) hypothesis is the first mechanism that was proposed regarding tDCS functioning, and is the more known and widely adopted explanation. To describe this hypothesis, we adopt the stimulation-dependent model. In simple words, at this level of description, the brain is considered a “passive organ” with output that can be driven based on simple stimulation characteristics. This model directly associates the effects at the neuronal level to the effects at the behavioral level. From this viewpoint, if you stimulate the brain with anodal tDCS, which depolarizes the membrane potential as demonstrated in animal studies (Box 1), a behavioural improvement will be obtained. In contrast, if you stimulate with cathodal tDCS, which hyperpolarizes the membrane potential, a behavioral

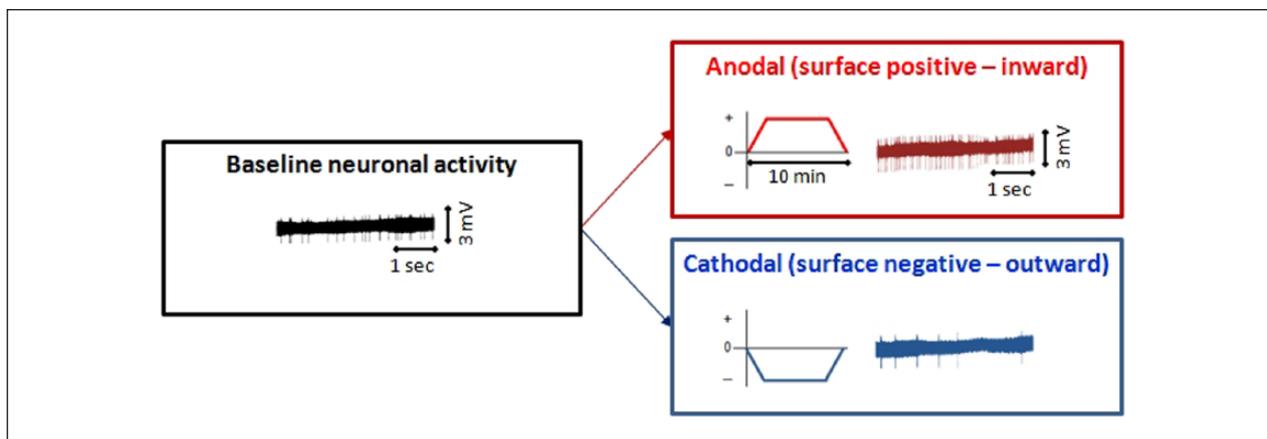


Figure 2. The figure shows how a transcortical direct current polarization (respectively anodal-positive and cathodal-negative) is able to modify the spontaneous activity of a neuron in the visual cortex of a cat. With the positive polarization there is an increase in the firing rate of the neuron, with the negative polarization a decrease in its activity. Modified from Creutzfeldt and others (1962).

worsening will be obtained (Fig. 2). The same reasoning can be applied to other current waveforms: tRNS may be considered “excitatory” stimulation because of its fast oscillating field that would depolarize neurons regardless of the current flow orientation, as demonstrated by several studies (Fertonani and others 2011; Terney and others 2008). Analogous to other rhythmic stimulations (e.g., repetitive transcranial magnetic stimulation [rTMS]; Thut and others 2012), tACS appears suitable for interacting with endogenous brain oscillations, which thereby depolarize and hyperpolarize membrane potentials at a given frequency. In reference to tACS entrainment in a stimulation-dependent framework, the idea is that stimulation at a specific frequency can drive internal frequencies and induce synchronization at the specific cortical rhythm that is imposed by tACS (Herrmann and others 2013) (see Box 2).

