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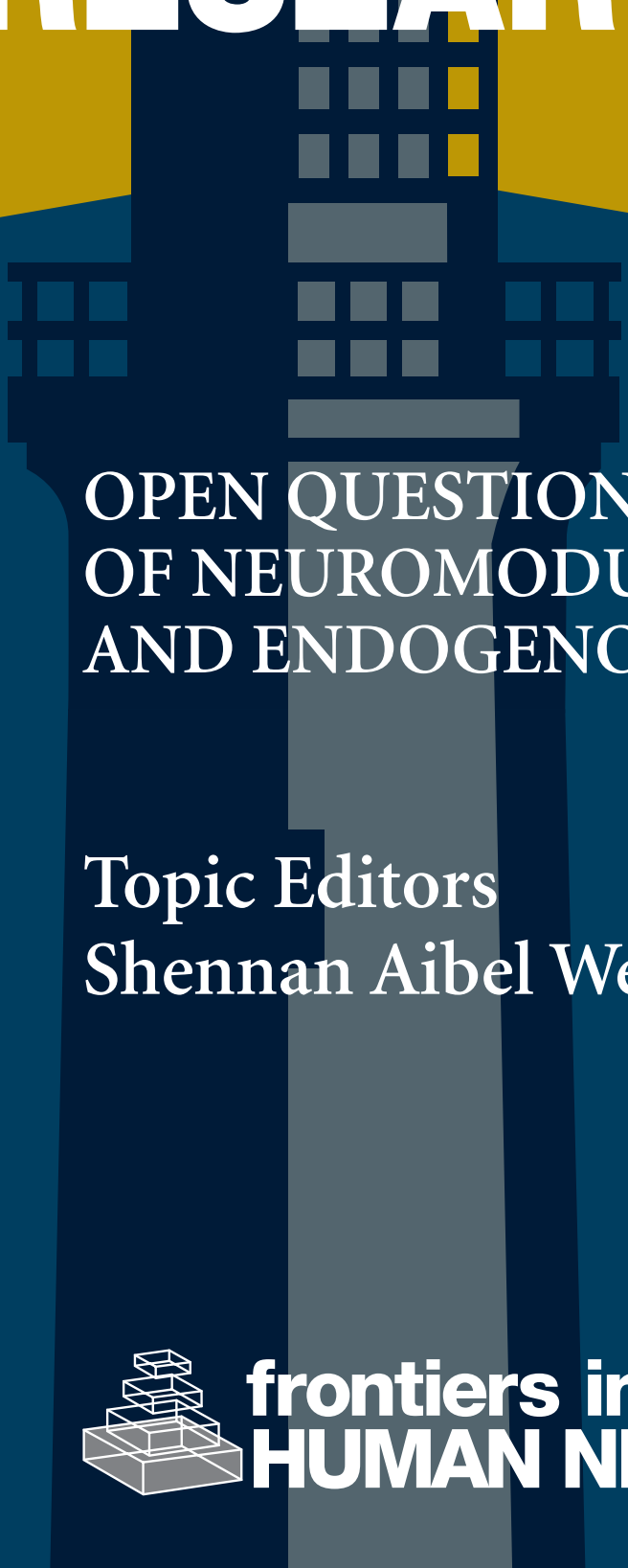

OPEN QUESTIONS ON THE MECHANISMS OF NEUROMODULATION WITH APPLIED AND ENDOGENOUS ELECTRIC FIELDS

Topic Editors
Shennan Aibel Weiss and Marom Bikson

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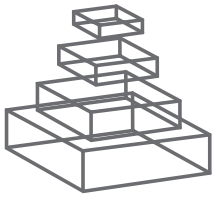

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OPEN QUESTIONS ON THE MECHANISMS OF NEUROMODULATION WITH APPLIED AND ENDOGENOUS ELECTRIC FIELDS

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Despite increased knowledge, and more sophisticated experimental and modeling approaches, fundamental questions remain about how electricity can interact with ongoing brain function in information processing or as a medical intervention. Specifically, what biophysical and network mechanisms allow for weak electric fields to strongly influence neuronal activity and function? How can strong and weak fields induce meaningful changes in CNS function? How do abnormal endogenous electric fields contribute to pathophysiology? Topics included in the review range from the role of field effects in cortical oscillations, transcranial electrical stimulation, deep brain stimulation, modeling of field effects, and the role of field effects in neurological diseases such as epilepsy, hemifacial spasm, trigeminal neuralgia, and multiple sclerosis.

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EDITORIAL
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Open questions on the mechanisms of neuromodulation with applied and endogenous electric fields

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Keywords: ephaptic, transcranial direct current stimulation (tDCS), transcranial magnetic stimulation, brain oscillation, stimulation, systems neuroscience

INTRODUCTION

Despite a long-standing recognition that bioelectric phenomena underpin brain function, fundamental questions remain about how extracellular current flow may influence neural activity and computation. The source of extracellular current flow may be exogenous, electrical exposure or stimulation, or the source may be endogenous, for currents produced by the brain itself. The former has recently gained increased urgency with the evolution of transcranial electrical therapy for a broad range of neurological and psychiatric disorders. The latter remains one of the longest standing open questions in neuroscience—is the electrical current flow that is a ubiquitous aspect of brain function (manifest for example in oscillations, EEG) an epiphenomenon or a key functional signal in the brain.

Field effects that are produced by transmembrane currents are called ephaptic. An ephapse "*Gr*: touching across" was originally coined to describe how two axons placed close together in mineral oil, which has a higher resistance than saline, transmit an action potential at what can be considered an artificial synapse (Katz and Schmitt, 1940; Arvanitaki, 1942). This finding led Sir John Eccles to propose the Golgi cell theory of inhibition in which he speculated that ephapses could mediate inhibitory neurotransmission (Brooks and Eccles, 1947). Eccles corrected this theory and was awarded a Nobel Prize for his subsequent work demonstrating that inhibitory neurotransmission is mediated by chemical synapses. However, in accord with Eccles original theory, ephaptic transmission has been found to mediate inhibitory neurotransmission at the Mauthner cell axon hillock (Weiss et al., 2008), and the Pinceau of the cerebellar Purkinje cell (Korn and Axelrad, 1980; Blot and Barbour, 2014). Research during the twenty-first century has demonstrated that field effects in the mammalian brain may be much more ubiquitous. Field effects generated by endogenous activity may influence network oscillations and computation throughout the cerebral cortex (Radman et al., 2007). Both physiologic (e.g., oscillations; Parra and Bikson, 2004) and pathologic (e.g., epilepsy; Haas and Jefferys, 1984) activity may be influenced by field effects. Because field effects are both generated by coherent population activity and influence networks in a coherent fashion, they may influence brain function as no neurotransmitter can.

Furthermore, weak direct and alternating current stimulation of the human cerebral cortex at low-intensity strengths have been found to influence network dynamics and behavior. The exploration of transcranial Direct Current Stimulation (tDCS) and transcranial Alternative Current Stimulation (tACS) over the past decade for both treatment and to enhance cognitive performance and learning in healthy individuals, has galvanized questions about how the brain responds to low-intensity stimulation. Indeed, the intensity of electric generated in these modalities can approximate the intensity of electricity generated by the bran itself (Datta et al., 2009).

Thus the science of field-effects and low-intensity electrotherapy overlap. The articles included in this e-book highlight some of the latest developments in understanding both endogenous field effects in the central nervous system, as well as the mechanisms and clinical applications of transcranial stimulation of the cortex. We hope that these articles are helpful for students, researchers, and clinicians who hope to better understand and utilize this often overlooked form of neurotransmission.

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REFERENCES

Arvanitaki, A. (1942). Effects evoked in an axon by the activity of a contiguous one. *J. Neurophysiol.* 5, 89–108.

Blot, A., and Barbour, B. (2014). Ultra-rapid axon-axon ephaptic inhibition of cerebellar Purkinje cells by the pinceau. *Nat. Neurosci.* 17, 289–295. doi: 10.1038/nn.3624

Brooks, C. M., and Eccles, J. C. (1947). Electrical hypothesis of central inhibition. *Nature* 159, 760–764. doi: 10.1038/159760a0

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., and Bikson, M. (2009). Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimul.* 2, 201-7, 207.e1. doi: 10.1016/j.brs.2009.03.005

Haas, H. L., and Jefferys, J. G. R. (1984). Low-Calcium field burst discharges of CA1 pyramidal neurons in rat hippocampal slices. *J. Physiol.* 354, 185–201.

Katz, B., and Schmitt, O. H. (1940). Electric interaction between two adjacent nerve fibres. *J. Physiol.* 97, 471–488.

Korn, H., and Axelrad, H. (1980). Electrical inhibition of Purkinje cells in the cerebellum of the rat. *Proc. Natl. Acad. Sci. U.S.A.* 77, 6244–6247. doi: 10.1073/pnas.77.10.6244

Parra, L. C., and Bikson, M. (2004). "Model of effect of extracellular fields on spike time coherence," in *IEEE Engineering in Medicine and Biology Conference* (New York, NY).

Radman, T., Su, Y., An, J. H., Parra, L. C., and Bikson, M. (2007). Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. *J. Neurosci.* 27, 3030–3036. doi: 10.1523/JNEUROSCI.0095-07.2007

Weiss, S. A., Preuss, T., and Faber, D. S. (2008). A role of electrical inhibition in sensorimotor integration. *Proc. Natl. Acad. Sci. U.S.A.* 105, 18047–18052. doi: 10.1073/pnas.0806145105

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Predicting the behavioral impact of transcranial direct current stimulation: issues and limitations

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The transcranial application of weak currents to the human brain has enjoyed a decade of widespread use, providing a simple and powerful tool for non-invasively altering human brain function. However, our understanding of current delivery and its impact upon neural circuitry leaves much to be desired. We argue that the credibility of conclusions drawn with transcranial direct current stimulation (tDCS) is contingent upon realistic explanations of how tDCS works, and that our present understanding of tDCS limits the technique's use to localize function in the human brain. We outline two central issues where progress is required: the localization of currents, and predicting their functional consequence. We encourage experimenters to eschew simplistic explanations of mechanisms of transcranial current stimulation. We suggest the use of individualized current modeling, together with computational neurostimulation to inform mechanistic frameworks in which to interpret the physiological impact of tDCS. We hope that through mechanistically richer descriptions of current flow and action, insight into the biological processes by which transcranial currents influence behavior can be gained, leading to more effective stimulation protocols and empowering conclusions drawn with tDCS.

Keywords: neuromodulation, modeling, computational neurostimulation, validation, neuroenhancement

Since the demonstration that transcranial direct current stimulation (tDCS) can modulate the size of motor evoked potentials (MEPs) elicited over human primary motor cortex (Nitsche and Paulus, 2000), tDCS has become a popular approach for non-invasive neurostimulation of the human brain. The success of the technique, as gauged by the breadth of publications, is striking, being employed over numerous brain areas, in variety of behavioral tasks, and in the treatment of a wide range of diseases (Brasil-Neto, 2012; Brunoni et al., 2012). It appears, however, that the growth in reported applications for tDCS has outstripped the growth in our understanding of the mechanistic underpinnings of direct current (DC) stimulation, both in terms of current delivery and the subsequent effect of electrical fields upon the cortex.

This imbalance has been exacerbated by the impressive and *a priori* surprising trend for tDCS, particularly when the anode is placed over the cortical region of interest, to facilitate behavioral performance (but see Iuculano and Kadosh, 2013). We believe that a deeper and more critical querying of (a) where currents actually flow when one applies transcranial DC stimulation and (b) the effects upon cellular and network activity, will help focus efforts to capitalize upon the remarkable achievements of the field to date. We here briefly summarize recent work on these issues, and highlight some of the key conclusions and remaining questions that are pertinent to current and future users of tDCS.

WHICH NEURAL STRUCTURES ARE TARGETED BY DC STIMULATION?

The arrangement of anode and cathode used by Nitsche and Paulus (2000) that led to a potentiation and suppression of MEP's is pictured in **Figure 1A**. This "classic montage" consists of a pair of sponges, one of which is placed over the motor cortex contralateral to the limb in which MEPs are measured, with the other positioned over the forehead of the opposite hemisphere. It is appropriate to recall here that in any montage using DC, an anode and a cathode will be present; which electrode is deemed the "reference" is merely a matter of convention and depends only upon the predicted effect of stimulation upon the measured behavior. It is also relevant to point out that in their original paper and subsequent work, Nitsche and co-workers do not attribute the observed change in MEP size to the stimulation of any one cortical area *per se*. Moreover, this group is careful to distinguish between montage-specific effects (e.g., the passage of current in various patterns across the brain) and focality (limited current flow to one region) (Nitsche et al., 2007). This discretion is not consistently observed in subsequent studies but is vindicated by neuroimaging data that implies that the classic montage influences numerous cortical areas (Lang et al., 2005; Zheng et al., 2011), and that standard DC stimulation protocols influence the excitability of numerous muscles (Roche et al., 2009).

One can be fairly confident, therefore, that conventional tDCS stimulation protocols, with two large electrodes placed across the head, induce widespread currents of varying intensity and therefore widespread changes in cortical activity, a conclusion further supported by numerous modeling approaches (Datta et al., 2009; Bikson et al., 2012; Ruffini et al., 2012) There is an important distinction between putting one electrode "over" a brain region, and targeting that brain region with focal current delivery – and indeed the peak brain currents in a bipolar array may be at some point

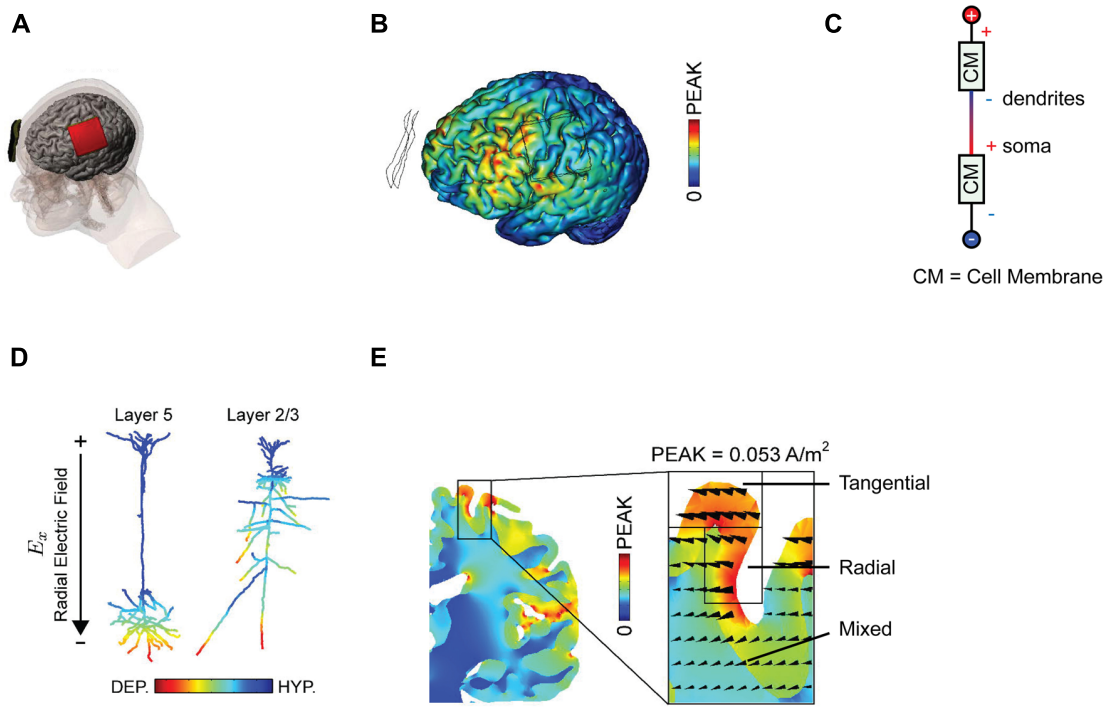

FIGURE 1 | Examining current distributions in the cortex. **(A)** The classic montage used by Nitsche and Paulus (2000) to modulate MEP size. **(B)** Finite element modeling of current distribution with the classic montage illustrates the broad swathes of cortex affected. **(C)** Voltage drops across membranes considered as resistors explain the mixture of hyperpolarization and depolarization seen in. **(D)** Superficially depolarizing currents produce hyperpolarization in dendrites and depolarization in the cell soma. **(E)** The direction of current flow varies considerably within the stimulated area. All figures bar **(C)** reprinted with permission from Rahman et al. (2013).

between the two electrodes. This interim conclusion suggests that we are rarely in a position to make conclusive inferences about the function of a specific stimulated area based upon an observed behavioral effect alone; the impact upon networks of activity is simply too broad for topologically specific statements, though it may be reasonable to suggest behavioral effects are consistent with modulation of at least one region of interest. We note that there is a subtle distinction between this phenomenon and network effects elicited by transcranial magnetic stimulation (TMS), where the initial intervention is relatively focal, but then is likely to propagate poly-synaptically to interconnected regions (Bestmann and Feredoes, 2013). By contrast, with conventional tDCS montages the primary effects are likely to occur in a non-spatially specific way (Nitsche, 2011).

The use of mathematical, finite element models for predicting current flow offers a principled way to estimate current distributions, optimize current delivery to target areas, and to circumscribe conclusions about the brain basis of observed effects (**Figure 1B**; Dmochowski et al., 2011; Bikson et al., 2012; Miranda et al., 2013). The use of individual head models is becoming increasingly feasible with improvements in the automatization of the process, reducing the time and expertise necessary and rendering such modeling accessible to more users of tDCS (Huang et al., 2012; Windhoff et al., 2013). Although direct physiological validation of such models is limited (Datta et al., 2013; Edwards et al., 2013), at the very least this approach highlights several important issues for the delivery of transcranial current. Furthermore, the key conclusions we discuss below will not change – they are dictated by the laws of physics – though specific details of these models are likely to yield subtly different results.

Firstly, the amount and distribution of current reaching different brain regions varies wildly as a function of individual physiology and anatomy (Datta et al., 2012) contributing substantial variance to our datasets. A recent study (Edwards et al., 2013), for example, showed that models of current flow based upon individual magnetic resonance imaging (MRI) scans accurately predicted the amount of current necessary to evoke a muscle twitch with strong transcranial electrical stimulation, and successfully explained the twofold variation in evoked response when using fixed stimulus parameters. Factors such as skull thickness, distribution of cerebrospinal fluid, and subcutaneous fat (Truong et al., 2013) have a radical effect upon current flow, and add to the uncertainty about the destination and strength of transcranially delivered DC current.

Secondly, experimenters looking to increase excitability will typically place the anode over the region of interest, analogous to the positioning of the anode over M1 in the classic MEP-modulating montage. One might suppose that this equates to delivering uniform inward positive current to the cortex beneath the electrode. However, this is emphatically not the case. The topography of the cortical surface places a large role in determining current flow, with dramatic reversals in polarity between

adjacent gyri and sulci (Rahman et al., 2013). It is thus simplistic to describe the entire area under the electrode as being "depolarized," or "excited" by the application of anodal currents. Furthermore, slice studies have recently demonstrated that the cellular effect of a depolarizing current applied to the cortical surface depends upon the depth of the observed compartment (Chan et al., 1988; Bikson et al., 2004). Simply by considering the cell membrane as a resistor in a classic cable model (**Figure 1C**), it follows that when superficial compartments are hyperpolarized then deep compartments in the same cell will be depolarized – and vice versa. Each neuron will inevitably have *both* depolarized and hyperpolarized compartments during tDCS. In a pyramidal cortical neuron aligned with an inward (relative to the cortical surface) directed electric field, this equates to hyperpolarization of the dendritic tree and depolarization of the soma (**Figure 1D**; Rahman et al., 2013). Expected variations in both electric field direction and relative cell morphologies will produce variations in polarization profiles (Radman et al., 2009). Apart from revealing that any simplistic distinction between "anodal" and "cathodal" stimulation provides incomplete mechanistic grounding of behavioral and clinical DC applications, this raises another question; how does direction of current flow affect cellular responses?

Current flow is vectorial, in the sense that we can estimate both the current intensity and its direction at a given point. It is widely acknowledged that increasing total applied current density at the electrodes results in an increase in the intensity of the electrical field generated in the brain and that this affects the physiological response to tDCS (Nitsche et al., 2007). Conversely, far less discussion has focused upon the importance of current orientation (Dmochowski et al., 2012), which in each brain region is typically defined as radial (into the cortex) or tangential (parallel to the cortex). The induction of an electric field in the longitudinal axis is not electrophysiologically equivalent to one that traverses the cell (Radman et al., 2009; Rahman et al., 2013). Whilst a radially aligned inward current will cause somatic depolarization, transverse currents have pathway specific effects upon cellular activity potentially linked to polarization of afferent axons (Rahman et al., 2013). Surprisingly, given the prevalent view that we are injecting current "into" the cortex, tDCS currents are primarily tangential; they flow parallel to the cortex (Rahman et al., 2013). It is interesting to note that the cellular populations that are aligned parallel to the cortical surface, such as intracortical and interhemispheric connections, will therefore be more optimally excited with standard tDCS montages than the radially aligned cortical columns within the stimulated area.

Additionally complicating is the fact that the direction of current flow will be dramatically influenced by the pattern of sulci and gyri in the stimulated area; an electrode configuration that induces primarily radial currents in a gyrus might induce exclusively tangential ones in an adjacent sulcus (**Figure 1E**; Miranda et al., 2013; Rahman et al., 2013). Idiosyncratic different in cortex anatomy across subjects may thus produce distinct patterns of current flow and hence neuromodulation.

Taken together, this suggests that the effect of a polarizing current will differ substantially between sulci and gyri, at different depths of cortex, and between differently aligned cellular populations. It is not yet clear what the significance of this variability is in terms of the design of tDCS montages; we are not aware of any systematic exploration of this issue in humans. It might be instructive, for instance, to examine the effect of current direction upon MEP modulation, a possibility afforded by inverse-modeling that allows us to optimize montages based upon current delivery in a particular direction (Bikson et al., 2012).

EXPLAINING THE EFFECTS OF tDCS UPON BEHAVIOR

The preceding section highlights the difficulties in delivering transcranial currents in a precise and principled manner, and the dangers of assuming homogeneity in induced currents and the simplistic predictions such assumptions spawn. However, this raises an even more fundamental question: even if we were able to deliver currents exactly as desired, it is not clear *a priori* how these would lead to the diverse and impressive behavioral effects reported in the literature. Similarly, given the complexity of current flow and limitations of achievable patterns, what is a "best" achievable current flow pattern for any given objective?

Consider the analogy of the brain as a computer, one that falls short in terms of describing the complexity and plasticity of neural networks. If one strapped a 9V battery to the processor of a laptop and improved the computer's processing, the result would be somewhat surprising. There is no reason to believe that computers, or brains, lack electricity, which should make it very startling when injecting current improves function. It is worth, therefore, reassessing the basic hypotheses about neural processing that underlie current explanations of tDCS's action.

Much of the current wisdom on the action of tDCS can be traced back to generalizations from the effects of DC on motor cortex. Given that we know that microstimulation of the primate motor cortex can produce MEPs (Fritsch and Hitzig, 1870), that magnetic stimulation of neurons in this area can also evoke MEPs (Hess et al., 1987), and that subthreshold stimulation of neurons in motor cortices can modulate the threshold for eliciting MEPs (Kujirai et al., 1993) it is reasonable to interpret the effects of tDCS in this area as alterations of membrane potential. Lasting effects of stimulation are consistent with the induction of long-term potentiation (LTP) between stimulated neurons, an effect that has been documented in animal models of tDCS (Márquez-Ruiz et al., 2012; Ranieri et al., 2012). It is thus parsimonious to suppose that an anodal current over M1 leads to increases in excitability and subsequently enhanced plasticity, whereas cathodal current over M1 decreases excitability and subsequent synaptic depression. This effect is plausibly attributable to depolarization of somatic membrane potential by anodal currents and hyperpolarization of soma by cathodal currents, as observed in slice studies (Chan et al., 1988; Bikson et al., 2004). A simple relationship between cellular activity and the magnitude of the evoked response renders such an explanation coherent.

It should be stressed, however, that this is an *inference*, based upon what is already known about the process of MEP production [and noting that there remains uncertainty about the neural sources controlling even this modest behavior (Di Lazzaro et al., 2008)]. Whether this can readily be generalized to other processes and other cortical areas remains unknown.

The critical point is that there is no theoretical or mechanistic explanation for why depolarizing cells would improve complex behaviors such as perceptual decision-making, mathematical ability, or motor learning. The injection of current into these processes constitutes the addition of random electrical activity that indiscriminately targets large swathes of neurons and has nothing to do with the ongoing activity pattern underlying the performance of the task at hand.

Furthermore, since subthreshold depolarization of a cell is likely to provoke plasticity of active synapses onto that cell, DC is likely to facilitate non-Hebbian plasticity (Hebb, 1949). If we accept that LTP constitutes a means for memory storage (Lisman et al., 2003), then if DC stimulation indeed produces depolarization, it will lead to the formation of irrelevant, interfering, memories. We believe that there are extensive and finely tuned mechanisms for controlling the induction and consolidation of cellular plasticity (Redondo and Morris, 2011). At risk of laboring the point, there is no *a priori* reason known to us to believe that merely depolarizing cells should make these processes more efficient, suggesting that we should challenge the simple assumption that this is what anodal tDCS does.

COMPUTATIONAL NEUROSTIMULATION

Where does this leave us? Our understanding of tDCS at the cellular level is growing, but there remains an explanatory gap between the abstract effects of stimulation upon cells in animals/slices and the large and impressive behavioral effects documented in humans. We believe that for meaningful progress to be made we must attempt description at the appropriate level, that of neural circuits.

We provide a few selected examples that highlight the potential for mechanistically cogent accounts of tDCS function: first, the formulation of physiological hypotheses concerning plausible mechanisms whereby tDCS *might* influence cortical function to enhance processing, and, second, the use of computational modeling to describe the network consequences of stimulation ("*computational neurostimulation*").

Stochastic resonance describes a phenomenon whereby the introduction of small amounts of noise into a non-linear system produces increases in performance when dealing with small amounts of signal (McDonnell and Ward, 2011). Schwarzkopf et al. (2011) demonstrated that the administration of low-intensity TMS to V5/MT improved discrimination in a dot-motion paradigm, an effect that was reversed at high intensities of TMS. This was interpreted as evidence that stochastic resonance plays a role in the facilitatory effects of TMS. Stochastic resonance would provide an equally compelling explanation of tDCS action; the injection of weak currents essentially constitutes the addition of neural noise. *A priori*, stochastic resonance seems a more probable outcome of tDCS than of TMS; the concerted, modulatory nature of transcranial currents make them more likely to modify existing processes than the large, abrupt disruption of normal function produced by TMS. Interestingly, a stochastic resonance account would also suggest that overstimulation might lead to a decrement in performance. Central to this suggestion is that there is a wealth of data about the underpinnings of stochastic resonance at a cellular and population level (McDonnell and Ward, 2011). Combined with individual variability in the efficacy of stimulation (Edwards et al., 2013), this might explain some of the inconsistency observed in responses to stimulation; the addition of too little or too much noise as a result of variable current delivery could produce negligible or detrimental effects upon behavior. We believe that such theoretically plausible accounts, grounded in knowledge of information processing in neural systems, may offer a productive way to enhance our understanding of tDCS action and how it should be applied in different behavioral settings.

Such efforts might be complemented by attempting to formalize the impact of stimulation upon brain networks via modeling of neural activity. Since it is *a priori* not clear why the concerted hypo- or hyperpolarization of thousands of neurons should improve the processing capacity of such populations, these models allow for exploring this issue in detail. We briefly mention two of many approaches. An elegant example for pulsed (TMS) stimulation is provided by Esser et al. (2005), who use a detailed model of thousands of neurons within a cortico-thalamic network including motor cortex, to investigate the precise impact of TMS on cortical circuits. By introducing perturbations analogous to those evoked by TMS, they were able to reproduce key features of MEPs generated by TMS administration. This approach relies on information about the effect of stimulation upon the cellular population modeled, which can then be simulated and outputs compared with empirical data.

The opposite approach, inferring the cellular perturbation from the network response, is made possible by biophysically informed network models such as dynamic causal modeling (DCM; Friston et al., 2003). A striking example of how DCMs can be used to infer the underlying changes in cellular physiology comes from Moran et al. (2011). These authors administered L-DOPA to subjects performing a working memory task, and recorded magnetoencephalography (MEG) responses. DCMs of the MEG response to drug administration recapitulated the changes in NMDA and AMPA receptor conductances known to underlie the action of dopamine in the frontal cortex (Goldman-Rakic, 1996). There is no reason why a similar approach should not be taken with tDCS, offering a rich toolkit with which to examine the neurophysiological changes underlying the immediate and delayed effects of tDCS upon behavior. Building upon combined neurostimulation and neuroimaging approaches that allow for identifying interactions between stimulation-induced behavioral change and neural activity (Siebner et al., 2009; Bestmann and Feredoes, 2013), this would involve the application of tDCS during recording of brain activity with magneto- and electroencephalography (M/EEG) or functional MRI (fMRI), and modeling of the resultant perturbation to infer the neurophysiological changes underlying the observed changes in gross brain activity and behavior.

SUMMARY

We believe that it is imperative that our understanding of the delivery and functional impact of transcranial current continues to grow. Improving current delivery by taking into account individual anatomical variation and the complex dynamics of polarity and orientation is likely to help optimizing established therapeutic

protocols. Similarly, improving and demonstrating the focality of tDCS through the use of high definition electrode arrays (HD-tDCS) (Kuo et al., 2013) might potentially make tDCS a far more valuable tool for systems neuroscientists looking to elucidate the function of specific structures. At present, experimenters should be circumspect in making claims that changes in behavior during or after tDCS are caused by an excitability change in the cortical area underlying one of the electrodes. The credibility of conclusions drawn with tDCS is contingent upon realistic explanations of how tDCS works. To this end, we promote the use of computational neurostimulation to refresh the theoretical frameworks in which to explain the impact of tDCS, in the hope of providing tDCS with a scientific credence which will also assist its use as an exploratory and therapeutic tool.

REFERENCES

Bestmann, S., and Feredoes, E. (2013). Combined neurostimulation and neuroimaging in cognitive neuroscience: past, present, and future. *Ann. N. Y. Acad. Sci.* 1296, 11–30. doi: 10.1111/nyas.12110

Bikson, M., Inoue, M., Akiyama, H., Deans, J. K., Fox, J. E., Miyakawa, H., et al. (2004). Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *J. Physiol. (Lond.)* 557, 175–190. doi: 10.1113/jphysiol.2003.055772

Bikson, M., Rahman, A., and Datta, A. (2012). Computational models of transcranial direct current stimulation. *Clin. EEG Neurosci.* 43, 176–183. doi: 10.1177/1550059412445138

Brasil-Neto, J. P. (2012). Learning, memory, and transcranial direct current stimulation. *Front. Psychiatry* 3:80. doi: 10.3389/fpsyt.2012.00080

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Fregni, F., et al. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* 5, 175–195. doi: 10.1016/j.brs.2011.03.002

Chan, C. Y., Hounsgaard, J., and Nicholson, C. (1988). Effects of electric fields on transmembrane potential and excitability of turtle cerebellar Purkinje cells in vitro. *J. Physiol. (Lond.)* 402, 751–771.

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., and Bikson, M. (2009). Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimul.* 2, 201–207.e1. doi: 10.1016/j.brs.2009.03.005

Datta, A., Truong, D., Minhas, P., Parra, L. C., and Bikson, M. (2012). Inter-Individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. *Front. Psychiatry* 3:91. doi: 10.3389/fpsyt.2012.00091

Datta, A., Zhou, X., Su, Y., Parra, L. C., and Bikson, M. (2013). Validation of finite element model of transcranial electrical stimulation using scalp potentials: implications for clinical dose. *J. Neural Eng.* 10, 036018. doi: 10.1088/1741-2560/10/3/036018

Di Lazzaro, V., Ziemann, U., and Lemon, R. N. (2008). State of the art: physiology of transcranial motor cortex stimulation. *Brain Stimul.* 1, 345–362. doi: 10.1016/j.brs.2008.07.004

Dmochowski, J. P., Bikson, M., Datta, A., Richardson, J., Fridriksson, J., and Parra, L. C. (2012). On the role of electric field orientation in optimal design of transcranial current stimulation. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2012, 6426–6429. doi: 10.1109/EMBC.2012.6347465

Dmochowski, J. P., Datta, A., Bikson, M., Su, Y., and Parra, L. C. (2011). Optimized multi-electrode stimulation increases focality and intensity at target. *J. Neural Eng.* 8, 046011. doi: 10.1088/1741-2560/8/4/046011

Edwards, D., Cortes, M., Datta, A., Minhas, P., Wassermann, E. M., and Bikson, M. (2013). Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS. *Neuroimage* 74, 266–275. doi: 10.1016/j.neuroimage.2013.01.042

Esser, S. K., Hill, S. L., and Tononi, G. (2005). Modeling the effects of transcranial magnetic stimulation on cortical circuits. *J. Neurophysiol.* 94, 622–639. doi: 10.1152/jn.01230.2004

Friston, K. J., Harrison, L., and Penny, W. (2003). Dynamic causal modelling. *Neuroimage* 19, 1273–1302. doi: 10.1016/S1053-8119(03)00202-7

Fritsch, G., and Hitzig, E. (1870). Ueber die elektrische Erregbarkeit des Grosshirns. Archiv. für Anatomie, Physiologie und wissenschaftliche Medicin. Leipzig: Veit, 300–332.

Goldman-Rakic, P. S. (1996). Regional and cellular fractionation of working memory. *Proc. Natl. Acad. Sci. U.S.A.* 93, 13473. doi: 10.1073/pnas.93.24.13473

Hebb, D. O. (1949). *The Organisation of Behaviour: A Neuropsychological Theory*. New York: Wiley

Hess, C. W., Mills, K. R., and Murray, N. M. (1987). Responses in small hand muscles from magnetic stimulation of the human brain. *J. Physiol. (Lond.)* 388, 397–419.

Huang, Y., Su, Y., Rorden, C., Dmochowski, J., Datta, A., and Parra, L. C. (2012). An automated method for high-definition transcranial direct current stimulation modeling. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2012, 5376–5379. doi: 10.1109/EMBC.2012.6347209

Iuculano, T. T., and Kadosh, R. R. C. (2013). The mental cost of cognitive enhancement. *J. Neurosci.* 33, 4482–4486. doi: 10.1523/JNEUROSCI.4927-12.2013

Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., et al. (1993). Corticocortical inhibition in human motor cortex. *J. Physiol.* 471, 501–519.

Kuo, H.-I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M. -F., et al. (2013). Comparing cortical plasticity induced by conventional and high-definition 4×1 ring tDCS: a neurophysiological study. *Brain Stimul.* 6, 644–648. doi: 10.1016/j.brs.2012.09.010

Lang, N., Siebner, H. R., Ward, N. S., Lee, L., Nitsche, M. A., Paulus, W., et al. (2005). How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur. J. Neurosci.* 22, 495–504. doi: 10.1111/j.1460-9568.2005.04233.x

Lisman, J., Lichtman, J. W., and Sanes, J. R. (2003). Opinion: LTP: perils and progress. *Nat. Rev. Neurosci.* 4, 926–929. doi: 10.1038/nrn1259

Márquez-Ruiz, J., Leal-Campanario, R., Sánchez-Campusano, R., Molaee-Ardekani, B., Wendling, F., Miranda, P. C., et al. (2012). Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. *Proc. Natl. Acad. Sci. U.S.A.* 109, 6710–6715. doi: 10.1073/pnas.1121147109

McDonnell, M. D., and Ward, L. M. (2011). The benefits of noise in neural systems: bridging theory and experiment. *Nat. Rev. Neurosci.* 12, 415–426. doi: 10.1038/nrn3061

Miranda, P. C., Mekonnen, A., Salvador, R., and Ruffini, G. (2013). The electric field in the cortex during transcranial current stimulation. *Neuroimage* 70, 48–58. doi: 10.1016/j.neuroimage.2012.12.034

Moran, R. J., Symmonds, M., Stephan, K. E., Friston, K. J., and Dolan, R. J. (2011). An in vivo assay of synaptic function mediating human cognition. *Curr. Biol.* 21, 1320–1325. doi: 10.1016/j.cub.2011.06.053

Nitsche, M. A. (2011). Beyond the target area: remote effects of non-invasive brain stimulation in humans. *J. Physiol. (Lond.)* 589, 3053–3054. doi: 10.1113/jphysiol.2011.211599

Nitsche, M. A., Doemkes, S., Karakose, T., Antal, A., Liebetanz, D., Lang, N., et al. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J. Neurophysiol.* 97, 3109–3117. doi: 10.1152/jn.01312.2006

Nitsche, M. A., and Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol. (Lond.)* 527, 633–639. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

Radman, T., Ramos, R. L., Brumberg, J. C., and Bikson, M. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimul.* 2, 215–228. doi: 10.1016/j.brs.2009.03.007

Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L. C., et al. (2013). Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. *J. Physiol. (Lond.)* 591, 2563–2578. doi: 10.1113/jphysiol.2012.247171

Ranieri, F. F., Podda, M. V. M., Riccardi, E. E., Frisullo, G. G., Dileone, M. M., Profice, P. P., et al. (2012). Modulation of LTP at rat hippocampal CA3-CA1 synapses by direct current stimulation. *J. Neurophysiol.* 107, 1868–1880. doi: 10.1152/jn.00319.2011

Redondo, R. L., and Morris, R. G. M. (2011). Making memories last: the synaptic tagging and capture hypothesis. *Nat. Rev. Neurosci.* 12, 17–30. doi: 10.1038/nrn2963

Roche, N., Lackmy, A., Achache, V., Bussel, B., and Katz, R. (2009). Impact of transcranial direct

current stimulation on spinal network excitability in humans. *J. Physiol. (Lond.)* 587, 5653–5664. doi: 10.1113/jphysiol.2009.177550

Ruffini, G., Wendling, F., Merlet, I., Molaee-Ardekani, B., Mekkonen, A., Salvador, R., et al. (2012). Transcranial current brain stimulation (tCS): models and technologies. *IEEE Trans. Neural Syst. Rehabil. Eng.* 21, 333–345. doi: 10.1109/TNSRE.2012.2200046

Schwarzkopf, D. S., Silvanto, J., and Rees, G. (2011). Stochastic resonance effects reveal the neural mechanisms of transcranial magnetic stimulation. *J. Neurosci.* 31, 3143–3147. doi: 10.1523/JNEUROSCI.4863-10.2011

Siebner, H. R., Bergmann, T. O., Bestmann, S., Massimini, M., Johansen-Berg, H., Mochizuki, H., et al. (2009). Consensus paper: combining transcranial stimulation with neuroimaging. *Brain Stimul.* 2, 58–80. doi: 10.1016/j.brs.2008.11.002

Truong, D. Q., Magerowski, G., Blackburn, G. L., Bikson, M., and Alonso-Alonso, M. (2013). Computational modeling of transcranial direct current stimulation (tDCS) in obesity: impact of head fat and dose guidelines. *Neuroimage (Amst.)* 2, 759–766. doi: 10.1016/j.nicl.2013.05.011

Windhoff, M., Opitz, A., and Thielscher, A. (2013). Electric field calculations in brain stimulation based on finite elements: an optimized processing pipeline for the generation and usage of accurate individual head models. *Hum. Brain Mapp.* 34, 923–935. doi: 10.1002/hbm.21479

Zheng, X., Alsop, D. C., and Schlaug, G. (2011). Effects of transcranial direct current stimulation (tDCS) on human regional cerebral blood flow. *Neuroimage* 58, 26–33. doi: 10.1016/j.neuroimage.2011.06.018

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Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms

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Transcranial Direct Current Stimulation (tDCS) is investigated for a broad range of neuropsychiatric indications, various rehabilitation applications, and to modulate cognitive performance in diverse tasks. Specificity of tDCS refers broadly to the ability of tDCS to produce precise, as opposed to diffuse, changes in brain function. Practically, specificity of tDCS implies application-specific customization of protocols to maximize desired outcomes and minimize undesired effects. Especially given the simplicity of tDCS and the complexity of brain function, understanding the mechanisms leading to specificity is fundamental to the rational advancement of tDCS. We define the origins of specificity based on *anatomical* and *functional* factors. Anatomical specificity derives from guiding current to targeted brain structures. Functional specificity may derive from either activity-selectivity, where active neuronal networks are preferentially modulated by tDCS, or input-selectivity, where bias is applied to different synaptic inputs. Rational advancement of tDCS may require leveraging all forms of specificity.