Thus, this model predicts that the behavioral results are based on changes in excitability that are induced by tES and ignores all of the intermediate levels that mediate and integrate the stimulation effects (Fig. 1). Furthermore, this model has a very coarse specificity, which localizes the tES effect to an area under the electrode (anatomical specificity, adopting the definition of Bikson and Rahman 2013), without considering the neural state or the cerebral cytoarchitecture of the stimulated area. Although this model has contributed to the renaissance of the tES method, the words and concepts that are used in reasoning about cause and effect are expressed in discrete terms, i.e., AeCi. This approach is clearly a coarse approximation to the principles of causation that govern the brain. In studies of motor physiology, where there is an approximately direct physiological output (e.g., the motor-evoked potential) that is substantially physiologically

constrained, such an approximation may be adequate; therefore, this explanation may be acceptable in this context. Similarly, at the micro-level of processing (e.g., cellular), this language of description can be considered satisfactory. However, in behavioral studies, the final output has a complex and not necessarily direct linear relationship with this basic mechanism. Thus, this model was valuable for initial experimentation; however, it fails to explain the complexity of the experimental evidence. For example, the effect of anodal stimulation is to increase the firing rate and enhance the excitability of a particular neural population; nevertheless, if we stimulate primarily inhibitory neurons, we can inhibit a specific cortical network (and, in a similar way, produce cathodal inhibition). Moreover, increasing the excitability of a specific network does not necessarily imply a behavioral facilitation; it could result in a decrease in performance or not affect performance at all. As previously reported, there are several examples in the literature that do not support the direct relationship between stimulation type and final result that is posited by this model (e.g., Antal and others 2004; Batsikadze and others 2013; Peters and others 2013; Moliadze and others 2012; Moos and others 2012; Pirulli and others 2014; Vallar and Bolognini 2011; Zwissler and others 2014). Therefore, the macro-level processes assessed require their own language of description; we must therefore separate explanations of cellular effects from those of behavioural effects (Miniussi and others 2010).

Activity-Dependent Model

An obvious improvement from the stimulation-dependent model includes the basic reasoning proposed by the

stimulation-dependent model but adds a level of complexity in which the effect of the stimulation depends on the activity of the system. We can therefore define this approach as activity-dependent. This proposal is reminiscent of the state-dependent approach that has been proposed with TMS (Silvanto and others 2008). Nevertheless, with tES, this state dependency has a different effect because tES affects the neurons that are close to the discharge threshold and not inactive neurons, such as with TMS (see also Siebner and others 2009 for a well-defined framework). Thus, this model assumes that because tES is a neuromodulation technique, it only modulates those neurons that are potentially engaged in the execution of a given task (Bikson and Rahman 2013; Dayan and others 2013; Miniussi and others 2013); this model therefore focuses on the activity level of the stimulated neurons. Therefore, this approach considers it relevant to have an increase/decrease in excitation within a group of neurons that are featured in a system, which can be defined as an “integrate and fire system,” where it is fundamental to reach a threshold through the accumulation of evidence, as well as stimulation, to provide a response (Wiesenfeld and Moss 1995).

Network Activity–Dependent Model

Nevertheless, given that sensory-motor, cognitive, affective and conative functions rely on the activity of brain circuits, tES effects can be better framed at the network level within a network activity–dependent model. This level of reasoning can be considered an improvement over the activity-dependent approach and focuses on network dynamics (Fig. 1). Consequently, in this process, the neuronal co-activation that is induced by tES induces an activity-dependent modification of the system not only in an area but also in one or more specific networks (Bikson and Rahman 2013; Luft and others 2014; Miniussi and others 2013). Regarding tDCS and tACS, it has been demonstrated that neuronal networks are more sensitive to field modulation than is the average single neuron (Francis and others 2003), and the efficacy of the effects induced by tACS depends on the phase of stimulation as well as the intrinsic network structure (Kutchko and Fröhlich 2013). The spatial (in the order of centimeters) and temporal (in the order of seconds or minutes) resolution of tES effects are considered to be poor; however, this limitation can be overcome by considering the network activity–dependent approach, which can better explain why specific cognitive effects are obtained with tES. Thus, if two networks overlap in neuroanatomical space, then it is predominantly the network that is activated by the task that should benefit from the stimulation based on the principle of winner-take-all (Maass 2000). Furthermore, in a network activity–dependent approach,

tES-induced effects are also sensitive to the specific state of the network(s). Thus, the stimulation effects will depend on the level of on-going activity (i.e., the excitability state) of the stimulated network(s). Several studies have demonstrated that tES can modulate behavior depending on the neural activity level induced by the task, even reverting the effects of the same tES type contingent on the level of network engagement (e.g., Antal and others 2004; Benwell and others 2015; Bortoletto and others 2015a; Furuya and others 2014; Hsu and others 2014; Gill and others 2015; Tseng and others 2012).