Keywords: transcranial direct current stimulation, anatomical brain connectivity, neuromodulation, transcranial magnetic stimulation, stimulation protocol

THE NEED FOR tDCS SPECIFICITY

As tDCS is a simple and general technique, applied to a wide range of clinical and cognitive neuroscience applications (Brunoni et al., 2012), a pivotal question to the rational advancement of tDCS is how is specificity achieved? More generally, why does low-intensity direct current produce (desirable) cognitive changes on highly complex tasks recruiting multiple neural pathways or treat multifarious neuropsychiatric disorders (Turkeltaub et al., 2012; Medina et al., 2013; Zimerman et al., 2013)? A question compounded when considering that the DC waveform is does not carry apparent information and that the induced electric field in the brain is low [<1 V/m; (Datta et al., 2009; Ruffini et al., 2012)] producing minimal cell membrane polarization [<1 mV; (Radman et al., 2009)]? Practically, how can stimulation protocols be optimized to promote specificity with the goal of increasing efficacy while reducing undesired side effects? Since these issues are central for the rational advancement of tDCS, here we define both anatomical and functional origins of specificity (Cano et al., 2013). Although task specific effects of tDCS have been shown (Saucedo Marquez et al., 2013; Tang and Hammond, 2013) the mechanistic substrate remains poorly explained.

ANATOMICAL tDCS SPECIFICITY AND THE "SLIDING-SCALE" MODEL

Anatomical specificity refers to the preferential neuromodulation of targeted brain regions by delivering stimulation current to the targeted area. The number, location, and size of anatomical targets are application specific. For example, the targeted brain region may be a specific cortical area implicated in a task or pathology. Anatomical specificity is achieved only through the control of tDCS electrode dose (defined as electrode montage and current) to guide current to specific brain regions (Peterchev et al., 2011). However, applied without consideration for functional specificity, anatomical specificity is technically and conceptually limited.

Both computational models of current flow in the brain and imaging studies indicate that conventional tDCS methodology using two large sponge pads (5 cm × 5 cm) positioned on the head disperse current through much of the cortex (Datta et al., 2009; Faria et al., 2011; Antal et al., 2012; Neuling et al., 2012) and even deep brain structures (Dasilva et al., 2012). It is important to distinguish between carefully designed studies that demonstrate dose-specific (e.g., electrode position) outcomes (Fiori et al., 2013; Hauser et al., 2013; Penolazzi et al., 2013), from implications that current flow is limited to one brain target. These studies also typically leverage other forms of functional targeting.

Technology for High-Definition tDCS using arrays of electrodes allows categorical increases in anatomical targeting by increasing the focality of current flow (Datta et al., 2009; Dmochowski et al., 2011), but even so, any brain region is evidently involved in multiple tasks. Which presents the inherent conceptual challenge when relying exclusively on anatomical specificity: how can passing DC current through a multi-tasking complex brain region produce specific functional changes?

In the absence of further sophistication, the goals of tDCS are often described as increasing excitability (near the anode) or decreasing excitability (near the cathode) of the target brain region, with brain function and disease thus reduced to a "sliding-scale" of excitability to be adjusted by stimulation (c.f., Rahman et al., 2013). For example, under the sliding-scale concept "anodal tDCS" can enhance the performance of a cognitive task by exciting an implicated brain region. Similarly anodal tDCS is intended to increase left-prefrontal cortex activity in depression

and enhance rehabilitation around lesions after stroke. Following early evaluation of Transcranial/transcortical polarization in humans and animal models (Bindman et al., 1962; Redfearn et al., 1964; Elbert et al., 1981), influential neurophysiological studies of tDCS (Nitsche and Paulus, 2000) established modulation of experimental evoked potentials [e.g., motor evoked potential responses to transcranial magnetic stimulation (TMS)]. There is significant extrapolation from these experimental findings to behavior and cognition [TMS evoked responses may provide poor evidence for effects on behavior; (Ridding and Rothwell, 2007)]. Moreover, even the direction of this basic modulation of experimentally evoked potentials is highly sensitive to both tDCS dose [intensity (Matsunaga et al., 2004; Dieckhofer et al., 2006; Batsikadze et al., 2013); direction (Chan and Nicholson, 1986; Bikson et al., 2004; Rahman et al., 2013)] and dependent on brain state (Fröhlich and McCormick, 2010; Reato et al., 2010). Animal studies showing anodal/cathodal DCS producing somatic depolarization/hyperpolarizing (Radman et al., 2009) and increase/decrease in firing rate (Purpura and McMurtry, 1965; Reato et al., 2010), are cited to support a sliding-scale concept, however, global changes in firing rate across a brain region implies a non-specific effect (Reato et al., 2013). In summary, it is reasonable to conclude from neurophysiologic studies that tDCS can produce dose-specific changes in brain functions (Nitsche and Paulus, 2000) that can, with careful extrapolation, serve as a basis for behavioral interventions (Kuo et al., 2013). However, relying only on anatomical specificity by guiding current to specific brain regions (and so the "sliding-scale" rationale) remains limited by the complex and divergent functions of any brain region.

Further sophistication in anatomical targeting follows from considering tangential as well as radial inward/outward currents (Dmochowski et al., 2012) as discussed in a separate article in this special issue. Indeed, the assumption of inward ("excitatory") and outward ("inhibitory") current under the anode and cathode, respectively, may be a further over-simplification. Electrophysiological studies in animal models of DC stimulation suggest differential processing of afferent information (Rahman et al., 2013) and that polarity-specific effects invert due to neuronal morphology (Bikson et al., 2004; Kabakov et al., 2012).

ACTIVITY-SELECTIVITY AND TASK-SPECIFIC MODULATION

Activity-selectivity refers to tDCS preferentially modulating a neuronal network that is already activated, while not modulating separate neuronal network that are inactive. The active neuronal network may be activated for a host of reasons described. The active and inactive networks can in fact overlap in space (e.g., in the same cortical column) such that activity-selectivity does not require physical separation in contrast to anatomical specificity – therefore, we refer to activity-selectivity as a form of functional specificity. The active network may represent a subset of neurons and/or a subset of connections (synapses). Because tDCS produces low-intensity electric fields in the brain, "sub-threshold" neuromodulation may reflect changes in ongoing processes (Reato et al., 2010) in contrast to supra-threshold driven firing by TMS. Activity-selectivity thus assumes there is some feature of the active network that makes it preferentially sensitive to modulation by tDCS compared to other inactive networks. We consider two neurophysiological substrates for this preferred sensitivity: ongoing activity-selectivity and input-selectivity.

Activity-selectivity is based on the assumption that tDCS will preferentially modulate specific forms of ongoing activity. For example, at a cellular level, direct current stimulation (DCS) may enhance plasticity in a given synaptic pathway while stimulated at a preferential frequency (0.1 Hz in Fritsch et al., 2010) or consolidate a specific pattern of activity presented during DCS (Morrell, 1961). DCS may preferentially modulate the level of potentiation in the activated pathway (Ranieri et al., 2012). DCS may facilitate long-term potentiation through membrane polarization and removal of Mg^{+} block (Stagg and Nitsche, 2011) but only those pathways activated during DCS (by a task or experimental stimulation) would benefit from this facilitation. DCS may be too weak and/or unspecific in isolation to enhance synaptic efficacy, but may boost ongoing (e.g., Hebbian) plasticity activated by task performance (i.e., modulation of input specific plasticity along an activated synaptic pathway while sparing quiescent synapses). In humans, transcranial electrical stimulation may also preferentially modulate networks with heightened oscillatory activity (Reato et al., 2010) or preferentially change the progression of an active network during memory consolidation or synaptic downscaling (Reato et al., 2013).

At a behavioral level, specific brain activity is often targeted by training in conjunction with tDCS with the goal that this select activity be sensitized to tDCS neuromodulation (and so implicitly other brain functions not active in training may be less so). For example use-dependent modulation and learning of motor skills is modulated by tDCS (Reis and Fritsch, 2011; Madhavan and Shah, 2012). Clinically, tDCS is often applied to enhance the efficacy of rehabilitation or cognitive training (Edwards et al., 2009; Kuo and Nitsche, 2012; Gomez et al., 2013; Leśniak et al., 2013; Ochi et al., 2013), which may further confer functional specificity through activity-selectivity. Clinically when tDCS is applied to subjects at rest, we can speculate that any functional-specificity results from increased sensitivity of pathological network activity to tDCS (e.g., dysfunctional pain or mood regulating networks). It has been speculated that altered network function associated with brain injury (stroke) may alter the susceptibility to tDCS (Olma et al., 2013). Generally, any interaction between brain activity and the efficacy of tDCS modulation (Kim and Ko, 2013; Pirulli et al., 2013) suggests "tDCS can be highly focal when guided by a behavioral task" (Lapenta et al., 2013).

Although the mechanisms may vary, in any case, functional specificity through activity-selectivity presumes the enhanced activity of the network makes it preferentially sensitive to modulation by tDCS. Thus activity-selectivity necessitates an ongoing network process becoming preferentially tuned to influence by DCS compared to the myriad of other ongoing (background) brain functions.

INPUT-SELECTIVITY AND BIAS

A third form of specificity we define here is input-selectivity, which assumes a neuronal network that is predisposed to serve at least two functions or operate in at least two states such that tDCS can switch the network from one function/state to another: for example

attentional bias in the prefrontal cortex (Eldar et al., 2013). tDCS would change the state of the system toward a different input bias and thus enhance information processing of a specific stream of information. Input-selectivity may activate endogenous "gating" systems (e.g., gate theory of pain) or bi-stable neuronal states – where a non-specific DC signal is able to "switch" a system between complex functions or modes. In contrast to a sliding-scale hypothesis for a stimulated brain region or activity-selectivity affecting a specific ongoing process, input-selectivity implies a regional process is enhanced at the cost of another process – not that input-selectivity results in a zero-sum effect in regards to lasting cognition or behavior outcomes. However, input-selectivity does emphasize the "cost" of acute stimulation. Input-selectivity is also considered a form of functional-specificity since it does not require gross anatomical targeting of current flow. Input-selectivity thus differs conceptually from functional-selectivity (as defined above) in that it does not presuppose co-activation (e.g., by training), and moreover implies that one process may be enhanced at the cost of enhancing another.

Many animal studies that have investigated the modulation of information processing, for example through synaptic efficacy [as opposed to simply membrane polarization and excitability (Chan and Nicholson, 1986; Radman et al., 2007)], have observed that DCS will differentially modulate incoming inputs. We initially showed in hippocampal slice that DCS enhances some and inhibits other afferent inputs (Bikson et al., 2004), a finding verified (Kabakov et al., 2012) and extended to the cortex (Rahman et al., 2013). The cellular origins of bias in favor of selective inputs are twofold. First, although anodal and cathodal tDCS are mistakenly referred to as depolarizing and hyperpolarizing, it is more accurate to describe tDCS as redistributing polarization across the cellular axis, for example one dendritic branch versus another (Fritsch et al., 2010; Rahman et al., 2013). This change in "weights" across the dendrite may provide a cellular substrate to influence the input bias of a network. Second, polarization of afferent axons itself appears to exert pathway specific modulation (Arlotti et al., 2012; Kabakov et al., 2012; Rahman et al., 2013).

Clinically, the concept of input-selectivity can be extended to (selective) attention and working-memory, as well as disease states such as ADHD (Levy, 2004), anxiety, and schizophrenia (Grace, 2000); which are indeed already indications explored for tDCS (Kang et al., 2009; Faber et al., 2012; Demirtas-Tatlidede et al., 2013; Shiozawa et al., 2013). The prefrontal cortex, an anatomical target for several indications including depression (Loo et al., 2012), is indeed implicated in executive function and differentiating among (conflicting) inputs. The concept of bias-selection is consistent with stimulation inhibiting some functions while enhancing others within any given region (Iuculano and Kadosh, 2013; Tang and Hammond, 2013) as well as modulation of relative value judgments (Vanderhasselt et al., 2013; Votinov et al., 2013), which can be considered as a form of weighting inputs so specific outcomes can be biased.

Future studies on the actions of input-selectivity using tDCS can explore applications of multimodal imaging technologies, including magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI), magneto-encephalogram (MEG), and electro-encephalogram (EEG), to further establish the different functional brain-states of a cortical region activated during tDCS (Soekadar et al., 2013). The topic of multimodal imaging in tDCS is discussed further in another article in this special issue of Frontiers in Human Neuroscience (Hunter et al., 2013).

OUTLOOK FOR tDCS

Anatomical specificity and functional specificity, through either ongoing activity-selectivity or input-selectivity, are not exclusive and may potentially be leveraged together in the development of rational tDCS protocols. In general, we propose that understanding the basis for tDCS selectivity is essential. Although we have focused our discussion to tDCS, the approaches described here would apply to other brain stimulation techniques including DBS, VNS, TMS, tRNS, and tACS (discussed further in another article in this special issue, Reato et al., 2013) as well as ultrasound and light based approaches. But the diversity of applications already investigated for tDCS, including increasing dosage (e.g., weeks of sessions), broader populations (e.g., children), suggests a need to address the basis of specificity to be especially acute. Both time-dependent and homeostatic effects (Penolazzi et al., 2013; Peters et al., 2013) increase the subtlety in tDCS protocol design that may require understanding origins of specificity.

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REFERENCES

Antal, A., Bikson, M., Datta, A., Lafon, B., Dechent, P., Parra, L. C., et al. (2012). Imaging artifacts induced by electrical stimulation during conventional fMRI of the brain. *Neuroimage* doi: 10.1016/j.neuroimage.2012.10.026 [Epub ahead of print].

Arlotti, M., Rahman, A., Minhas, P., and Bikson, M. (2012). Axon terminal polarization induced by weak uniform DC electric fields: a modeling study. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2012, 4575–4578. doi: 10.1109/EMBC.2012.6346985

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., and Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J. Physiol.* 591, 1987–2000. doi: 10.1113/jphysiol.2012.249730

Bikson, M., Inoue, M., Akiyama, H., Deans, J. K., Fox, J. E., Miyakawa, H., et al. (2004). Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *J. Physiol.* 557, 175–190. doi: 10.1113/jphysiol.2003.055772

Bindman, L. J., Lippold, O. C., and Redfearn, J. W. (1962). Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. *Nature* 196, 584–585. doi: 10.1038/196584a0

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., et al. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* 5, 175–195. doi: 10.1016/j.brs.2011.03.002

Cano, T., Morales-Quezada, J. L., Bikson, M., and Fregni, F. (2013). Methods to focalize noninvasive electrical brain stimulation: principles and future clinical development for the treatment of pain. *Expert Rev. Neurother.* 13, 465–467. doi: 10.1586/ern.13.41

Chan, C. Y., and Nicholson, C. (1986). Modulation by applied electric fields of Purkinje and stellate cell activity in the isolated turtle cerebellum. *J. Physiol.* 371, 89–114.

Dasilva, A. F., Mendonca, M. E., Zaghi, S., Lopes, M., Dossantos, M. F., Spierings, E. L., et al. (2012). tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. *Headache* 52, 1283–1295. doi: 10.1111/j.1526-4610.2012.02141.x

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., and Bikson, M. (2009). Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimul.* 2, 201–207. doi: 10.1016/j.brs.2009.03.005

Demirtas-Tatlidede, A., Vahabzadeh-Hagh, A. M., and Pascual-Leone, A. (2013). Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? *Neuropharmacology* 64, 566–578. doi: 10.1016/j.neuropharm.2012.06.020

Dieckhofer, A., Waberski, T. D., Nitsche, M., Paulus, W., Buchner, H., and Gobbele, R. (2006). Transcranial direct current stimulation applied over the somatosensory cortex – differential effect on low and high frequency SEPs. *Clin. Neurophysiol.* 117, 2221–2227. doi: 10.1016/j.clinph.2006.07.136

Dmochowski, J. P., Bikson, M., Datta, A., Richardson, J., Fridriksson, J., and Parra, L. C. (2012). On the role of electric field orientation in optimal design of transcranial current stimulation. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2012, 6426–6429. doi: 10.1109/EMBC.2012.6347465

Dmochowski, J. P., Datta, A., Bikson, M., Su, Y., and Parra, L. C. (2011). Optimized multi-electrode stimulation increases focality and intensity at target. *J. Neural Eng.* 8, 046011. doi: 10.1088/1741-2560/8/4/046011

Edwards, D. J., Krebs, H. I., Rykman, A., Zipse, J., Thickbroom, G. W., Mastaglia, F. L., et al. (2009). Raised corticomotor excitability of M1 forearm area following anodal tDCS is sustained during robotic wrist therapy in chronic stroke. *Restor. Neurol. Neurosci.* 27, 199–207. doi: 10.3233/RNN-2009-0470

Elbert, T., Lutzenberger, W., Rockstroh, B., and Birbaumer, N. (1981). The influence of low-level transcortical DC-currents on response speed in humans. *Int. J. Neurosci.* 14, 101–114. doi: 10.3109/00207458108985821

Eldar, E., Cohen, J. D., and Niv, Y. (2013). The effects of neural gain on attention and learning. *Nat. Neurosci.* 16, 1146–1153. doi: 10.1038/nn.3428

Faber, M., Vanneste, S., Fregni, F., and De Ridder, D. (2012). Top down prefrontal affective modulation of tinnitus with multiple sessions of tDCS of dorsolateral prefrontal cortex. *Brain Stimul.* 5, 492–498. doi: 10.1016/j.brs.2011.09.003

Faria, P., Hallett, M., and Miranda, P. C. (2011). A finite element analysis of the effect of electrode area and inter-electrode distance on the spatial distribution of the current density in tDCS. *J. Neural Eng.* 8, 066017. doi: 10.1088/1741-2560/8/6/066017

Fiori, V., Cipollari, S., Di Paola, M., Razzano, C., Caltagirone, C., and Marangolo, P. (2013). tDCS stimulation segregates words in the brain: evidence from aphasia. *Front. Hum. Neurosci.* 7:269. doi: 10.3389/fnhum.2013.00269

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., et al. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron* 66, 198–204. doi: 10.1016/j.neuron.2010.03.035

Fröhlich, F., and McCormick, D. A. (2010). Endogenous electric fields may guide neocortical network activity. *Neuron* 67, 129–143. doi: 10.1016/j.neuron.2010.06.005

Gomez, P. S. A., Faraji, J., Metz, G. A., Tatsuno, M., and Luczak, A. (2013). Transcranial direct current stimulation in stroke rehabilitation: a review of recent advancements. *Stroke Res. Treat.* 2013, 170256. doi: 10.1155/2013/170256

Grace, A. A. (2000). Gating of information flow within the limbic system and the pathophysiology of schizophrenia. *Brain Res. Brain Res. Rev.* 31, 330–341. doi: 10.1016/S0165-0173(99)00049-1

Hauser, T. U., Rotzer, S., Grabner, R. H., Merillat, S., and Jancke, L. (2013). Enhancing performance in numerical magnitude processing and mental arithmetic using transcranial direct current stimulation (tDCS). *Front. Hum. Neurosci.* 7:244. doi: 10.3389/fnhum.2013.00244

Hunter, M., Coffman, B., Trumbo, M., and Clark, V. (2013). Tracking the neuroplastic changes associated with transcranial direct current stimulation: a push for multimodal imaging. *Front. Hum. Neurosci.* 7:495. doi: 10.3389/fnhum.2013.00495

Iuculano, T., and Kadosh, R. C. (2013). The mental cost of cognitive enhancement. *J. Neurosci.* 33, 4482–4486. doi: 10.1523/JNEUROSCI.4927-12.2013

Kabakov, A. Y., Muller, P. A., Pascual-Leone, A., Jensen, F. E., and Rotenberg, A. (2012). Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. *J. Neurophysiol.* 107, 1881–1889. doi: 10.1152/jn.00715.2011

Kang, E. K., Baek, M. J., Kim, S., and Paik, N. J. (2009). Non-invasive cortical stimulation improves post-stroke attention decline. *Restor. Neurol. Neurosci.* 27, 645–650. doi: 10.3233/RNN-2009-0514

Kim, G. W., and Ko, M. H. (2013). Facilitation of corticospinal tract excitability by transcranial direct current stimulation combined with voluntary grip exercise. *Neurosci. Lett.* 548, 181–184. doi: 10.1016/j.neulet.2013.05.037

Kuo, M. F., and Nitsche, M. A. (2012). Effects of transcranial electrical stimulation on cognition. *Clin. EEG Neurosci.* 43, 192–199. doi: 10.1177/1550059412444975

Kuo, M. F., Paulus, W., and Nitsche, M. A. (2013). Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage* doi: 10.1016/j.neuroimage.2013.05.117 [Epub ahead of print].

Lapenta, O. M., Minati, L., Fregni, F., and Boggio, P. S. (2013). Je pense donc je fais: transcranial direct current stimulation modulates brain oscillations associated with motor imagery and movement observation. *Front. Hum. Neurosci.* 7:256. doi: 10.3389/fnhum.2013.00256

Leśniak, M., Polanowska, K., Seniów, J., Członkowska, A. (2013). Effects of repeated anodal tDCS coupled with cognitive training for patients with severe traumatic brain injury: a pilot randomized controlled trial. *J. Head Trauma Rehabil.* doi: 10.1097/HTR.0b013e318292a4c2 [Epub ahead of print].

Levy, F. (2004). Synaptic gating and ADHD: a biological theory of comorbidity of ADHD and anxiety. *Neuropsychopharmacology* 29, 1589–1596. doi: 10.1038/sj.npp.1300469

Loo, C. K., Alonzo, A., Martin, D., Mitchell, P. B., Galvez, V., and Sachdev, P. (2012). Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *Br. J. Psychiatry* 200, 52–59. doi: 10.1192/bjp.bp.111.097634

Madhavan, S., and Shah, B. (2012). Enhancing motor skill learning with transcranial direct current stimulation – a concise review with applications to stroke. *Front. Psychiatry* 3:66. doi: 10.3389/fpsyt.2012.00066

Matsunaga, K., Nitsche, M. A., Tsuji, S., and Rothwell, J. C. (2004). Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. *Clin. Neurophysiol.* 115, 456–460. doi: 10.1016/S1388-2457(03)00362-6

Medina, J., Beauvais, J., Datta, A., Bikson, M., Coslett, H. B., and Hamilton, R. H. (2013). Transcranial direct current stimulation accelerates allocentric target detection. *Brain Stimul.* 6, 433–439. doi: 10.1016/j.brs.2012.05.008

Morrell, F. (1961). Effect of anodal polarization on the firing pattern of single cortical cells. *Ann. N. Y. Acad. Sci.* 92, 860–876. doi: 10.1111/j.1749-6632.1961.tb40962.x

Neuling, T., Wagner, S., Wolters, C. H., Zaehle, T., and Herrmann, C. S. (2012). Finite-element model predicts current density distribution for clinical applications of tDCS and tACS. *Front. Psychiatry* 3:83. doi: 10.3389/fpsyt.2012.00083

Nitsche, M. A., and Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol.* 527(Pt 3), 633–639. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

Ochi, M., Saeki, S., Oda, T., Matsushima, Y., and Hachisuka, K. (2013). Effects of anodal and cathodal transcranial direct current stimulation combined with robotic therapy on severely affected arms in chronic stroke patients. *J. Rehabil. Med.* 45, 137–140. doi: 10.2340/16501977-1099

Olma, M. C., Dargie, R. A., Behrens, J. R., Kraft, A., Irlbacher, K., Fahle, M., et al. (2013). Long-term effects of serial anodal tDCS on motion perception in subjects with occipital stroke measured in the unaffected visual hemifield. *Front. Hum. Neurosci.* 7:314. doi: 10.3389/fnhum.2013.00314

Penolazzi, B., Pastore, M., and Mondini, S. (2013). Electrode montage dependent effects of transcranial direct current stimulation on semantic fluency. *Behav. Brain Res.* 248, 129–135. doi: 10.1016/j.bbr.2013.04.007

Peterchev, A. V., Wagner, T. A., Miranda, P. C., Nitsche, M. A., Paulus, W., Lisanby, S. H., et al. (2011). Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices. *Brain Stimul.* 5, 435–453. doi: 10.1016/j.brs.2011.10.001

Peters, M. A., Thompson, B., Merabet, L. B., Wu, A. D., and Shams, L. (2013). Anodal tDCS to V1 blocks visual perceptual learning consolidation. *Neuropsychologia* 51, 1234–1239.

doi: 10.1016/j.neuropsychologia.2013.03.013

Pirulli, C., Fertonani, A., and Miniussi, C. (2013). The role of timing in the induction of neuromodulation in perceptual learning by transcranial electric stimulation. *Brain Stimul.* 6, 683–689. doi: 10.1016/j.brs.2012.12.005

Purpura, D. P., and McMurtry, J. G. (1965). Intracellular activities and evoked potential changes during polarization of motor cortex. *J. Neurophysiol.* 28, 166–185.

Radman, T., Ramos, R. L., Brumberg, J. C., and Bikson, M. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimul.* 2, 215–228. doi: 10.1016/j.brs.2009.03.007

Radman, T., Su, Y. Z., An, J. H., Parra, L. C., and Bikson, M. (2007). Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. *J. Neurosci.* 27, 3030–3036. doi: 10.1523/JNEUROSCI.0095-07.2007

Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L. C., et al. (2013). Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. *J. Physiol.* 591(Pt 10), 2563–2578. doi: 10.1113/jphysiol.2012.247171

Ranieri, F., Podda, M. V., Riccardi, E., Frisullo, G., Dileone, M., Profice, P., et al. (2012). Modulation of Ltp at rat hippocampal Ca3-Ca1 synapses by direct current stimulation. *J. Neurophysiol.* 107, 1868–1880. doi: 10.1152/jn.00319.2011

Reato, D., Gasca, F., Datta, A., Bikson, M., Marshall, L., and Parra, L. C. (2013). Transcranial electrical stimulation accelerates human sleep homeostasis. *PLoS Comput. Biol.* 9:e1002898. doi: 10.1371/journal.pcbi.1002898

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2010). Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J. Neurosci.* 30, 15067–15079. doi: 10.1523/JNEUROSCI.2059-10.2010

Redfearn, J. W., Lippold, O. C., and Costain, R. (1964). A preliminary account of the clinical effects of polarizing the brain in certain psychiatric disorders. *Br. J. Psychiatry* 110, 773–785. doi: 10.1192/bjp.110.469.773

Reis, J., and Fritsch, B. (2011). Modulation of motor performance and motor learning by transcranial direct current stimulation. *Curr. Opin. Neurol.* 24, 590–596. doi: 10.1097/WCO.0b013e32834c3db0

Ridding, M. C., and Rothwell, J. C. (2007). Is there a future for therapeutic use of transcranial magnetic stimulation? *Nat. Rev. Neurosci.* 8, 559–567. doi: 10.1038/nrn2169

Ruffini, G., Wendling, F., Merlet, I., Molaee-Ardekani, B., Mekkonen, A., Salvador, R., et al. (2012). Transcranial current brain stimulation (tCS): models and technologies. *IEEE Trans. Neural. Syst. Rehabil. Eng.* 21, 333–345. doi: 10.1109/TNSRE.2012.2200046

Saucedo Marquez, C. M., Zhang, X., Swinnen, S. P., Meesen, R., and Wenderoth, N. (2013). Task-specific effect of transcranial direct current stimulation on motor learning. *Front. Hum. Neurosci.* 7:333. doi: 10.3389/fnhum.2013.00333

Shiozawa, P., Da Silva, M. E., Cordeiro, Q., Fregni, F., and Brunoni, A. R. (2013). Transcranial direct current stimulation (tDCS) for the treatment of persistent visual and auditory hallucinations in schizophrenia: a case study. *Brain Stimul.* 6, 831–833. doi: 10.1016/j.brs.2013.03.003

Soekadar, S. R., Witkowski, M., Cossio, E. G., Birbaumer, N., Robinson, S. E., and Cohen, L. G. (2013). In vivo assessment of human brain oscillations during application of transcranial electric currents. *Nat. Commun.* 4, 2032. doi: 10.1038/ncomms3032

Stagg, C. J., and Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist* 17, 37–53. doi: 10.1177/1073858410386614

Tang, M. F., and Hammond, G. R. (2013). Anodal transcranial direct current stimulation over auditory cortex degrades frequency discrimination by affecting temporal, but not place, coding. *Eur. J. Neurosci.* 38, 2802–2811. doi: 10.1111/ejn.12280

Turkeltaub, P. E., Benson, J., Hamilton, R. H., Datta, A., Bikson, M., and Coslett, H. B. (2012). Left lateralizing transcranial direct current stimulation improves reading efficiency. *Brain Stimul.* 5, 201–207 doi: 10.1016/j.brs.2011.04.002

Vanderhasselt, M. A., De Raedt, R., Brunoni, A. R., Campanha, C., Baeken, C., Remue, J., et al. (2013). tDCS over the left prefrontal cortex enhances cognitive control for positive affective stimuli. *PLoS ONE* 8:e62219. doi: 10.1371/journal.pone.0062219

Votinov, M., Aso, T., Koganemaru, S., Fukuyama, H., and Mima, T. (2013). Transcranial direct current stimulation changes human endowment effect. *Neurosci. Res.* 76, 251–256. doi: 10.1016/j.neures.2013.05.007

Zimerman, M., Nitsch, M., Giraux, P., Gerloff, C., Cohen, L. G., and Hummel, F. C. (2013). Neuroenhancement of the aging brain: restoring skill acquisition in old subjects. *Ann. Neurol.* 73, 10–15. doi: 10.1002/ana.23761

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Contribution of transcranial oscillatory stimulation to research on neural networks: an emphasis on hippocampo-neocortical rhythms

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EEG rhythms reflect the synchronized activity of underlying biological neuronal network oscillations, and certain predominant frequencies are typically linked to certain behavioral states. For instance, slow wave activity characterized by sleep slow oscillation (SO) emerges normally during slow-wave sleep (SWS). In this mini-review we will first give a background leading up to the present day association between specific oscillations and their functional relevance for learning and memory consolidation. Following, some principles on oscillatory activity are summarized and finally results of studies employing slowly oscillating transcranial electric stimulation are given. We underscore that oscillatory transcranial electric stimulation presents a tool to study principles of cortical network function.

Keywords: tACS, tDCS, sleep, memory, learning, brain rhythms

The concept that oscillatory brain electric activity—as measured in the EEG or as local field potentials—is more than just an epiphenomenon and can directly impact biological neuronal network activity has existed for some time (Buser and Rougeul-Buser, 1995; Jefferys, 1995; Vigmond et al., 1997). An upsurge of interest in modulating oscillatory activity by applying oscillatory weak electric currents results on the one hand from the recent accumulation of studies on the functional efficiency of applied oscillatory weak electric fields and currents in modulating EEG, local field potentials and neuronal firing rates (reviewed in Weiss and Faber, 2010; Herrmann et al., 2013). On the other hand, the interest in neuronal oscillations and their behavioral relevance has become of increasing interest in the last decade, resulting mainly from studies indicating that precise timing of neuronal activity within oscillatory neuronal networks is essential for information coding and that network oscillations can be a mode of communication between distinct neuronal groups and across brain structures (e.g., Buzsáki and Draguhn, 2004; Fujisawa and Buzsáki, 2011; Hyman et al., 2011; Maris et al., 2011). The study on effects of (transcranially) applied weak oscillatory electric currents is therefore of at least three-fold importance: firstly, as a non-invasive tool for modulating endogenous bioelectric activity, and thus with therapeutic potential; secondly, for investigating the dependence of behavior on brain oscillatory activity; and thirdly, as a tool to study principles of cortical network function.

This mini-review focuses on effects of oscillatory transcranial electric stimulation in particular for learning and for the consolidation of hippocampus-dependent memory. First, an introduction leading up to present concepts and questions on hippocampus-dependent memory consolidation is given. Then we discuss correlates of brain electric activity, cellular and network dynamics. In the second part, features of neuronal and network activity are pointed out which we find relevant to consider when attempting to employ oscillatory stimulation as a tool to study cortical network function.

An association between the hippocampus and memory was established from findings on memory performance in relation to temporal lobe lesions in monkeys (Brown and Schäfer, 1888), hippocampal atrophy (Bechterew, 1900), reports on memory flash backs with hippocampal stimulation (Penfield, 1974), and from reports in the mid-twentieth century differentiating anterograde and retrograde amnesia following well-defined hippocampal lesions as in the case of H.M., the probably most well-known amnestic patient in the history of neuroscientific memory research (Scoville and Milner, 1957). Concepts for neurophysiological memory trace formation, two stage models of memory stage formation, emerged, within which information is transferred to the long term memory store, the neocortex, via hippocampo-cortico connections during the hippocampal sharp wave ripple (SWR) events of slow wave sleep (SWS; Marr, 1970, 1971; Buzsáki, 1989). Later developments of the two stage model aimed to integrate the mechanism of long term potentiation (LTP) in the normal brain (Buzsáki, 1989). It suggested that neuronal firing patterns during hippocampal sharp waves must be the most favorable conditions for enhancement of synaptic plasticity, as SWRs produce powerful synchronization within the pathways connecting the hippocampus to the neocortex (Chrobak and Buzsáki, 1996). The model furthermore incorporated the relevance of behavior and state-dependent changes for defining neuronal patterns (Buzsáki et al., 1987; Buzsáki, 1989).

This concept in which hippocampal theta activity during exploratory behavior in rats supported memory trace formation led to renewed interest in hippocampal place cells (O'Keefe and Dostrovsky, 1971; O'Keefe and Recce, 1993). Subsequent discovery of spatially selective firing of hippocampal place cells in regard to tasks involving spatial memory was the impetus for many investigations on post-experience hippocampal spatiotemporal activity patterns, i.e., reactivation, mostly during SWS (Pavlides and Winson, 1989; Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996; Nadasdy et al., 1999; Hirase et al., 2001; Lee and Wilson, 2002), but also during rapid eye-movement (REM) sleep (Louie and Wilson, 2001); for comprehensive reviews see, Buhry et al. (2011) and Sadowski et al. (2011). Experience-dependent reactivation in sleep was also shown in humans (Rasch et al., 2007; Oudiette and Paller, 2013).

A hallmark of SWS is the endogenous cortical slow oscillations (SO), which coordinates not only thalamo-cortical sleep spindle activity, but also hippocampal SWRs (Timofeev and Steriade, 1996; Isomura et al., 2006; Mölle et al., 2006), slow field potentials with superimposed fast ripple oscillations closely associated with memory consolidation (Fogel and Smith, 2011; Girardeau and Zugaro, 2011). The sleep SO with its coordinating function plays a crucial role in sleep-dependent memory consolidation, specifically for cortico-hippocampal communication (Marshall and Born, 2007). A schematic depiction of these supposed mechanisms is given in **Figure 1**.

Outstanding experimental support at the level of cell-pairs for the relevance of SWRs for hippocampo-to-neocortical information transfer was given by Wierzynski et al. (2009). During SWRs of SWS, but not during REM sleep, cell pairs showed strong correlations with firing of CA1 hippocampal cells preceding that of prefrontal cell. A functional synaptic connection between hippocampus and prefrontal cortex (PFC) has also been indicated by prefrontal phase locking to hippocampal units during hippocampal theta oscillations while performing a task (Siapas and Wilson, 1998; Hyman et al., 2005). Together these studies indicate nicely that the same neuromorphological structures and pathways are differentially activated dependent on global brain state, i.e., sleep or active task performance. Most importantly, temporally coordinated hippocampal and PFC activity has been most frequently characterized in association with population level activity (Siapas and Wilson, 1998; Sirota et al., 2003; Isomura et al., 2006; Mölle et al., 2006; Peyrache et al., 2011). Aside from being technically more easily obtained than paired single cell recordings, population activity can contain different and vastly more complex information than obtained from single cell recordings (Kopell et al., 2010; Wallace et al., 2011). Coherent firing patterns and enhanced synchronization of rodents' hippocampal and prefrontal activity has been associated with enhanced memory performance (Benchenane et al., 2010; Fell and Axmacher, 2011; Kim et al., 2011). For instance, Hyman et al. (2010) showed entrainment of medial PFC to the hippocampal theta rhythm correlated with successful performance in a working memory task. Based on these findings it has been suggested that oscillations regulate communication between the hippocampus and medial PFC (Benchenane et al., 2011; Colgin, 2013). However the rules underlying this oscillatory communication, in fact even the rules regarding the relationship of single cells to network activity as well

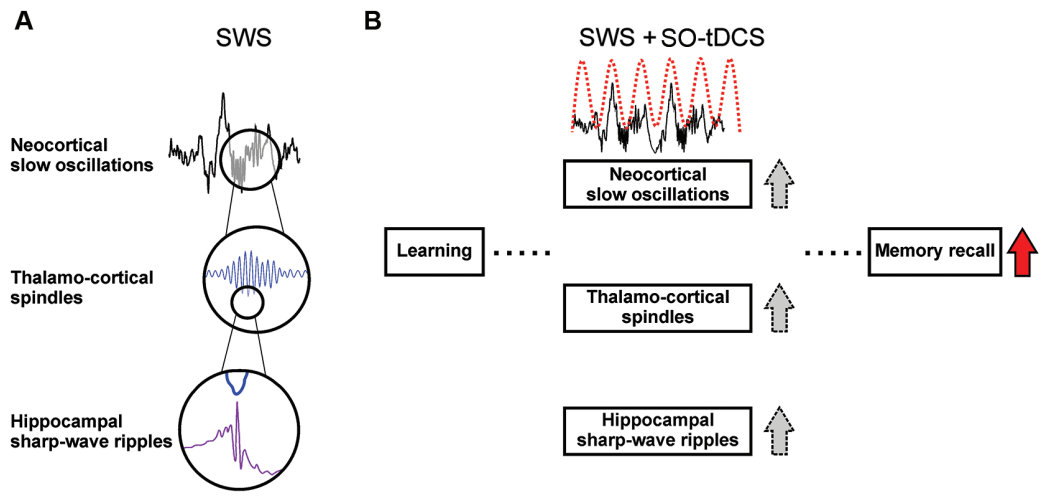

FIGURE 1 | Sleep-associated brain oscillations relevant for memory consolidation and supposed effects of SO-tDCS (slow oscillatory transcranial direct current stimulation). (A) Temporal relation of SO, sleep spindles and hippocampal SWRs. Sleep spindles and hippocampal SWRs occur preferentially within the Up-state of the SO (Isomura et al., 2006; Mölle et al., 2009). SWRs are temporally coupled to spindles, with individual SWRs nesting into the troughs of spindles (Siapas and Wilson, 1998; Wierzynski et al., 2009; Clemens et al., 2011). Pre-sleep learning enhances activity of and coherence between these oscillations (Mölle et al., 2009), and it is assumed that the interplay of these oscillations subserve the communication between hippocampus and neocortex (Sirota et al., 2003) and therefore the transfer of hippocampus-dependent memory traces from the hippocampal short-term-store to the neocortical long-term store (for review see Marshall and Born, 2007). **(B)** SO-tDCS is assumed to enhance endogenous SO activity, and thus improve the consolidation of memory. It was shown that SO-tDCS enhances post-stimulation power of EEG SO and spindle activity as well as memory consolidation in a hippocampus-dependent task (Marshall et al., 2006). A simultaneous enhancement of these rhythms and SWRs during SO-tDCS yet needs to be shown.

as the interplay between intrinsic properties of the neuron and its inputs, are matters of ongoing research (Akam and Kullmann, 2012).