Therefore, the level of network activity is an important aspect for predicting the final outcome of tES, as illustrated in Figure 3. In the nervous system, if the task is not trivial and performance is not at ceiling, there are often competing networks (or components of a network) that attempt to solve a task, and the final output results from this competition. This is the “winner-take-all” computational principle (Maass 2000) in which neurons within a layer compete with each other for activation. Ultimately, only the neurons with the highest activation stay active, and the remaining neurons do not convey the information.

According to the network activity–dependent model, tES may be able to switch the network state to perform better (or worse) in one of two functions that are typically conducted by the network. More specifically, tES-induced excitability modifications could induce a modulation of the input-gating mechanisms (e.g., tES could modulate the gate threshold) or a bias in networks with binary states (Bikson and Rahman 2013; Tiwari and others 2011). In summary, the system could switch more frequently or easily between two states, thereby modifying the response criterion in a specific process. This model consequently implies that, in some cases, the enhancement of one process is associated with the worsening of another (which is also assumed by the zero-sum model). Given its formulation, tES can bias/prime the final response via synaptic changes that affect the state of the stimulated area, and one network will gain more compared with other networks. This proposal can be easily integrated into the concept of priming a system before or during the system “assignments” (online or offline stimulation). In this context, the only fundamental difference is the interaction between the tES and the stimulated system, which is in a different state in the two conditions. Therefore, different stimulation parameters will have different effects on the system, which depend on the role of the stimulated area and the activation level (e.g., Pirulli and others 2014). Following this line of reasoning, if stimulation is applied during the resting state, it will primarily affect the dynamics of the resting-state networks (e.g., the default mode network) (Fig. 1). One limitation of this mechanism is the lack of engagement of the stimulated system during the stimulation; therefore,