In the following we point out some essential principles of brain rhythms which indicate how studies employing transcranial weak oscillatory currents can contribute to understanding cortical network function.

Single neurons involved in oscillatory activity do not necessarily fire once per cycle, nor even with the frequency of the network oscillation, but properties of neurons matter with regard to determining collective network synchrony (Jacobs et al., 2007; Csercsa et al., 2010; Wang, 2010). One intrinsic neuronal property relevant for cellular responsiveness and therefore ultimately influencing resultant network activity is preferred resonant frequency. At the single cell level, neuronal resonance typically requires a combination of active and passive properties of a neuron, i.e., passive membrane properties functioning as a low pass filter and voltage-gated active channels which give rise to high pass filtering (Hutcheon and Yarom, 2000; Wang, 2010; Yoshida et al., 2011). Pyramidal neurons in the neocortex can have two resonances which occur at different membrane potential levels (Hutcheon and Yarom, 2000) and neurons of different brain regions have been shown to phase-lock to oscillations at multiple frequencies (Jacobs et al., 2007). Supra- and subthreshold noise, in part arising from neuromodulatory activity, can furthermore significantly affect the interplay between intrinsic properties of the neuron, its inputs and oscillations at network level (Hutcheon and Yarom, 2000; Richardson et al., 2003; Jacobson et al., 2005; Giocomo and Hasselmo, 2007; Wang, 2010; Heys and Hasselmo, 2012).

At the network level, the application of weak oscillatory currents is most effective at the resonance frequency of the network, characterized by the presence of an Arnold's tongue (i.e., preferred enhancement occurs at this resonance frequency at weak amplitude of the applied current; Ali et al., 2013). Transcranial weak oscillatory currents most commonly induce enhanced EEG activity at the frequency of the applied current. This has been shown and modeled for currents applied at gamma (Strüber et al., 2013), mu/beta (Pogosyan et al., 2009), alpha (Zaehle et al., 2010; Neuling et al., 2012; Merlet et al., 2013), theta (Marshall et al., 2011) and SO's, the latter in human subjects (Marshall et al., 2006) as well as in animal and in slice experiments (Fröhlich and McCormick, 2010; Ozen et al., 2010). We will focus the below discussion on SO-tDCS, which refers to any stimulation of the same frequency as the endogenous sleep SO (ca. 0.75 Hz in humans), and has a direct current (DC) bias. Another term used so far is transcranial slow oscillation stimulation (tSOS). Precise stimulation parameters (amplitude, duration, shape of the periodic signal and on-/off-set of the oscillatory train) may however vary between experiments. Which effects most of these variables have are yet unclear (see e.g., Groppa et al., 2010, who compared effects of similarly parameterized constant and SO-tDCS).

The mechanisms and prerequisites responsible for resonant EEG activity induced by transcranial weak oscillatory stimulation are still in need of further research. While it is in line with theoretical concepts described above and in **Figure 1** that SO-tDCS over the dorso-lateral PFC during SWS in humans enhanced EEG power both in the SO and spindle frequency ranges (Marshall et al., 2006), effects of SO-tDCS during waking are more difficult to reconcile. In waking SO-tDCS enhanced SO's locally as well as widespread theta activity (4–8 Hz), but not centro-parietal beta activity (Kirov et al., 2009). Was this theta enhancement, also shown to enhance learning, i.e., of functional relevance, only observed because theta was a predominant brain rhythm at this time? Or could EEG theta arise from interactions with specific properties of cellular resonance and/or recurrent network activity? Associations between slow wave and theta band activity exist at many levels, for instance theta nesting in delta activity (Laktos et al., 2005; Carracedo et al., 2013) and parallel modulations in ontogenetic development (Campbell and Feinberg, 2009). Furthermore, similar mechanisms, namely balanced recurrent excitatory and inhibitory activity, have been suggested to underlie the persistent activity during the SO UP state and working memory, the latter being characterized by theta oscillatory activity (McCormick et al., 2003; Reato et al., 2010). However, information on brain state-dependent network dynamics of the interaction between rhythms is still scarce.

The variability in results we and others have observed employing SO-tDCS (e.g., Eggert et al., 2013, who were unable to replicate the results of Marshall et al., 2006, in elderly subjects; Göder et al., 2013, who reported less forgetfulness in schizophrenic patients after stimulation) may in part be inherent to the system. For instance, two studies on SO-tDCS during sleep in healthy individuals showed different results regarding faster rhythms. SO-tDCS during an afternoon nap did not modify spindle power, but did enhance wide-band beta activity as compared to sham (Antonenko et al., 2013). The nap-study differed however in behavioral and temporal parameters from the former, e.g., there was no pre-sleep learning and sleep occurred during a different time of day. Thus not only did experience-dependent features of the neuronal networks differ, but also circadian factors and sleep propensity (such as neuromodulators; Vittoz and Berridge, 2006; Morris et al., 2012; Schmitt et al., 2012). Considering transcranial weak oscillatory stimulation affects subthreshold activity (cp. Reato et al., 2013a, this issue), it is well conceivable that any of the above factors affected single cell and cortical network properties. By virtue of its primary effect on cortical networks we hypothesize that SO-tDCS modifies the efficiency of hippcampo-to-neocortical activity.

Finally, up until now only rather short term effects have been considered, yet memory can improve across days with repeated learning. Constant tDCS has been shown to modify plasticity related products (Fritsch et al., 2010; Stagg and Nitsche, 2011). Long term modifications in oscillatory neuronal activity have to our knowledge only been reported up to 30 min in a state-dependent manner for alpha-activity following transcranial alternating current stimulation (tACS) at individual alpha frequency following stimulation (Neuling et al., 2013), and a putative role of spike-time dependent plasticity for after-effects of alpha-tACS were tested so far in simulations only (Zaehle et al., 2010). At the network level, responsiveness to acute SO-tDCS in rats appears to be affected after about 1 week of daily stimulation subsequent to learning on a spatial task (Binder et al., 2012). Although we can as yet not ascertain that learning or plastic changes in the cortical network occurred throughout the above experiment, the

long-term implications of the study are that network "learning" can be induced and the dynamics and mechanisms of this process could in future be measured in detail.

Findings that the most consistent effect of SO-tDCS during SWS is on the endogenous sleep slow oscillatory rhythm implies that this oscillation of neocortical origin was primarily impacted by SO-tDCS, and causally affected memory consolidation and learning. But, selective activation and deactivation of other brain structures within the circuit, in combination with other methods, e.g., optogenetics, is furthermore required to highlight the specific function of the neocortical network for memory consolidation. Furthermore, the differential results of transcranial weak oscillatory stimulation due to brain state point out the necessity, as technical capabilities develop, to consider this state-dependency in research approaches investigating local networks and neuronal properties, e.g., by mimicking different brain states in slice preparations. Finally, development and extension of computational network models can help guide systematic studies on transcranial weak oscillatory stimulation investigating coupled rhythms (e.g., Reato et al., 2013b).

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REFERENCES

Akam, T. E., and Kullmann, D. M. (2012). Efficient "communication through coherence" requires oscillations structured to minimize interference between signals. *PLoS Comput. Biol.* 8:e1002760. doi: 10.1371/journal.pcbi.1002760

Ali, M. M., Sellers, K. K., and Frohlich, F. (2013). Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. *J. Neurosci.* 33, 11262–11275. doi: 10.1523/jneurosci.5867-12.2013

Antonenko, D., Diekelmann, S., Olsen, C., Born, J., and Mölle, M. (2013). Napping to renew learning capacity: enhanced encoding after stimulation of sleep slow oscillations. *Eur. J. Neurosci.* 37, 1142–1151. doi: 10.1111/ejn.12118

Bechterew, V. (1900). Demonstration eines gehirns mit zerstörung der vorderen und inneren theile der hirnrinde beider schläfenlappen. *Neurol. Centralbl.* 19, 990–991.

Benchenane, K., Peyrache, A., Khamassi, M., Tierney, P. L., Gioanni, Y., Battaglia, F. P., et al. (2010). Coherent theta oscillations and reorganization of spike timing in the hippocampal- prefrontal network upon learning. *Neuron* 66, 921–936. doi: 10.1016/j.neuron.2010.05.013

Benchenane, K., Tiesinga, P. H., and Battaglia, F. P. (2011). Oscillations in the prefrontal cortex: a gateway to memory and attention. *Curr. Opin. Neurobiol.* 21, 475–485. doi: 10.1016/j.conb.2011.01.004

Binder, S., Rawohl, J., Born, J., and Marshall, L. (2012). Anodal slow oscillatory transcranial direct current stimulation (sotDCS) during sleep in rats: effects on radial maze performance and cortical activity. Poster Presented at the Federation of European Neuroscience (FENS) Meeting in Barcelona, Spain, July 14–18, http://fens.ekonnect.co/FENS_331/poster_35655/program.aspx

Brown, S., and Schäfer, E. A. (1888). An investigation into he functions of the occipital and temporal lobes of the monkey's brain. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 179, 303–327. doi: 10.1098/rstb.1888.0011

Buhry, L., Azizi, A. H., and Cheng, S. (2011). Reactivation, replay, and preplay: how it might all fit together. *Neural Plast.* 2011:203462. doi: 10.1155/2011/203462

Buser, P., and Rougeul-Buser, A. (1995). Do cortical and thalamic bioelectric oscillations have a functional role? A brief survey and discussion. *J. Physiol. Paris* 89, 249–254. doi: 10.1016/0928-4257(96)83641-2

Buzsáki, G. (1989). Two-stage model of memory trace formation: a role for "noisy" brain states. *Neuroscience* 31, 551–570. doi: 10.1016/0306-4522(89)90423-5

Buzsáki, G., and Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science* 304, 1926–1929. doi: 10.1126/science.1099745

Buzsáki, G., Haas, H. L., and Anderson, E. G. (1987). Long-term potentiation induced by physiologically relevant stimulus patterns. *Brain Res.* 435, 331–333. doi: 10.1016/0006-8993(87)91618-0

Campbell, I. G., and Feinberg, I. (2009). Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation. *Proc. Natl. Acad. Sci. U S A* 106, 5177–5180. doi: 10.1073/pnas.0812947106

Carracedo, L. M., Kjeldsen, H., Cunnington, L., Jenkins, A., Schofield, I., Cunningham, M. O., et al. (2013). A neocortical delta rhythm facilitates reciprocal interlaminar interactions via nested theta rhythms. *J. Neurosci.* 33, 10750–10760. doi: 10.1523/jneurosci.0735-13.2013

Chrobak, J. J., and Buzsáki, G. (1996). High-frequency oscillations in the output networks of the hippocampal-entorhinal axis of the freely behaving rat. *J. Neurosci.* 16, 3056–3066.

Clemens, Z., Mölle, M., Eross, L., Jakus, R., Rasonyi, G., Halasz, P., et al. (2011). Fine-tuned coupling between human parahippocampal ripples and sleep spindles. *Eur. J. Neurosci.* 33, 511–520. doi: 10.1111/j.1460-9568.2010.07505.x

Colgin, L. L. (2013). Mechanisms and functions of theta rhythms. *Annu. Rev. Neurosci.* 36, 295–312. doi: 10.1146/annurev-neuro-062012-170330

Csercsa, R., Dombovari, B., Fabo, D., Wittner, L., Eross, L., Entz, L., et al. (2010). Laminar analysis of slow wave activity in humans. *Brain* 133, 2814–2829. doi: 10.1093/brain/awq169

Eggert, T., Dorn, H., Sauter, C., Nitsche, M. A., Bajbouj, M., and Danker-Hopfe, H. (2013). No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. *Brain Stimul.* doi: 10.1016/j.brs.2013.05.006. [Epub ahead of print].

Fell, J., and Axmacher, N. (2011). The role of phase synchronization in memory processes. *Nat. Rev. Neurosci.* 12, 105–118. doi: 10.1038/nrn2979

Fogel, S. M., and Smith, C. T. (2011). The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. *Neurosci. Biobehav. Rev.* 35, 1154–1165. doi: 10.1016/j.neubiorev.2010.12.003

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., et al. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron* 66, 198–204. doi: 10.1016/j.neuron.2010.03.035

Fröhlich, F., and McCormick, D. A. (2010). Endogenous electric fields may guide neocortical network activity. *Neuron* 67, 129–143. doi: 10.1016/j.neuron.2010.06.005

Fujisawa, S., and Buzsáki, G. (2011). A 4 Hz oscillation adaptively synchronizes prefrontal, VTA, and hippocampal activities. *Neuron* 72, 153–165. doi: 10.1016/j.neuron.2011.08.018

Giocomo, L. M., and Hasselmo, M. E. (2007). Neuromodulation by glutamate and acetylcholine can change circuit dynamics by regulating the relative influence of afferent input and excitatory feedback. *Mol. Neurobiol.* 36, 184–200. doi: 10.1007/s12035-007-0032-z

Girardeau, G., and Zugaro, M. (2011). Hippocampal ripples and memory consolidation. *Curr. Opin. Neurobiol.* 21, 452–459. doi: 10.1016/j.conb.2011.02.005

Göder, R., Baier, P. C., Beith, B., Baecker, C., Seeck-Hirschner, M., Junghanns, K., et al. (2013). Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia. *Schizophr. Res.* 144, 153–160. doi: 10.1016/j.schres.2012.12.014

Groppa, S., Bergmann, T. O., Siems, C., Mölle, M., Marshall, L., and Siebner, H. R. (2010). Slow-oscillatory transcranial direct current stimulation can induce bidirectional shifts in motor cortical excitability in awake humans. *Neuroscience* 166, 1219–1225. doi: 10.1016/j.neuroscience.2010.01.019

Herrmann, C. S., Rach, S., Neuling, T., and Struber, D. (2013). Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Front. Hum.*

Neurosci. 7:279. doi: 10.3389/fnhum.2013.00279

Heys, J. G., and Hasselmo, M. E. (2012). Neuromodulation of I(h) in layer II medial entorhinal cortex stellate cells: a voltage-clamp study. *J. Neurosci.* 32, 9066–9072. doi: 10.1523/jneurosci.0868-12.2012

Hirase, H., Leinekugel, X., Czurko, A., Csicsvari, J., and Buzsáki, G. (2001). Firing rates of hippocampal neurons are preserved during subsequent sleep episodes and modified by novel awake experience. *Proc. Natl. Acad. Sci. U S A* 98, 9386–9390. doi: 10.1073/pnas.161274398

Hutcheon, B., and Yarom, Y. (2000). Resonance, oscillation and the intrinsic frequency preferences of neurons. *Trends Neurosci.* 23, 216–222. doi: 10.1016/s0166-2236(00)01547-2

Hyman, J. M., Hasselmo, M. E., and Seamans, J. K. (2011). What is the functional relevance of prefrontal cortex entrainment to hippocampal theta rhythms? *Front. Neurosci.* 5:24. doi: 10.3389/fnins.2011.00024

Hyman, J. M., Zilli, E. A., Paley, A. M., and Hasselmo, M. E. (2005). Medial prefrontal cortex cells show dynamic modulation with the hippocampal theta rhythm dependent on behavior. *Hippocampus* 15, 739–749. doi: 10.1002/hipo.20106

Hyman, J. M., Zilli, E. A., Paley, A. M., and Hasselmo, M. E. (2010). Working memory performance correlates with prefrontal-hippocampal theta interactions but not with prefrontal neuron firing rates. *Front. Integr. Neurosci.* 4:2. doi: 10.3389/neuro.07.002.2010

Isomura, Y., Sirota, A., Ozen, S., Montgomery, S., Mizuseki, K., Henze, D. A., et al. (2006). Integration and segregation of activity in entorhinal-hippocampal subregions by neocortical slow oscillations. *Neuron* 52, 871–882. doi: 10.1016/j.neuron.2006.10.023

Jacobson, G. A., Diba, K., Yaron-Jakoubovitch, A., Oz, Y., Koch, C., Segev, I., et al. (2005). Subthreshold voltage noise of rat neocortical pyramidal neurones. *J. Physiol.* 564, 145–160. doi: 10.1113/jphysiol.2004.080903

Jacobs, J., Kahana, M. J., Ekstrom, A. D., and Fried, I. (2007). Brain oscillations control timing of single-neuron activity in humans. *J. Neurosci.* 27, 3839–3844. doi: 10.1523/jneurosci.4636-06.2007

Jefferys, J. G. (1995). Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. *Physiol. Rev.* 75, 689–723.

Kim, J., Delcasso, S., and Lee, I. (2011). Neural correlates of object-in-place learning in hippocampus and prefrontal cortex. *J. Neurosci.* 31, 16991–17006. doi: 10.1523/jneurosci.2859-11.2011

Kirov, R., Weiss, C., Siebner, H. R., Born, J., and Marshall, L. (2009). Slow oscillation electrical brain stimulation during waking promotes EEG theta activity and memory encoding. *Proc. Natl. Acad. Sci. U S A* 106, 15460–15465. doi: 10.1073/pnas.0904438106

Kopell, N., Kramer, M. A., Malerba, P., and Whittington, M. A. (2010). Are different rhythms good for different functions? *Front. Hum. Neurosci.* 4:187. doi: 10.3389/fnhum.2010.00187

Laktos, P., Shah, A. S., Knuth, K. H., Ulbert, I., Karmos, G., and Schroeder, C. E. (2005). An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. *J. Neurophysiol.* 94, 1904–1911. doi: 10.1152/jn.00263.2005

Lee, A. K., and Wilson, M. A. (2002). Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* 36, 1183–1194. doi: 10.1016/s0896-6273(02)01096-6

Louie, K., and Wilson, M. A. (2001). Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron* 29, 145–156. doi: 10.1016/s0896-6273(01)00186-6

Maris, E., van Vugt, M., and Kahana, M. (2011). Spatially distributed patterns of oscillatory coupling between high-frequency amplitudes and low-frequency phases in human iEEG. *Neuroimage* 54, 836–850. doi: 10.1016/j.neuroimage.2010.09.029

Marr, D. (1970). A theory for cerebral neocortex. *Proc. R. Soc. Lond. B Biol. Sci.* 176, 161–234.

Marr, D. (1971). Simple memory: a theory for archicortex. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 262, 23–81. doi: 10.1098/rstb.1971.0078

Marshall, L., and Born, J. (2007). The contribution of sleep to hippocampus-dependent memory consolidation. *Trends Cogn. Sci.* 11, 442–450. doi: 10.1016/j.tics.2007.09.001

Marshall, L., Helgadottir, H., Mölle, M., and Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature* 444, 610–613. doi: 10.1038/nature05278

Marshall, L., Kirov, R., Brade, J., Molle, M., and Born, J. (2011). Transcranial electrical currents to probe EEG brain rhythms and memory consolidation during sleep in humans. *PLoS One* 6:e16905. doi: 10.1371/journal.pone.0016905

McCormick, D. A., Shu, Y.-S., and Hasenstaub, A. (2003). "Balanced recurrent excitation and inhibition in local cortical networks," in *Excitatory-Inhibitory Balance: Synapses, Circuits, and Systems*, eds T. K. Hensch and M. Fagioloni, (New York: Kluwer Academic/Plenum Publishers), 113–124.

Merlet, I., Birot, G., Salvador, R., Molaee-Ardekani, B., Mekonnen, A., Soria-Frish, A., et al. (2013). From oscillatory transcranial current stimulation to scalp EEG changes: a biophysical and physiological modeling study. *PLoS One* 8:e57330. doi: 10.1371/journal.pone.0057330

Mölle, M., Eschenko, O., Gais, S., Sara, S. J., and Born, J. (2009). The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. *Eur. J. Neurosci.* 29, 1071–1081. doi: 10.1111/j.1460-9568.2009.06654.x

Mölle, M., Yeshenko, O., Marshall, L., Sara, S. J., and Born, J. (2006). Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. *J. Neurophysiol.* 96, 62–70. doi: 10.1152/jn.00014.2006

Morris, C. J., Aeschbach, D., and Scheer, F. A. (2012). Circadian system, sleep and endocrinology. *Mol. Cell. Endocrinol.* 349, 91–104. doi: 10.1016/j.mce.2011.09.003

Nadasdy, Z., Hirase, H., Czurko, A., Csicsvari, J., and Buzsáki, G. (1999). Replay and time compression of recurring spike sequences in the hippocampus. *J. Neurosci.* 19, 9497–9507.