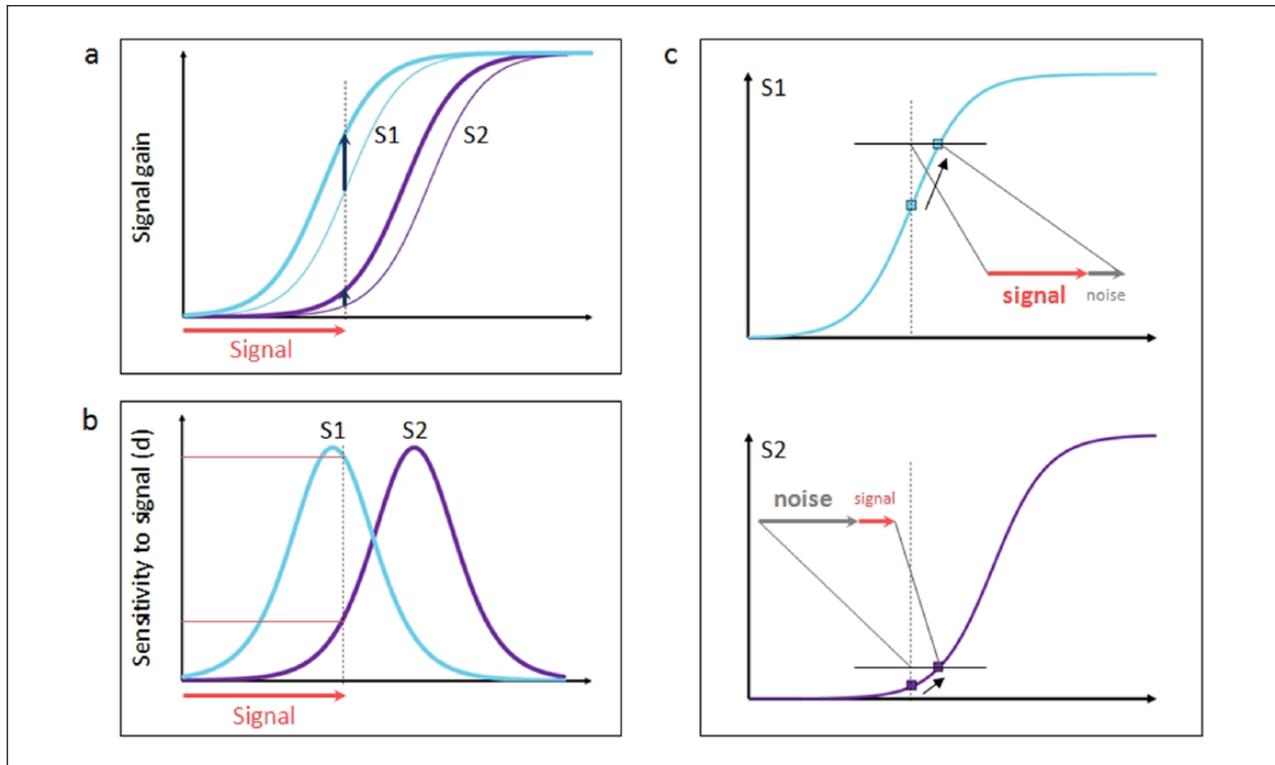


Figure 3. (a) The panel represents sigmoid input-response functions before (thin line) and after (thick line) the application of transcranial electrical stimulation (tES) in two different situations (subjects/populations). tES induces a shift of the system sensitivity that differs between the two situations. The differential response, d , to signal varies as a function of the baseline condition (S1 vs. S2). (b) The function shown here is based on a cumulative gamma function. It shows how d , the sensitivity of the response to signal, changes after tES for one subject/population. Given an amount of introduced noise, for example, $N = 10$, the effects will depend on the state of excitability of the system. Thus, there will be a greater improvement in subject S1 than in subject S2. (c) The same amount of tES will induce different amounts of signal and noise increase in relation to the subject's/population's state (S1, S2). The horizontal arrow represents an arbitrary addition of activity (noise) to the system via tES, which then results in a major increase in signal (first graph S1) or noise (second graph S2). The occurrence of condition one or two should depend on the state of activation of the system.

homeostatic mechanisms may also be at play that induce a gain or loss of responsiveness to specific stimuli via threshold modification (a reduction or an increase) and subsequently enhance or counteract tES-induced effects.

An interesting result regarding the interaction between brain activity and stimulation characteristics was recently reported by Accornero et al. (2014). They evaluated changes in EEG mean frequency as a marker of excitability changes induced by different tES electrode montages that targeted the prefrontal cortex, as described in Figure 4. They measured the relative power in the EEG frequency bands (delta, theta, alpha, and beta) before and during tDCS and found that the changes induced by anodal and cathodal tDCS (increases or decreases in EEG mean frequency) were similar in terms of absolute size (anodal tDCS induced increases, whereas cathodal tDCS induced decreases) but were specific to the stimulated site. As illustrated in Figure 4, left anodal tDCS, right cathodal tDCS, or both (bipolar stimulation) increased

the EEG mean frequency; conversely, when the polarity was inverted only in left cathodal tDCS or right anodal tDCS, but not both, the EEG mean frequency decreased. These results reveal that the primary aspect to determine the decrease or increase in the EEG mean frequency was the role of the frontal cortex network (Accornero and others 2014). Furthermore, some recent papers (Hsu and others 2014; Tseng and others 2012) have demonstrated that tDCS effects are contingent on the participant's original capability. In a visual short-term memory task, anodal tDCS over the posterior parietal cortex was able to increase both performance and related EEG components (reflecting improvement in attentional deployment and memory access) only in low performers. High performers did not benefit from concurrent anodal tDCS, as demonstrated by a lack of behavioural improvement as well as unchanged EEG components after tDCS.

The previous reasoning is based on general networks; nevertheless, we can enhance the level of detail and

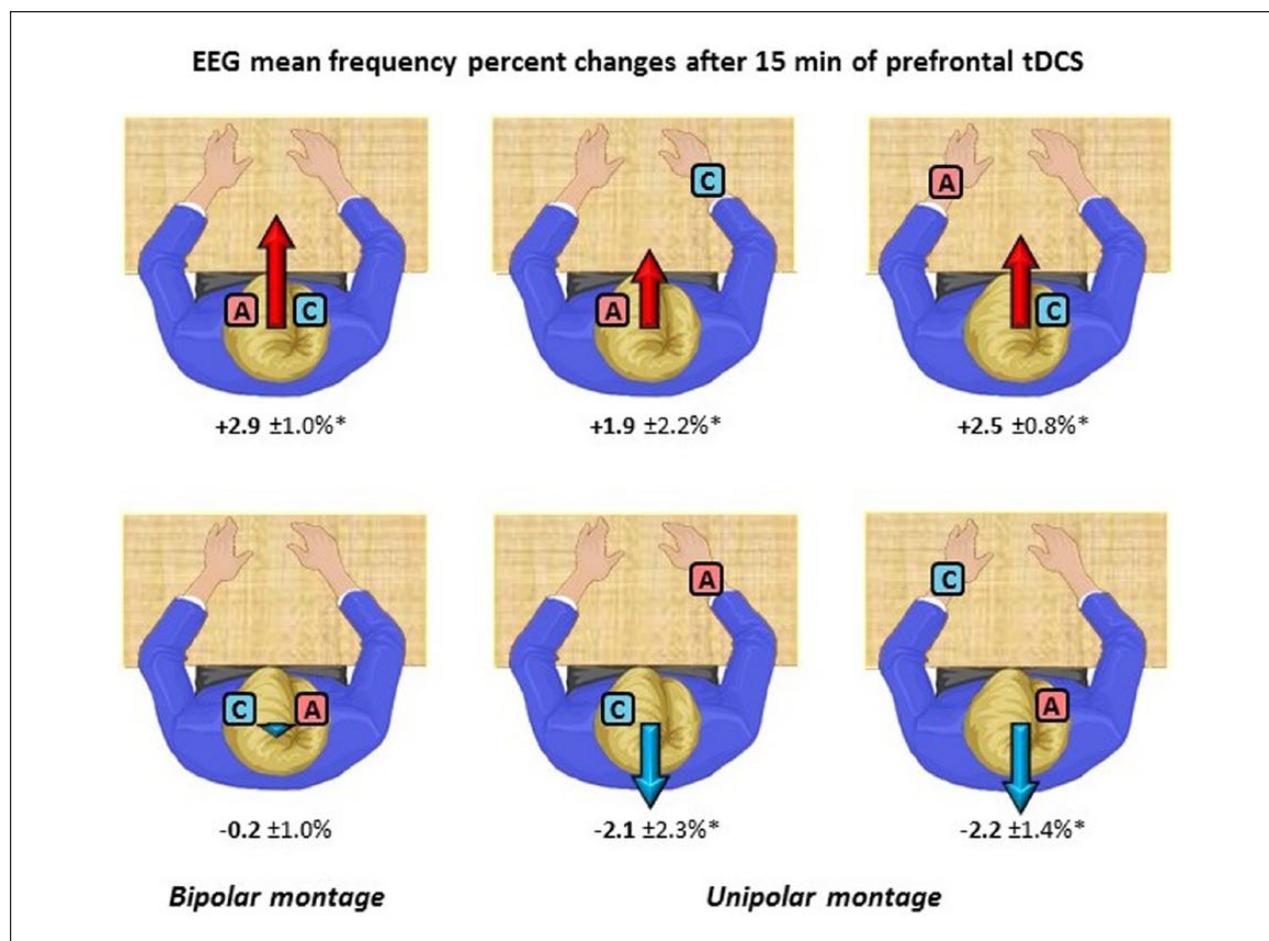


Figure 4. This figure shows percentage change in the electroencephalography (EEG) mean frequency (recorded after 15 minutes of stimulation compared with that recorded at baseline 5 minutes before transcranial electrical stimulation [tES]) induced by different electrode montages, bipolar and unipolar, that targeted the prefrontal cortex. The bipolar montage involved positioning both electrodes over prefrontal areas (cathodal right and anodal left, or vice versa), whereas in the unipolar montage, one electrode was positioned over the prefrontal cortex, while the other was positioned on the opposite wrist. The vertical arrow height indicates the magnitude of the intensity of the effect. A = anodal, C = cathodal. Values are the mean \pm standard deviation. It can be seen how prefrontal areas act as a dedicated network to modulate the brain activity recorded by EEG, highlighting that the primary aspect that determines whether the mean frequency will decrease or increase is the combination of stimulation type with the stimulated network. Drawn using the data of Accornero and others (2014).

reasoning at a local network level as well as explain several interesting dynamic properties that are related to the effects of stimulation. As suggested by neuroimaging studies that used TMS-EEG (Bortoletto and others 2015b) and tDCS-EEG (Luft and others 2014), if a node or hub of a specific cortical network is stimulated, then the effect should spread to functionally interconnected areas based on effective cortical connectivity. Recording the changes that are elicited by tES via neuroimaging can provide a clearer understanding of the activity and connectivity of the entire brain. Therefore, neurostimulation studies can facilitate investigations of brain network architecture and the identification of the consequences of tES stimulation on these networks. This approach presents interesting hypotheses that should

be tested through a combination of tES and neuroimaging methods to assess the cortical connections and their causal relations.