Neuling, T., Rach, S., and Herrmann, C. S. (2013). Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Front. Hum. Neurosci.* 7:161. doi: 10.3389/fnhum.2013.00161

Neuling, T., Rach, S., Wagner, S., Wolters, C. H., and Herrmann, C. S. (2012). Good vibrations: oscillatory phase shapes perception. *Neuroimage* 63, 771–778. doi: 10.1016/j.neuroimage.2012.07.024

O'Keefe, J., and Dostrovsky, J. (1971). The hippocampus as a spatial map. preliminary evidence from unit activity in the freely-moving rat. *Brain Res.* 34, 171–175. doi: 10.1016/0006-8993(71)90358-1

O'Keefe, J., and Recce, M. L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3, 317–330. doi: 10.1002/hipo.450030307

Oudiette, D., and Paller, K. A. (2013). Upgrading the sleeping brain with targeted memory reactivation. *Trends Cogn. Sci.* 17, 142–149. doi: 10.1016/j.tics.2013.01.006

Ozen, S., Sirota, A., Belluscio, M. A., Anastassiou, C. A., Stark, E., Koch, C., et al. (2010). Transcranial electric stimulation entrains cortical neuronal populations in rats. *J. Neurosci.* 30, 11476–11485. doi: 10.1523/jneurosci.5252-09.2010

Pavlides, C., and Winson, J. (1989). Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *J. Neurosci.* 9, 2907–2918.

Penfield, W. (1974). Memory. autopsy findings and comments on the role of the hippocampus in experiential recall. *Arch. Neurol.* 31, 145–154. doi: 10.1001/archneur.1974.00490390027001

Peyrache, A., Battaglia, F. P., and Destexhe, A. (2011). Inhibition recruitment in prefrontal cortex during sleep spindles and gating of hippocampal inputs. *Proc. Natl. Acad. Sci. U S A* 108, 17207–17212. doi: 10.1073/pnas.1103612108

Pogosyan, A., Gaynor, L. D., Eusebio, A., and Brown, P. (2009). Boosting cortical activity at beta-band frequencies slows movement in humans. *Curr. Biol.* 19, 1637–1641. doi: 10.1016/j.cub.2009.07.074

Rasch, B., Büchel, C., Gais, S., and Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science* 315, 1426–1429. doi: 10.1126/science.1138581

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2013a). Effects of weak transcranial Alternating Current Stimulation on brain activity – a review of known mechanisms. *Front. Hum. Neurosci.* 7.

Reato, D., Gasca, F., Datta, A., Bikson, M., Marshall, L., and Parra, L. C. (2013b). Transcranial electrical stimulation accelerates human sleep homeostasis. *PLoS Comput. Biol.* 9:e1002898. doi: 10.1371/journal.pcbi.1002898

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2010). Low-intensity electrical stimulation affects network dynamics by modulating

population rate and spike timing. *J. Neurosci.* 30, 15067–15079. doi: 10.1523/jneurosci.2059-10.2010

Richardson, M. J., Brunel, N., and Hakim, V. (2003). From subthreshold to firing-rate resonance. *J. Neurophysiol.* 89, 2538–2554. doi: 10.1152/jn.00955.2002

Sadowski, J. H., Jones, M. W., and Mellor, J. R. (2011). Ripples make waves: binding structured activity and plasticity in hippocampal networks. *Neural Plast.* 2011:960389. doi: 10.1155/2011/960389

Schmitt, L. I., Sims, R. E., Dale, N., and Haydon, P. G. (2012). Wakefulness affects synaptic and network activity by increasing extracellular astrocyte-derived adenosine. *J. Neurosci.* 32, 4417–4425. doi: 10.1523/jneurosci.5689-11.2012

Scoville, W. B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* 20, 11–21. doi: 10.1093/neucas/2.4.259-af

Siapas, A. G., and Wilson, M. A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron* 21, 1123–1128. doi: 10.1016/s0896-6273(00)80629-7

Sirota, A., Csicsvari, J., Buhl, D., and Buzsáki, G. (2003). Communication between neocortex and hippocampus during sleep in rodents. *Proc. Natl. Acad. Sci. U S A* 100, 2065–2069. doi: 10.1073/pnas.0437938100

Skaggs, W. E., and McNaughton, B. L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science* 271, 1870–1873. doi: 10.1126/science.271.5257.1870

Stagg, C. J., and Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist* 17, 37–53. doi: 10.1177/1073858410386614

Strüber, D., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., and Herrmann, C. S. (2013). Antiphasic 40 Hz oscillatory current stimulation affects bistable motion perception. *Brain Topogr.* doi: 10.1007/s10548-013-0294-x. [Epub ahead of print].

Timofeev, I., and Steriade, M. (1996). Low-frequency rhythms in the thalamus of intact-cortex and decorticated cats. *J. Neurophysiol.* 76, 4152–4168.

Vigmond, E. J., Perez Velazquez, J. L., Valiante, T. A., Bardakjian, B. L., and Carlen, P. L. (1997). Mechanisms of electrical coupling between pyramidal cells. *J. Neurophysiol.* 78, 3107–3116.

Vittoz, N. M., and Berridge, C. W. (2006). Hypocretin/orexin selectively increases dopamine efflux within the prefrontal cortex: involvement of the ventral tegmental area. *Neuropsychopharmacology* 31, 384–395. doi: 10.1038/sj.npp.1300807

Wallace, E., Benayoun, M., van Drongelen, W., and Cowan, J. D. (2011). Emergent oscillations in networks of stochastic spiking neurons. *PLoS One* 6:e14804. doi: 10.1371/journal.pone.0014804

Wang, X. J. (2010). Neurophysiological and computational principles of cortical rhythms in cognition. *Physiol. Rev.* 90, 1195–1268. doi: 10.1152/physrev.00035.2008

Weiss, S. A., and Faber, D. S. (2010). Field effects in the CNS play functional roles. *Front. Neural Circuits* 4:15. doi: 10.3389/fncir.2010.00015

Wierzynski, C. M., Lubenov, E. V., Gu, M., and Siapas, A. G. (2009). State-dependent spike-timing relationships between hippocampal and prefrontal circuits during sleep. *Neuron* 61, 587–596. doi: 10.1016/j.neuron.2009.01.011

Wilson, M. A., and McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science* 265, 676–679. doi: 10.1126/science.8036517

Yoshida, M., Giocomo, L. M., Boardman, I., and Hasselmo, M. E. (2011). Frequency of subthreshold oscillations at different membrane potential voltages in neurons at different anatomical positions on the dorsoventral axis in the rat medial entorhinal cortex. *J. Neurosci.* 31, 12683–12694. doi: 10.1523/jneurosci.1654-11.2011

Zaehle, T., Rach, S., and Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS One* 5:e13766. doi: 10.1371/journal.pone.0013766

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Transcranial alternating current stimulation (tACS)

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Transcranial alternating current stimulation (tACS) seems likely to open a new era of the field of noninvasive electrical stimulation of the human brain by directly interfering with cortical rhythms. It is expected to synchronize (by one single resonance frequency) or desynchronize (e.g., by the application of several frequencies) cortical oscillations. If applied long enough it may cause neuroplastic effects. In the theta range it may improve cognition when applied in phase. Alpha rhythms could improve motor performance, whereas beta intrusion may deteriorate them. TACS with both alpha and beta frequencies has a high likelihood to induce retinal phosphenes. Gamma intrusion can possibly interfere with attention. Stimulation in the "ripple" range induces intensity dependent inhibition or excitation in the motor cortex (M1) most likely by entrainment of neuronal networks, whereas stimulation in the low kHz range induces excitation by neuronal membrane interference. TACS in the 200 kHz range may have a potential in oncology.

Keywords: tACS, oscillations, human brain, motor, visual

INTRODUCTION

Transcranial alternating current stimulation (tACS)—the external application of oscillating electrical currents—is able to influence cortical excitability and activity (Antal et al., 2008; Chaieb et al., 2011; Moliadze et al., 2012; Wach et al., 2013). With exceptions (Marshall et al., 2006; Neuling et al., 2012) tACS is applied in most studies without a DC offset. It's simple form uses sinusoidal stimulation; however, any other waveform appears possible, such as rectangular current shapes. Ten Hz tACS was modeled in a realistic head model and was suggested to generate larger and more focused fields than DC stimulation (Manoli et al., 2012); with applied frequencies of 100 up to 1000 Hz a decrease of the size of this electrical field was assumed. This claim was, however, only based on differences in skin resistance at low frequencies which renders the statement quite doubtful (Paulus and Opitz, 2013). The major parameters that can shape the direction and the duration of the tACS-induced effects are the frequency, the intensity and the phase of the stimulation. The effect of duration of tACS on motor evoked potential (MEP) has not been systematically investigated yet. Increasing the duration of transcranial direct current stimulation (tDCS) results in a prolongation of the induced aftereffects (Nitsche and Paulus, 2000) up to about 13 min whereas doubling the 13 stimulation to 26 min inverses MEP aftereffects into inhibition (Batsikadze et al., 2013) It is unclear if this can be translated to tACS, too.

ACS EFFECTS IN THE NORMAL BRAIN

FREQUENCY OF THE STIMULATION

tACS may be applied in a wide frequency range. At present data are available between close to DC up to 5 kHz for plasticity studies (Chaieb et al., 2011) and 200 kHz for tumor therapy (Kirson et al., 2007) using a single frequency. However, any combination of frequencies is possible: one special form of tACS is transcranial random noise stimulation (tRNS), which so far has been studied with a frequency spectrum between 0.1 Hz and 640 Hz with a "white noise" characteristic (Terney et al., 2008).

tACS applied at conventional EEG frequencies (0.1–80 Hz) and in the so called "ripple" range (140 Hz, see below) (Moliadze et al., 2010) may be able to interact with ongoing rhythms in the cortex. A very low frequency (0.75 Hz) stimulation combined with DC offset during non-rapid-eye-movement sleep in healthy humans enhances the retention of hippocampus-dependent declarative memories when tested the next morning (Marshall et al., 2006). The DC offset used in this study leaves open the possibility of a DC effect (Bergmann et al., 2009).

Effects of tACS applied in the EEG range might differ depending on the outread parameters. A trend toward MEP inhibition following 10 Hz AC stimulation over the primary motor cortex (M1) was observed (Antal et al., 2008), while 10 Hz stimulation improved visuomotor implicit learning, using a serial reaction time task. In the MEP measurement shorter stimulation duration (5 min) was applied whereas tACS in the implicit learning study lasted about twice as long. Nevertheless, a dissociation between MEP excitability changes and implicit learning under tACS has already been described (Moliadze et al., 2010). 140 Hz stimulation induces the largest MEP increase, whereas only 250 Hz improved implicit motor learning.

In another study, whereas 20 Hz tACS over the M1 increased corticospinal excitability (Feurra et al., 2011) as measured by MEP size, it slowed down voluntary movements using a visuomotor task (Pogosyan et al., 2009) but in parallel it increased beta coherence between scalp-recorded activity and electromyographic activity (EMG) of the first dorsal interosseus muscle. Opposing effects at beta and gamma frequencies depending on phase of a of motor task exist (Joundi et al., 2012): using a visually driven go—no-go task stimulation at 20 Hz afforded a significant but modest slowing of force production in the go task, however, stimulation in no-go trials, where the triggered motor task

involved inhibition, led to a major reduction in force generation. In contrast, 70 Hz tACS was ineffective during errors of commission following no-go cues, but increased performance during go trials.

TACS up to 80 Hz elicits phosphenes in a frequency- and intensity dependent way (Turi et al., 2013). When applied over the occipital cortex, the perception of phosphenes was peaking at about 15 Hz in brightness with a lower peak in darkness (Kanai et al., 2008). Although electrodes were placed over Oz and Cz, this effect was probably induced by far field stimulation at the retina (Schutter and Hortensius, 2010). TACS can probably only influence visual cortical functions at a subthreshold level as shown by modification of transcranial magnetic stimulation (TMS)-induced phosphene-thresholds (Kanai et al., 2010). Furthermore, contrast-discrimination thresholds were decreased only during 60 Hz tACS, but not during 40 and 80 Hz stimulations (Laczo et al., 2012).

TACS applied over the PO9 and PO10 EEG electrode positions at the individual alpha frequency range (8–12 Hz) induced an entrainment of the applied oscillatory activity (Zaehle et al., 2010). However, it was recently documented that the after-effects of tACS applied at the individual alpha frequency may depend on the individual endogenous power: tACS was effective only under conditions of low endogenous alpha frequency power (Neuling et al., 2013). Furthermore, when stimulation frequency was fixed at 6 and 10 Hz, tACS impaired performance in the visual detection task (Brignani et al., 2013).

tACS applied outside the conventional EEG frequency range, e.g., with frequencies of 140 Hz and in the low kHz range (1–5 kHz) increases excitability in a similar way than anodal tDCS, when 1 mA intensity is used (Moliadze et al., 2010; Chaieb et al., 2011). Stimulation at 80 Hz remains without an effect, while 250 Hz clearly had a delayed onset and shorter lasting response, compared to the MEP increase observed during and after 140 Hz tACS.

The tRNS paradigm was developed with a potential to desynchronize normal and pathological cortical rhythms (Terney et al., 2008). The rationale behind this method is a possible entrainment with cortical oscillations of different frequencies at the same time. This may apply for intra-areal with higher oscillation frequencies or for inter-areal oscillations with lower frequencies. Input noise plays a role in sensitizing neuronal systems through a mechanism known as stochastic resonance (Wiesenfeld and Moss, 1995). Alternatively, impaired signal detection might be improved by input noise in order to sensitise sensory processing (Moss et al., 2004). An excitability increase lasting up to 90 min, observed both for MEP measures and behavioral tasks, was induced after 10 min of tRNS. Unexpectedly higher frequencies (100–640 Hz) and not frequencies less than 100 Hz were responsible for this excitability increase.

The efficacy of the stimulation seems to be dependent on the type of the task and on the power of intrinsic oscillations at baseline (Neuling et al., 2013) and the involvement of the different memory systems in a given cognitive task: when tRNS was applied over the dorsolateral prefontal cortex (DLPFC) subjects made more mistakes in a probabilistic classification task (Ambrus et al., 2011), whereas when using the n-back task no significant change in performance was found (Mulquiney et al., 2011). When tRNS was applied of the visual cortex improved neuroplasticity in a perceptual learning paradigm (Fertonani et al., 2011). Nevertheless, the neuronal mechanisms underlying the effect of tRNS might be different from those of tACS, using a single stimulation frequency.

INTENSITY OF THE STIMULATION

The effect of tACS appears to be intensity dependent. A trend in a first study (Antal et al., 2008) using a low intensity of 0.4 mA over the M1 toward MEP inhibition following 10 Hz AC stimulation was confirmed later with higher frequencies (Moliadze et al., 2012). Other tACS frequencies between 5 and 40 Hz failed to induce any measurable aftereffects at this (too) low intensity.

Interestingly, both tACS at 140 Hz and tRNS show an intensity-dependent aftereffect: whereas 0.2 mA intensity has no effect an intensity of 0.4 mA leads to inhibition, 0.6 and 0.8 mA do not provide a significant effect (Moliadze et al., 2012). With 1 mA an increase of the MEP amplitudes can be seen. This suggests that inhibitory circuits can be excited preferentially with lower intensities, an effect which has also been documented for TMS (Berger et al., 2011). Nevertheless, the reason for this observed reversal in the direction of MEP effects induced by higher frequency stimulation at different intensities has not been clarified yet. It is likely that 140 Hz and tRNS at the lower intensity only facilitate intracortical inhibitory networks of corticospinal motoneurons, thus resulting in net inhibition of MEP amplitudes (Pashut et al., 2011). It also cannot be excluded that stimulation applied at 0.4 mA may inhibit intracortical facilitatory effects on corticospinal motoneurons. When recording in a pyramidal neuron located in layer 5 of the rat cortex the composite response to an electrical stimulation of various layers (2–3, 4, or 6), in terms of excitation–inhibition balance, resulted in conductance changes consisting of 20% excitation and 80% inhibition, independent from the stimulated layer. Moreover, it was shown that excitatory circuits are strongly controlled by inhibitory circuits (Maffei et al., 2004) by feedback and feed-forward connections (Bannister, 2005).

PHASE OF THE STIMULATION

Brain oscillations are characterized in addition to frequency and power by their phase. Modeling studies propose that in active neuronal networks weak electrical fields can induce small but coherent changes in the firing rate and timing of neuronal populations that can be magnified by dynamic network activity (Radman et al., 2007; Reato et al., 2010) When stimulating the left frontal and parietal cortex by 6 Hz tACS in phase, cognitive performance in a delayed letter discrimination task was improved, when stimulating out of phase it was delayed (Polania et al., 2012). In a recent study stimulating the temporal cortex using 10 Hz with DC-offset it was found that manipulation of the phase resulted in different auditory detection thresholds, which supports the notion that perception can be periodically modulated by oscillatory processes (Neuling et al., 2012). Nevertheless, the DC offset used in this study leaves open the possibility of a DC effect.

MECHANISMS OF ACTION

tACS applied in the EEG range is believed to mainly entrain with or synchronize neuronal networks, thus inducing changes in ongoing oscillatory brain activity. Indeed, spike synchrony of converging input has been shown to enhance the information transfer and speed up processing (e.g., Butts et al., 2007). Nevertheless, stimulation applied in the kHz range probably does not interfere with oscillatory activity, but targets the membrane excitability of neurons more selectively. It could be that the temporary modification of the synapse once exposed to a rapidly alternating electrical field, alters the associated biochemical mechanisms, such as accumulation of calcium in the presynaptic nerve terminals leading to short-term synaptic plasticity effects (Citri and Malenka, 2008).

The mechanisms of tRNS so far are unclear, if e.g., repeated opening of Na^+ channels or a higher sensitivity of neuronal networks to electrical field modulation than the single neuron threshold (Francis et al., 2003).

APPLICATIONS IN DISEASE

tACS would have a particular indication in disorders in which abnormal oscillatory patterns may play a role, such as Parkinson's disease or schizophrenia (Gonzalez-Burgos and Lewis, 2008; Burns et al., 2011) by attenuating or resetting anomalous oscillations. Indeed, Parkinsonian resting tremor could be bisected by tACS of the M1 at specified phase alignments (Brittain et al., 2013).

Using 200 kHz frequency a pilot clinical trial was carried out treating human patients suffering from recurrent gliobastoma (Kirson et al., 2007). By transcranial application of continuous high frequency stimulation inhibits the growth of this treatment-resistant tumor, with little or no side effects, pursuing the concept that dividing tumor cells can be destroyed during mitosis.

Applying the current transorbitally at the individual phosphene thresholds ACS is effective in the therapy following optic nerve injury in human (Gall et al., 2010; Sabel et al., 2011).

COMPARISON TO rTMS?

Both rTMS and tACS could provide the basis to interact with or induce local, probably also remote oscillatory activity. While rTMS involves delivering a brief, repetitive, high-intensity magnetic pulses to the head through a coil that induces electrical currents in a focal area underneath this area, with regard to tACS, oscillatory current is delivered with a battery-driven stimulator by means of a large electrode located on the area of interest and a reference electrode that is placed over a neutral area. tACS has some advantages compared to rTMS: (1) it is clearly cheaper due to the small and compact equipment; (2) it can be more easily combined with online cognitive projects; (3) it produces no acoustic noise and muscle twitching of cranial muscles and it causes much less or no perceptual skin sensations (Ambrus et al., 2010; Turi et al., 2013) and is hereby more suitable for double-blind, sham-controlled studies. Nevertheless, there are disadvantages, including shunting of the electric currents through the scalp and the skin irritations that sometimes can be observed under electrodes.