Excitation–Inhibition Balance Model

A widely studied and influential neurophysiological model is the excitation-inhibition balance (Okun and Lampl 2008), which was introduced into the tES field by Krause et al (2013). This proposal integrates basic knowledge from neuroscience and tES effects to identify the key factor in the maintenance of optimal brain functioning in the balance between excitatory and inhibitory inputs in the neocortex. According to this model, tES may

induce a shift in this balance by modifying the manner in which the brain processes information. tES data that support this model originate from magnetic resonance spectroscopy studies that demonstrate the tES effects on the concentrations of inhibitory (GABA) and excitatory (glutamate) neurotransmitters (for a review, see Stagg and Johansen-Berg 2013). Nevertheless, this conceptualization appears to overlap with the principles of causation proposed by the AeCi model at the neurotransmitter level such that the entities at one level (AeCi) are transformed into new entities at a higher level (GABA, glutamate). Neurotransmitter release is part of the same neural communication process; however, an increase in neural specificity means identifying the activation of specific inhibitory or excitatory circuitry (a network). It is important to note that all of the mechanisms proposed in the previous sections are based on the activation of neurons via currents, with activation that is primarily transformed in the release of a neurotransmitter in a second instance. Therefore, there is potential for the integration of the previously described approaches and the present approach, and the final explanation may not be limited to the basic sliding-scale assumption of an anodal-cathodal dichotomy that is transformed into the GABA-to-glutamate ratio. Nevertheless, it has been difficult to integrate this more general method of brain functioning with specific tES effects. The problem is that we are not considering two “competing” networks where one network prevails over the other network for a specific task but rather the induction of an “out-of-balance” aspect of the system. Therefore, it is likely that tES can change the general brain homeostasis depending on the current used and the areas stimulated.

Zero-Sum Model

A further approach that considers brain homeostasis is the zero-sum model, which may be a useful framework within which to place general reasoning regarding the brain. The zero-sum gain model is a specific theoretical framework that is adopted by game theory; when applied to the brain, it states that for every gain in cognitive functioning, there must be a loss (Brem and others 2014; but see Luber 2014 for an alternative view). To date, the validity of the zero-sum model, even if highly plausible, has not been significantly demonstrated in this field because it is difficult to test more than one function within the same experimental design. Moreover, it is also difficult to “localize” the hypothesized loss in the same cognitive domain (e.g., speed/accuracy trade-off) or in different brain capabilities. To date, the only study that has adopted this approach has demonstrated that the improvement in one function is associated with the worsening of another cognitive aspect (Iuculano and Cohen Kadosh 2013);

thus, it induces an advantage to one system compared with another competing system. This interesting finding may provide a rationale for discarding the potential use of these techniques as omnipotent neuroenhancement tools in normal subjects. The idea that it is possible to modify a single cognitive process/function without the induction of changes in other processes/functions appears to be utopian (Luft and others 2014). The concept of limited resources in the brain is not new in the psychology field and is present in the majority of cognitive models of brain function (e.g., attention, see Anderson 2005). Thus, the information-processing capacity of the human mind is limited, and solving a task will result in competition between two task-related networks; if one network prevails over the other network by means of tES, then this mechanism of action supports the idea of a bistable system, which was previously introduced and can explain this competition. Therefore, the conceptualization of this competition can be included in a network activity-dependent framework.

Thus far, we have exposed several views regarding how applied currents (tES) may interact with the brain to produce the final effects. Nevertheless, a crucial question remains to be addressed, that is, what mechanisms are concretely at play when the current reaches the cortex?