FUTURE DIRECTIONS

tACS is only in its beginnings. A seemly indefinitely number of stimulation paradigms will have to be condensed to those with highest physiological relevance. As a prerequisite, this requires a clearer picture of the neuronal mechanisms involved in tACS-induced entrainment. Knowledge of their dynamics over time would enable to formulate optimized protocols for future tACS studies.

REFERENCES

Ambrus, G. G., Paulus, W., and Antal, A. (2010). Cutaneous perception thresholds of electrical stimulation methods: comparison of tDCS and tRNS. *Clin. Neurophysiol.* 121, 1908–1914. doi: 10.1016/j.clinph.2010.04.020

Ambrus, G. G., Zimmer, M., Kincses, Z. T., Harza, I., Kovacs, G., Paulus, W., et al. (2011). The enhancement of cortical excitability over the DLPFC before and during training impairs categorization in the prototype distortion task. *Neuropsychologia* 49, 1974–1980.

Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., and Paulus, W. (2008). Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimul.* 1, 97–105. doi: 10.1016/j.brs.2007.10.001

Bannister, A. P. (2005). Inter- and intra-laminar connections of pyramidal cells in the neocortex. *Neurosci. Res.* 53, 95–103.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., and Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J. Physiol.* 591, 1987–2000.

Berger, U., Korngreen, A., Bar-Gad, I., Friedman, A., Wolfus, S., Yeshurun, Y., et al. (2011). Magnetic stimulation intensity modulates motor inhibition. *Neurosci. Lett.* 504, 93–97. doi: 10.1016/j.neulet.2011.09.004

Bergmann, T. O., Groppa, S., Seeger, M., Molle, M., Marshall, L., and Siebner, H. R. (2009). Acute changes in motor cortical excitability during slow oscillatory and constant anodal transcranial direct current stimulation. *J. Neurophysiol.* 102, 2303–2311. doi: 10.1152/jn.00437.2009

Brignani, D., Ruzzoli, M., Mauri, P., and Miniussi, C. (2013). Is transcranial alternating current stimulation effective in modulating brain oscillations. *PLoS ONE* 8:e56589. doi: 10.1371/journal.pone.0056589

Brittain, J. S., Probert-Smith, P., Aziz, T. Z., and Brown, P. (2013). Tremor suppression by rhythmic transcranial current stimulation. *Curr. Biol.* 23, 436–440. doi: 10.1016/j.cub.2013.01.068

Burns, S. P., Xing, D., and Shapley, R. M. (2011). Is gamma-band activity in the local field potential of V1 cortex a "clock" or filtered noise. *J. Neurosci.* 31, 9658–9664.

Butts, D. A., Weng, C., Jin, J., Yeh, C. I., Lesica, N. A., Alonso, J. M., et al. (2007). Temporal precision in the neural code and the timescales of natural vision. *Nature* 449, 92–95. doi: 10.1038/nature06105

Chaieb, L., Antal, A., and Paulus, W. (2011). Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. *Restor. Neurol. Neurosci* 29, 167–175.

Citri, A., and Malenka, R. C. (2008). Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropsychopharmacology* 33, 18–41. doi: 10.1038/sj.npp.1301559

Fertonani, A., Pirulli, C., and Miniussi, C. (2011). Random noise stimulation improves neuroplasticity in perceptual learning. *J. Neurosci.* 31, 15416–15423. doi: 10.1523/JNEUROSCI.2002-11.2011

Feurra, M., Paulus, W., Walsh, V., and Kanai, R. (2011). Frequency specific modulation of human somatosensory cortex. *Front. Psychol.* 2:13. doi: 10.3389/fpsyg.2011.00013

Francis, J. T., Gluckman, B. J., and Schiff, S. J. (2003). Sensitivity of neurons to weak electric fields. *J. Neurosci.* 23, 7255–7261.

Gall, C., Fedorov, A. B., Ernst, L., Borrmann, A., and Sabel, B. A. (2010). Repetitive transorbital alternating current stimulation in optic neuropathy. *NeuroRehabilitation* 27, 335–341.

Gonzalez-Burgos, G., and Lewis, D. A. (2008). GABA neurons and the mechanisms of network oscillations: implications for understanding cortical

dysfunction in schizophrenia. *Schizophr. Bull.* 34, 944–961. doi: 10.1093/schbul/sbn070

Joundi, R. A., Jenkinson, N., Brittain, J. S., Aziz, T. Z., and Brown, P. (2012). Driving oscillatory activity in the human cortex enhances motor performance. *Curr. Biol.* 22, 403–407. doi: 10.1016/j.cub.2012.01.024

Kanai, R., Chaieb, L., Antal, A., Walsh, V., and Paulus, W. (2008). Frequency-dependent electrical stimulation of the visual cortex. *Curr. Biol.* 18, 1839–1843.

Kanai, R., Paulus, W., and Walsh, V. (2010). Transcranial alternating current stimulation (tACS) modulates cortical excitability as assessed by TMS-induced phosphene thresholds. *Clin. Neurophysiol.* 121, 1551–1554. doi: 10.1016/j.clinph.2010.03.022

Kirson, E. D., Dbaly, V., Tovarys, F., Vymazal, J., Soustiel, J. F., Itzhaki, A., et al. (2007). Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc. Natl. Acad. Sci. U.S.A.* 104, 10152–10157. doi: 10.1073/pnas.0702916104

Laczo, B., Antal, A., Niebergall, R., Treue, S., and Paulus, W. (2012). Transcranial alternating stimulation in a high gamma frequency range applied over V1 improves contrast perception but does not modulate spatial attention. *Brain Stimul.* 5, 484–491. doi: 10.1016/j.brs.2011.08.008

Maffei, A., Nelson, S. B., and Turrigiano, G. G. (2004). Selective reconfiguration of layer 4 visual cortical circuitry by visual deprivation. *Nat. Neurosci.* 7, 1353–1359.

Manoli, Z., Grossman, N., and Samaras, T. (2012). Theoretical investigation of transcranial alternating current stimulation using realistic head model. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2012, 4156–4159. doi: 10.1109/EMBC.2012.6346882

Marshall, L., Helgadottir, H., Molle, M., and Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature* 444, 610–613. doi: 10.1038/nature05278

Moliadze, V., Antal, A., and Paulus, W. (2010). Boosting brain excitability by transcranial high frequency stimulation in the ripple range. *J. Physiol.* 588, 4891–4904.

Moliadze, V., Atalay, D., Antal, A., and Paulus, W. (2012). Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain Stimul.* 5, 505–511. doi: 10.1016/j.brs.2011.11.004

Moss, F., Ward, L. M., and Sannita, W. G. (2004). Stochastic resonance and sensory information processing: a tutorial and review of application. *Clin. Neurophysiol.* 115, 267–281. doi: 10.1016/j.clinph.2003.09.014

Mulquiney, P. G., Hoy, K. E., Daskalakis, Z. J., and Fitzgerald, P. B. (2011). Improving working memory: exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. *Clin. Neurophysiol.* 122, 2384–2389. doi: 10.1016/j.clinph.2011.05.009

Neuling, T., Rach, S., and Herrmann, C. S. (2013). Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Front. Hum. Neurosci.* 7:161. doi: 10.3389/fnhum.2013.00161

Neuling, T., Rach, S., Wagner, S., Wolters, C. H., and Herrmann, C. S. (2012). Good vibrations: oscillatory phase shapes perception. *Neuroimage* 63, 771–778. doi: 10.1016/j.neuroimage.2012.07.024

Nitsche, M. A., and Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol.* 527(Pt 3), 633–639.

Pashut, T., Wolfus, S., Friedman, A., Lavidor, M., Bar-Gad, I., Yeshurun, Y., et al. (2011). Mechanisms of magnetic stimulation of central nervous system neurons. *PLoS Comput. Biol.* 7:e1002022. doi: 10.1371/journal.pcbi.1002022

Paulus, W., and Opitz, A. (2013). Ohm's law and tDCS over the centuries. *Clin. Neurophysiol.* 124, 429–430. doi: 10.1016/j.clinph.2012.08.019

Pogosyan, A., Gaynor, L. D., Eusebio, A., and Brown, P. (2009). Boosting cortical activity at Beta-band frequencies slows movement in humans. *Curr. Biol.* 19, 1637–1641.

Polania, R., Nitsche, M. A., Korman, C., Batsikadze, G., and Paulus, W. (2012). The importance of timing in segregated theta phase-coupling for cognitive performance. *Curr. Biol.* 22, 1314–1318.

Radman, T., Su, Y., An, J. H., Parra, L. C., and Bikson, M. (2007). Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. *J. Neurosci.* 27, 3030–3036.

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2010). Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J. Neurosci.* 30, 15067–15079. doi: 10.1523/JNEUROSCI.2059-10.2010

Sabel, B. A., Fedorov, A. B., Naue, N., Borrmann, A., Herrmann, C., and Gall, C. (2011). Non-invasive alternating current stimulation improves vision in optic neuropathy. *Restor. Neurol. Neurosci.* 29, 493–505.

Schutter, D. J., and Hortensius, R. (2010). Retinal origin of phosphenes to transcranial alternating current stimulation. *Clin. Neurophysiol.* 121, 1080–1084. doi: 10.1016/j.clinph.2009.10.038

Terney, D., Chaieb, L., Moliadze, V., Antal, A., and Paulus, W. (2008). Increasing human brain excitability by transcranial high-frequency random noise stimulation. *J. Neurosci.* 28, 14147–14155. doi: 10.1523/JNEUROSCI.4248-08.2008

Turi, Z., Ambrus, G. G., Janacsek, K., Emmert, K., Hahn, L., Paulus, W., et al. (2013). Both the cutaneous sensation and phosphene perception are modulated in a frequency-specific manner during transcranial alternating current stimulation. *Restor. Neurol. Neurosci.* 31, 275–285. doi: 10.3233/RNN-120297

Wach, C., Krause, V., Moliadze, V., Paulus, W., Schnitzler, A., and Pollok, B. (2013). Effects of 10 Hz and 20 Hz transcranial alternating current stimulation (tACS) on motor functions and motor cortical excitability. *Behav. Brain Res.* 241, 1–6. doi: 10.1016/j.bbr.2012.11.038

Wiesenfeld, K., and Moss, F. (1995). Stochastic resonance and the benefits of noise: from ice ages to crayfish and SQUIDs. *Nature* 373, 33–36. doi: 10.1038/373033a0

Zaehle, T., Rach, S., and Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS ONE* 5:e13766. doi: 10.1371/journal.pone.0013766

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Rational design of transcranial current stimulation (TCS) through mechanistic insights into cortical network dynamics

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Transcranial current stimulation (TCS) is a promising method of non-invasive brain stimulation to modulate cortical network dynamics. Preliminary studies have demonstrated the ability of TCS to enhance cognition and reduce symptoms in both neurological and psychiatric illnesses. Despite the encouraging results of these studies, the mechanisms by which TCS and endogenous network dynamics interact remain poorly understood. Here, we propose that the development of the next generation of TCS paradigms with increased efficacy requires such mechanistic understanding of how weak electric fields (EFs) imposed by TCS interact with the nonlinear dynamics of large-scale cortical networks. We highlight key recent advances in the study of the interaction dynamics between TCS and cortical network activity. In particular, we illustrate an interdisciplinary approach that bridges neurobiology and electrical engineering. We discuss the use of (1) hybrid biological-electronic experimental approaches to disentangle feedback interactions; (2) large-scale computer simulations for the study of weak global perturbations imposed by TCS; and (3) optogenetic manipulations informed by dynamic systems theory to probe network dynamics. Together, we here provide the foundation for the use of rational design for the development of the next generation of TCS neurotherapeutics.

Keywords: transcranial current stimulation, electric field, brain stimulation, rational design, optogenetics, feedback control, resonance, cortical oscillation

INTRODUCTION

Modulating cortical network dynamics with transcranial current stimulation (TCS) has shown promise as a treatment of neurological and psychiatric illnesses (Brunoni et al., 2012; Demirtas-Tatlidede et al., 2013; Floel, 2013) and as an enhancer of cognition in healthy subjects (Hamilton et al., 2011; Kuo and Nitsche, 2012; McKinley et al., 2012). TCS creates a small (subthreshold) change in the membrane voltage of cortical neurons (Jefferys, 1995). The effect of a weak electric field on the membrane voltage depends on the cell morphology, such that large pyramidal cells with extended dendritic trunks are substantially more susceptible to TCS than inhibitory interneurons with more symmetric cell morphologies (Tranchina and Nicholson, 1986; Radman et al., 2009). Importantly, the resulting depolarization induced by TCS is likely limited to about 2 mV, and therefore is insufficient to cause action potential firing in absence of depolarization caused by endogenous network activity. Therefore, any study of TCS will need to include considerations of the ongoing activity during stimulation. In particular, several recent studies have shown that periodic stimulation with alternating current (to mimic transcranial alternating current stimulation (tACS)) enhances endogenous or pharmacologically induced oscillatory activity in slice preparations of cortical tissue. These studies have provided fundamental insights into how TCS interacts with endogenous activity. Here we highlight several recent conceptual and methodological advances that build on this earlier work and together provide the foundation for the rational design of new TCS paradigms.

PROBING ENDOGENOUS ELECTRIC FIELDS (EFS) WITH A HYBRID SYSTEM

We propose that understanding the effects of externally applied electric fields (EFs) requires mechanistic insight into the functional role of endogenous EFs that have been historically discounted as an epiphenomenon of cortical oscillations. Despite a number of studies (Francis et al., 2003; Deans et al., 2007; Radman et al., 2007) that have demonstrated the effect of weak EFs on rodent hippocampal networks *in vitro* (feed-forward stimulation with artificial waveforms such as sine-waves), a direct demonstration of a causal role of *endogenous* EFs in shaping cortical network dynamics has lacked. In particular, the open questions are: (1) if *naturalistic* EF waveforms have similar effects on network

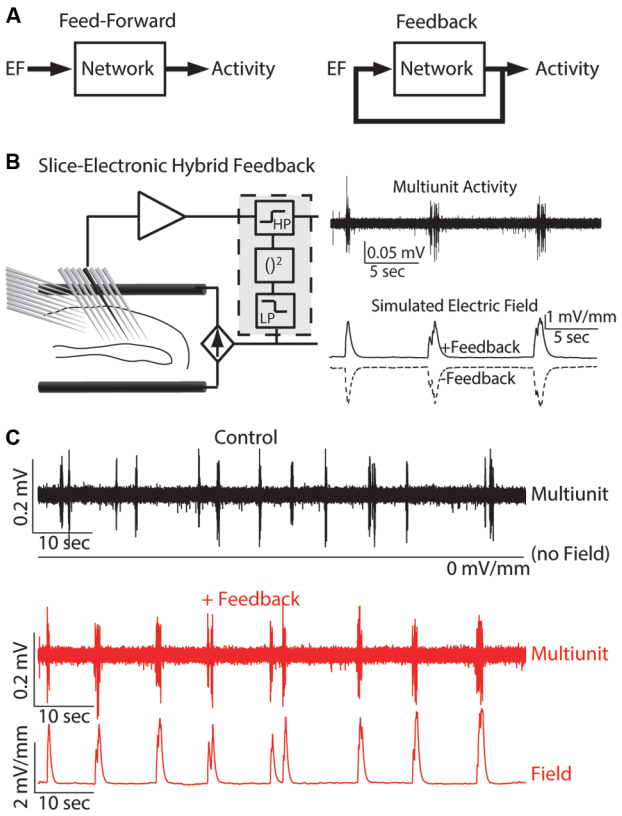

FIGURE 1 | Hybrid biological-electrical system. (A) Control diagrams for both feed-forward and feedback application of EF stimulation. **(B)** Left: Schematic of the system where EF is applied based on the ongoing neuronal activity. Right: Example multiunit trace of typical endogenous activity (top) and the simulated EF applied for both positive and negative feedback. **(C)** Multiunit activity and applied EF for both control (top, black) and positive feedback (bottom, red). Reprinted with permission (Frohlich and McCormick, 2010).

dynamics; (2) if the interaction dynamics differ between feed-forward and feedback application of EFs (**Figure 1A**); and (3) if neocortical areas, which typically exhibit lower cell densities, are equally sensitive to weak EFs. A recent study (Frohlich and McCormick, 2010) that leveraged the presence of spontaneous rhythmic activity in neocortical slices of ferrets addressed these questions. Indeed, EF waveforms that were previously recorded *in vivo* caused a pronounced enhancement of the spontaneous rhythmic activity in slices of visual cortex. Furthermore, the use of a hybrid biological-electronic system (**Figure 1B**) demonstrated that modulation of the endogenous electric field by real-time feedback stimulation altered the structure of spontaneous cortical oscillations in neocortex. Both positive and negative feedback stimulation were evaluated. In the case of positive feedback (**Figure 1C**), a depolarizing, activity-dependent EF computed in real-time from the multiunit activity was applied. This stimulation resulted in increased rhythmic structure of the spontaneous slow oscillation (measured by rhythmicity of UP states). However, when negative feedback was applied, the times between UP states exhibited greater variability resulting in decreased rhythmic structure. The positive feedback stimulation was designed to mimic the hypothesized interaction between endogenous EF and network activity *in vivo*. The enhancement and suppression of oscillatory structure with positive and negative feedback, respectively, therefore supports the conclusion that the endogenous EF causally modulates cortical network dynamics. These results not only propose endogenous EFs as a fundamental mechanism by which cortical synchronization is enhanced but also demonstrate the pronounced susceptibility of active cortical networks to weak EFs as provided by TCS.

Furthermore, the application of feedback EF waveforms also has potential as a novel class of brain stimulation therapeutics for the treatment of disorders of the central nervous system. Pioneering work on animal epilepsy models demonstrated the efficacy of such a non-pharmacological approach (Nakagawa and Durand, 1991; Schiff et al., 1994; Jerger and Schiff, 1995). These feasibility studies used similar hybrid systems where neural activity was recorded and a feedback stimulation signal computed and applied to a slice preparation. Seizure events are characterized by large amounts of highly synchronized network activity and may be modeled in tissue slices by elevation of extracellular concentration of potassium in the artificial cerebrospinal fluid (Frohlich et al., 2008). Seizure events are characterized by hyper-activity and thus hyperpolarizing neurons could be sufficient to reduce seizures by hyperactivity (Gluckman et al., 1996). However, the complex dynamics of neuronal networks caused hyperpolarizing DC stimulation to have only short-term effects in seizure suppression. In contrast, a hybrid system that applied EF stimulation based on the ongoing network dynamics (negative feedback) was able to suppress seizure-like events for up to 16 min (Gluckman et al., 2001). Translation to *in vivo* models has provided further support for the efficacy of such stimulation paradigms (Berenyi et al., 2012). This result highlights both the therapeutic possibilities of hybrid stimulation systems and the benefits of rational design of stimulation paradigms.

OPTIMIZING STIMULATION WITH LARGE-SCALE COMPUTER SIMULATIONS

Computer simulations are an important tool to investigate the interactions between endogenous oscillations and TCS. These simulations enable the study of network dynamics with single-cell resolution at the scale of millions of neurons by leveraging advances in parallel scientific computing and introduction of efficient models which retain the network-level accuracy of prior, computationally more expensive models (Izhikevich, 2004). In such simulations, the interaction between endogenous oscillations and TCS may be studied by applying a simulated EF to the model network (Reato et al., 2010, 2013; Ali et al., 2013). For example, one recent study from our group (Ali et al., 2013) contrasted the effects of both tACS and tDCS on an endogenously oscillating model network. The application of tACS at a stimulation frequency matched to the frequency of the endogenous oscillation enhanced the endogenous oscillation to a greater extent than tDCS. Importantly, networks exhibited the greatest enhancement when stimulated near the frequency of the endogenous oscillation (3 Hz), a sign of resonance dynamics (**Figure 2A**).