Stochastic Resonance

A proposal that considers not only the nature of the effects on the brain but also the “specificity” of these effects refers to the concept of noise and stochastic resonance. One important aspect of the stochastic resonance mechanism, is the assumption that the current application that uses tES is not focal, thus, it will modulate the activity of not only those neurons that are functional for the execution of a specific process/function (i.e., the neurons that produce the signal) but also the entire stimulated area. With this assumption, the injected electric field can be considered noise (because it is not specific) and a sub-threshold signal into a network of neurons. Therefore, noise will primarily affect the neurons of a network that are nearer to their discharge threshold, that is, network-activity dependent (see Miniussi and others 2013). This model references the well-known contribution of noise to information processing. Specifically, it predicts that an addition of noise to nonlinear systems may enhance or worsen the signal detection depending on the relations between the state of the signal (i.e., the level of the network that was activated) and the level of noise introduced into the system (i.e., tES) (e.g., Gammaitoni and others 1998; Kitajo and others 2003; Miniussi and others 2013). Therefore, according to this view, the induction of weak currents in the brain by tES corresponds to an injection of random activity (noise) in our self-organizing, nonlinear

dynamic system. We consequently expect that depending on the intensity of the activity induced by tES (noise) and the state of the system evaluated with a threshold, we will facilitate or inhibit the emergence of a subthreshold signal and induce a subsequent enhancement or worsening of behavioral performance, as depicted in Figure 3c.

All the proposals described above should be incorporated in a more inclusive reasoning because the emergent quality of the system will determine what will be influenced by the stimulation. We can use several sublevels of explanation, ranging from molecule-level to function-level, in which the entities of one level can be integrated into new entities at the subsequent level. Lower level processes are the cause of higher level effects; nevertheless, the contribution of each part cannot be understood if it is not considered as part of a whole. Similarly, the whole can affect the properties of lower-level components. In short, the final outcomes originate from the interactions of all elements; indeed, complex cognitive processes are difficult to describe because they are more than the sum of their parts. The key aspect of this approach is to accept that the process is highly complex. Moreover, to date, it can only be explained with an approximation, and understanding the interaction of stimulation with brain activity is fundamental for accurately predicting the results. Therefore, the process based on the stimulation characteristics is not driving the brain in one direction or another but eventually facilitates the system to choose one direction or another (bistability).

The stochastic-resonance approach is especially interesting because it can explain several cases of “paradoxical” facilitation or inhibition that have been demonstrated by tES based on the interaction between the current and the system level of activity (e.g., Antal and others 2004; Benwell and others 2015; Bortoletto and others 2015a; Furuya and others 2014). This formulation also includes the concept of a bistable system because the term stochastic resonance was initially introduced to describe the response of the system between two locally stable states. Therefore, when subjected to periodic weak forces (in our case, via tES), an open system can switch from one state to another (activate one or the other network) even if the driving force is not sufficiently strong (i.e., neuromodulation) (Aihara and Suzuki 2010; Kutchko and Fröhlich 2013; Tognoli and Kelso 2014). These formulations suggest that the concept of noise is relevant to the definition of a system’s output, in which we can only observe the changes of an output (i.e., the behavior) and cannot directly measure the weak neural signals that drive this output (Wiesenfeld and Moss 1995).

Stochastic-resonance mechanisms have also been hypothesized to explain the action of tRNS (Fertonani and others 2011; Miniussi and others 2013). Consistent with this proposal, there are data that demonstrate the

efficacy of tRNS during the execution of a task (Pirulli and others 2013) and with subthreshold stimuli (van der Groen and Wenderoth 2015). Along the same line of reasoning, tACS can also modulate the system via resonance; in this case, a weak periodic stimulation is added to the system’s fluctuations (spike timing-based brain activity), which enhances the biological signal. Therefore, for tACS, the addition of a particular amount of noise to an excitable system could result in the most coherent and proficient oscillatory responses that engage a specific system (network activity dependent) and modulate the firing rate depending on the relation between the frequency and spike timing of the network (spike timing-dependent plasticity). Here, the brain’s response to external timing-embedded stimulation can result in a decrease in the phase variance and an enhanced alignment (clustering) of the phase components of the ongoing EEG activity, which can change the signal-to-noise ratio and increase (or decrease) the signal efficacy (Miniussi and others 2013). The effect of tACS could therefore rely on the intrinsic resonance of the system, and even small alternating currents can produce larger amplitude ringing, which causes the system’s oscillatory responses to become more coherent and favor one behavior over others. This framework can explain why we can modulate cortical oscillations with tACS but not superimpose a frequency that is not in the capability of the system in a given state or moment.

Conclusions

In summary, almost all of the models that have been proposed to date are perspectives that originated from different fields but that attempt to precisely conceptualize the same issue, with slightly different points of view. Each model offers concepts and valuable indications regarding how to develop tES effects in terms of comprehension and description. They are means to simplify the brain’s enormous complexity. We can likely only explain the final observed behavioral tES effect by using an integrated version of most of the concepts that are discussed in the previous sections. The main problem is that, although all of these conceptualizations are interesting, they cannot be satisfactorily tested at present. Nevertheless, an important next step toward properly interpreting the results is to define the level that is engaged by the task, and our level of explanation must be strictly focused at this level of complexity.

When we apply a tES protocol, our goal is to test specific hypotheses regarding the results that we can expect. This approach explains the appeal and success of the simplistic sliding-scale model of tDCS effects or the model of entrainment for tACS. Unfortunately, there are several levels of complexity that presently prevent us from

making specific predictions regarding the physiological and behavioral effects of our experimental protocols.

Currently, we do not precisely understand how different parameters of stimulation can modify neuronal excitability. Several important indications have been provided by studies on animal models (Brunoni and others 2011) and methodological and modeling studies in humans (Opitz and others 2015). However, generalization of these results is very difficult, and the effects obtained by stimulating a specific cortical area may not be easily extended to other cortices because of anatomical and functional specificities. As clearly emerges from the previous discussion, we believe that it is not possible to know “the real effect” of a specific stimulation protocol (intended as a combination of current type, intensity, and duration) based only on the stimulation-dependent definition because the induced effect will also rely, in a critical way, on the excitability state of the stimulated area, the individual characteristics of the subject (Krause and Cohen Kadosh 2014; Li and others 2015; Wiethoff and others 2014), the behavioral request, and the relation between the task and time of the stimulation, that is, the network activity dependency (Fig. 1). Therefore, the tES efficacy will depend on the network that has been stimulated as well as the general change in the permeability at the membrane level.

However, collecting stimulation parameters and controlling for interindividual variability are important, and we suggest that it is necessary for the scientific community to share related data regardless of whether the results are significant. It is also of great importance to measure indexes at the neurophysiological, imaging and behavioral levels (see also Bestmann and others 2015) to evaluate the patterns that emerge from network-level changes. This step is necessary to formulate hypotheses regarding the final behavioral effect of a specific protocol. Moreover, some uncertainty in the response is intrinsic to the tES neuromodulation approach. Stimulation must change the brain states that compete with the homeostatic mechanism or the neuromodulation induced by the task (or state) itself. Consequently, an important aspect is to understand what the system is doing.

In studying behavior, regardless of the state of the system, the network activity-dependent model would better represent the system that we are testing. tES will induce activity in such a system that act as a “pedestal” to increase (or decrease) the sensitivity of the neurons to an input via stochastic resonance. Therefore, the input that will lead to an increase (or decrease) will be based on the interaction between these elements.

Researchers are largely confident that tES works (Riggall and others 2015); however, many factors influence its effects and make it difficult to use. As discussed above, the ongoing network state and its topology will

determine the response to brain stimulation to a greater extent than what will do the polarity used, which demonstrates the important role of the brain’s adaptive response. This consideration has important implications in many fields because we are not “taking over” the brain but instead “coaching” it to favor the optimal direction. For example, in rehabilitation, we must apply tES not as a unique approach to cure the patient but as support for the rehabilitation protocol that is adopted. Learning (synaptic potentiation) is not a passive consequence of changing the cortical activity via tES; rather, it is driven by experience (Blais and others 2008). We can change the threshold response via tES, which could favor the relearning of a function; however, we must be certain that the change in threshold moves in the correct direction in relation to the rehabilitation protocol that is implemented (Cho and Bear 2010). We emphasize that tES is not an “easy-to-use” technique; however, it can be very fruitful if applied within rigorous protocols (Woods and others 2016) and a deep knowledge of the behavioral and cognitive aspects and the more recent advances in stimulation.

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