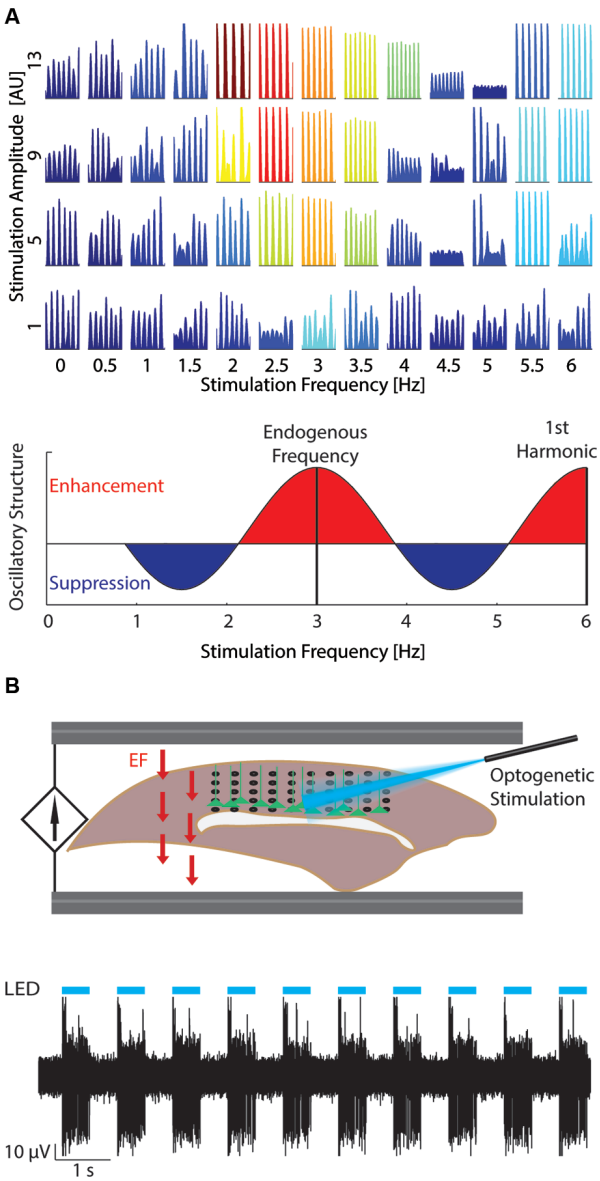

FIGURE 2 | Studying resonance dynamics with large-scale computational models and optogenetics. **(A)** Top: Network response to varying stimulation amplitude (increasing bottom to top) and frequency (left to right). Color indicates power of network activity at the stimulation frequency. At low stimulation amplitudes, the network was most entrained by stimulation at the endogenous frequency (~3 Hz). Increased stimulation amplitude expanded the stimulation frequencies that entrained the network. Reprinted with permission (Ali et al., 2013). Bottom: Change in oscillatory structure for increasing tACS frequency. Red areas represent relative enhancement of oscillatory structure with maxima at the endogenous oscillation frequency and harmonics of the endogenous oscillation. Blue areas represent relative suppression with minima between harmonics of the endogenous oscillation. **(B)** Top: Experimental set-up (Schmidt et al., 2013). Optogenetic stimulation (blue) is applied to layer V pyramidal cells (green) from above to entrain the network at the desired frequency. EF (field arrows, red) is then applied through AgCl wires to model the effect of TCS. Neural data may then be recorded, for example with a multielectrode array pictured here (black). Bottom: Example multiunit trace (black) displaying strong entrainment to the optogenetic stimulation (cyan). Reprinted with permission (Schmidt et al., 2013).

In contrast, network activity was reduced when stimulation at a frequency (4.5 Hz) between the endogenous frequency and its first harmonic was applied. Therefore a key component of rational design of tACS is measuring the ongoing oscillations and matching the stimulation frequency accordingly.

The balance of excitatory and inhibitory synaptic activity is another important characteristic of neuronal networks that can be studied at the network level in simulations only. Inhibitory interneurons are less susceptible to changes in EF due to their small size compared to pyramidal neurons. However, inhibitory activity may be increased to balance increased excitatory activity caused by stimulation (Reato et al., 2010). Modulation of inhibitory activity by tACS was described in a computational model of a network that intrinsically oscillated at 25 Hz. The net firing rate of neurons did not change with low frequency tACS applied, however the temporal patterning was changed. Inhibitory activity increased at a greater rate than excitatory activity, which had a balancing effect on the firing rate. This study demonstrated a means by which tACS can modulate inhibitory activity, through indirect action on excitatory/inhibitory balance rather than by a direct modulation of membrane potential. Therefore, tACS modulation of excitatory/inhibitory balance may have applications in the treatment of autism and schizophrenia where the underlying cortical circuits exhibit abnormal excitatory/inhibitory balance (Rubenstein and Merzenich, 2003; Kehrer et al., 2008; Yizhar et al., 2011).

COMBINING OPTOGENETICS AND DYNAMIC SYSTEMS THEORY

Optogenetics is typically used to activate specific neural pathways, which allows examination of the underlying circuitry involved in different behaviors (Miesenbock and Kevrekidis, 2005; Gradinaru et al., 2007; Fenno et al., 2011). Yet, optogenetic stimulation can also be a valuable tool for entraining network activity in a wide range of frequencies. For example, slow-wave oscillations have been entrained using optogenetic stimulation of layer five (LV) pyramidal cells *in vivo* (Beltramo et al., 2013). The depolarizing action of optogenetic stimulation was sufficient to evoke UP states across the network in both LV and LII/III. Faster rhythms have also been entrained using optogenetic stimulation of fast-spiking inhibitory interneurons (Cardin et al., 2009). Indeed, *in vivo* optogenetic stimulation of varying frequencies caused the greatest effect on the rhythmic structure of the local field potential (LFP) when the stimulation frequency was between 40 and 50 Hz (Carlen et al., 2012). Isolated *in vitro* networks of cultured neurons may also be entrained with optogenetic stimulation (Pina-Crespo et al., 2012). *In vivo* cortical networks are nonlinear systems that exhibit ongoing rhythmic activity. Due to this nonlinearity, the response to TCS will likely be different based on the current state of activity. We here propose that interaction dynamics of TCS and endogenous activity can be studied with optogenetic stimulation to induce *in vivo*-like activity patterns. For example, a slow oscillation can be entrained using optogenetic stimulation *in vitro* and EF can be applied while the resulting modulation of activity by TCS is measured using whole-cell patch clamp, multiunit, or LFP recordings (**Figure 2B**; Schmidt et al., 2013).

TRANSLATING FUNDAMENTAL CONCEPTS INTO BRAIN STIMULATION THERAPEUTICS

The above discussed approaches enable fundamental insights into how active cortical networks respond to stimulation. In particular, the application of modern neuroscience tools provides the unique opportunity to understand how non-invasive brain stimulation with EFs can modulate cortical oscillations that are impaired in a broad range of disorders of the central nervous system, such as schizophrenia (Uhlhaas and Singer, 2012) and epilepsy (Bazhenov et al., 2008). However, it is important to recognize that several major obstacles remain before successful translation of these novel basics findings to the clinical realm. First, the proposed approaches have not yet been broadly applied to cortical oscillations of different frequencies and underlying generators. For example, modulation of alpha oscillations with TCS has been successfully demonstrated in humans (Zaehle et al., 2010; Neuling et al., 2013), but the underlying mechanism is likely different from the enhancement of slow cortical oscillations discussed here. Specifically, alpha oscillations likely emerge from the dynamic interaction of the thalamus and cortex, whereas slow cortical oscillations are considered to be mostly of cortical origin (Timofeev et al., 2000) (yet see Blethyn et al., 2006). To what extent there will be convergence on one fundamental mechanism that applies to rhythmic activity patterns with different generators remains unknown. Second, computational simulations and *in vitro* animal experiments do not consider the complexity of delivering EFs to the brain through multiple layers of tissue and bone. Furthermore, targeting of specific cortical locations is difficult in gyrencephalic brains due to the different neuronal orientation across gyri and sulci. Since the effect of EFs on the membrane voltage depends on the relative orientation of the field to the somato-dendritic axis of neurons (Tranchina and Nicholson, 1986), the evaluation of TCS in an intact animal model with a gyrencephalic brain is a further important step towards the development of novel therapeutic TCS paradigms in humans.

CONCLUSION

Rational design of TCS requires an understanding of the interaction between endogenous EF and network activity and the interaction between network activity and stimulation EFs. Hybrid systems have both established the role of endogenous EFs and resulted in successful control of network activity. Recent studies with large-scale computer models have begun to mechanistically elucidate the interaction dynamics between endogenous network activity and EF stimulation. We further propose *in vivo* and *in vitro* studies that leverage optogenetic stimulation to first entrain network activity which allows the targeted study of these interaction dynamics. Together, these interdisciplinary approaches will provide a foundation for the rational design of TCS.

REFERENCES

Ali, M. M., Sellers, K. K., and Frohlich, F. (2013). Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. *J. Neurosci.* 33, 11262–11275. doi: 10.1523/jneurosci.5867-12.2013

Bazhenov, M., Timofeev, I., Frohlich, F., and Sejnowski, T. J. (2008). Cellular and network mechanisms of electrographic seizures. *Drug Discov. Today Dis. Models* 5, 45–57. doi: 10.1016/j.ddmod.2008.07.005

Beltramo, R., D'urso, G., Dal Maschio, M., Farisello, P., Bovetti, S., Clovis, Y., et al. (2013). Layer-specific excitatory circuits differentially control recurrent network dynamics in the neocortex. *Nat. Neurosci.* 16, 227–234. doi: 10.1038/nn.3306

Berenyi, A., Belluscio, M., Mao, D., and Buzsaki, G. (2012). Closed-loop control of epilepsy by transcranial electrical stimulation. *Science* 337, 735–737. doi: 10.1126/science.1223154

Blethyn, K. L., Hughes, S. W., Toth, T. I., Cope, D. W., and Crunelli, V. (2006). Neuronal basis of the slow (<1 Hz) oscillation in neurons of the nucleus reticularis thalami in vitro. *J. Neurosci.* 26, 2474–2486. doi: 10.1523/jneurosci.3607-05.2006

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., et al. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* 5, 175–195. doi: 10.1016/j.brs.2011.03.002

Cardin, J. A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., et al. (2009). Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature* 459, 663–667. doi: 10.1038/nature08002

Carlen, M., Meletis, K., Siegle, J. H., Cardin, J. A., Futai, K., Vierling-Claassen, D., et al. (2012). A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior. *Mol. Psychiatry* 17, 537–548. doi: 10.1038/mp.2011.31

Deans, J. K., Powell, A. D., and Jefferys, J. G. (2007). Sensitivity of coherent oscillations in rat hippocampus to AC electric fields. *J. Physiol.* 583, 555–565. doi: 10.1113/jphysiol.2007.137711

Demirtas-Tatlidede, A., Vahabzadeh-Hagh, A. M., and Pascual-Leone, A. (2013). Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? *Neuropharmacology* 64, 566–578. doi: 10.1016/j.neuropharm.2012.06.020

Fenno, L., Yizhar, O., and Deisseroth, K. (2011). The development and application of optogenetics. *Annu. Rev. Neurosci.* 34, 389–412. doi: 10.1146/annurev-neuro-061010-113817

Floel, A. (2013). tDCS-enhanced motor and cognitive function in neurological diseases. *Neuroimage* doi: 10.1016/j.neuroimage.2013.05.098. [Epub ahead of print].

Francis, J. T., Gluckman, B. J., and Schiff, S. J. (2003). Sensitivity of neurons to weak electric fields. *J. Neurosci.* 23, 7255–7261.

Frohlich, F., Bazhenov, M., Iragui-Madoz, V., and Sejnowski, T. J. (2008). Potassium dynamics in the epileptic cortex: new insights on an old topic. *Neuroscientist* 14, 422–433. doi: 10.1177/1073858408317955

Frohlich, F., and McCormick, D. A. (2010). Endogenous electric fields may guide neocortical network activity. *Neuron* 67, 129–143. doi: 10.1016/j.neuron.2010.06.005

Gluckman, B. J., Neel, E. J., Netoff, T. I., Ditto, W. L., Spano, M. L., and Schiff, S. J. (1996). Electric field suppression of epileptiform activity in hippocampal slices. *J. Neurophysiol.* 76, 4202–4205.

Gluckman, B. J., Nguyen, H., Weinstein, S. L., and Schiff, S. J. (2001). Adaptive electric field control of epileptic seizures. *J. Neurosci.* 21, 590–600.

Gradinaru, V., Thompson, K. R., Zhang, F., Mogri, M., Kay, K., Schneider, M. B., et al. (2007). Targeting and readout strategies for fast optical neural control in vitro and in vivo. *J. Neurosci.* 27, 14231–14238. doi: 10.1523/jneurosci.3578-07.2007

Hamilton, R., Messing, S., and Chatterjee, A. (2011). Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation. *Neurology* 76, 187–193. doi: 10.1212/wnl.0b013e318205d50d

Izhikevich, E. M. (2004). Which model to use for cortical spiking neurons? *IEEE Trans. Neural Netw.* 15, 1063–1070. doi: 10.1109/tnn.2004.832719

Jefferys, J. G. (1995). Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. *Physiol. Rev.* 75, 689–723.

Jerger, K., and Schiff, S. J. (1995). Periodic pacing an in vitro epileptic focus. *J. Neurophysiol.* 73, 876–879.

Kehrer, C., Maziashvili, N., Dugladze, T., and Gloveli, T. (2008). Altered excitatory-inhibitory balance in the NMDA-Hypofunction model of Schizophrenia. *Front. Mol. Neurosci.* 1:6. doi: 10.3389/neuro.02.006.2008

Kuo, M. F., and Nitsche, M. A. (2012). Effects of transcranial electrical stimulation on cognition. *Clin. EEG Neurosci.* 43, 192–199. doi: 10.1177/1550059412444975

McKinley, R. A., Bridges, N., Walters, C. M., and Nelson, J. (2012). Modulating the brain at work using noninvasive transcranial stimulation. *Neuroimage* 59, 129–137. doi: 10.1016/j.neuroimage.2011.07.075

Miesenbock, G., and Kevrekidis, I. G. (2005). Optical imaging and control of genetically designated neurons in functioning circuits. *Annu. Rev. Neurosci.* 28, 533–563. doi: 10.1146/annurev.neuro.28.051804.101610

Nakagawa, M., and Durand, D. (1991). Suppression of spontaneous epileptiform activity with applied currents. *Brain Res.* 567, 241–247. doi: 10.1016/0006-8993(91)90801-2

Neuling, T., Rach, S., and Herrmann, C. S. (2013). Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Front. Hum. Neurosci.* 7:161. doi: 10.3389/fnhum.2013.00161

Pina-Crespo, J. C., Talantova, M., Cho, E. G., Soussou, W., Dolatabadi, N., Ryan, S. D., et al. (2012). High-frequency hippocampal oscillations activated by optogenetic stimulation of transplanted human ESC-derived neurons. *J. Neurosci.* 32, 15837–15842. doi: 10.1523/jneurosci.3735-12.2012

Radman, T., Ramos, R. L., Brumberg, J. C., and Bikson, M. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimul.* 2, 215–228, e211–e213. doi: 10.1016/j.brs.2009.03.007

Radman, T., Su, Y., An, J. H., Parra, L. C., and Bikson, M. (2007). Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. *J. Neurosci.* 27, 3030–3036. doi: 10.1523/jneurosci.0095-07.2007

Reato, D., Gasca, F., Datta, A., Bikson, M., Marshall, L., and Parra, L. C. (2013). Transcranial electrical stimulation accelerates human sleep homeostasis. *PLoS Comput. Biol.* 9:e1002898. doi: 10.1371/journal.pcbi.1002898

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2010). Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J. Neurosci.* 30, 15067–15079. doi: 10.1523/jneurosci.2059-10.2010

Rubenstein, J. L., and Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav.* 2, 255–267. doi: 10.1034/j.1601-183x.2003.00037.x

Schiff, S. J., Jerger, K., Duong, D. H., Chang, T., Spano, M. L., and Ditto, W. L. (1994). Controlling chaos in the brain. *Nature* 370, 615–620. doi: 10.1038/370615a0

Schmidt, S. L., Foulser, A. A., and Frohlich, F. (2013). Brain stimulation by network resonance with weak electric fields probed by optogenetics in vitro. *Proc. of the 6th International IEEE EMBS Conference on Neural Engineering*, 1186–1189. In press.

Timofeev, I., Grenier, F., Bazhenov, M., Sejnowski, T. J., and Steriade, M. (2000). Origin of slow cortical oscillations in deafferented cortical slabs. *Cereb. Cortex* 10, 1185–1199. doi: 10.1093/cercor/10.12.1185

Tranchina, D., and Nicholson, C. (1986). A model for the polarization of neurons by extrinsically applied electric fields. *Biophys. J.* 50, 1139–1156. doi: 10.1016/s0006-3495(86)83558-5

Uhlhaas, P. J., and Singer, W. (2012). Neuronal dynamics and neuropsychiatric disorders: toward a translational paradigm for dysfunctional large-scale networks. *Neuron* 75, 963–980. doi: 10.1016/j.neuron.2012.09.004

Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O'shea, D. J., et al. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature* 477, 171–178. doi: 10.1038/nature10360

Zaehle, T., Rach, S., and Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS One* 5:e13766. doi: 10.1371/journal.pone.0013766

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Effects of weak transcranial alternating current stimulation on brain activity—a review of known mechanisms from animal studies

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Rhythmic neuronal activity is ubiquitous in the human brain. These rhythms originate from a variety of different network mechanisms, which give rise to a wide-ranging spectrum of oscillation frequencies. In the last few years an increasing number of clinical research studies have explored transcranial alternating current stimulation (tACS) with weak current as a tool for affecting brain function. The premise of these interventions is that tACS will interact with ongoing brain oscillations. However, the exact mechanisms by which weak currents could affect neuronal oscillations at different frequency bands are not well known and this, in turn, limits the rational optimization of human experiments. Here we review the available *in vitro* and *in vivo* animal studies that attempt to provide mechanistic explanations. The findings can be summarized into a few generic principles, such as periodic modulation of excitability, shifts in spike timing, modulation of firing rate, and shifts in the balance of excitation and inhibition. These effects result from weak but simultaneous polarization of a large number of neurons. Whether this can lead to an entrainment or a modulation of brain oscillations, or whether AC currents have no effect at all, depends entirely on the specific dynamic that gives rise to the different brain rhythms, as discussed here for slow wave oscillations (~1 Hz) and gamma oscillations (~30 Hz). We conclude with suggestions for further experiments to investigate the role of AC stimulation for other physiologically relevant brain rhythms.

Keywords: transcranial alternating current stimulation (tACS), oscillations, animal models, slow wave, gamma, electroencephalogram (EEG), entrainment, transcranial direct current stimulation (tDCS)

OSCILLATIONS IN THE BRAIN AND tACS

Oscillations are ubiquitous in the human brain, ranging from ultra-slow (0.05 Hz) to ultra-fast oscillations (500 Hz) (Ward, 2003; Buzsaki and Draguhn, 2004). These oscillations occur in the brain during different behavioral states and their power (amplitude) is commonly modulated during cognitive/behavioral tasks (Buzsaki and Wang, 2012). Many oscillatory rhythms are usually simultaneously present and can modulate each other (e.g., fast-oscillations vary in amplitude with the phase of the slower rhythm, and this has been hypothesized to be relevant i.e., during sensory selection) (Schroeder and Lakatos, 2009). Abnormal brain rhythms have also been shown to correlate with pathological conditions, like Parkinson's disease, Alzheimer's and epileptic seizures (Brown et al., 2001; Worrell et al., 2004; Montez et al., 2009). Therefore, a number of research studies are based on the assumption that modulating brain rhythms has the potential to affect cognitive performance and may be used to treat neurological disorders. This is particularly true for interventions using transcranial alternating current stimulation (tACS), which target specific brain oscillations (Antal et al., 2008; Pogosyan et al., 2009; Moliadze et al., 2012; Brignani et al., 2013; Santarnecchi et al., 2013; Struber et al., 2013). This short review intends to: (1) elucidate the known mechanisms of AC stimulation from recent *in vitro* and *in vivo* animal findings, (2) suggest the key mechanisms that determine the effects of AC stimulation and (3) propose future animal studies that may guide further development of tACS clinical protocols. We focus exclusively on electrophysiological animal data that provide direct experimental evidence for the cellular and network mechanisms of AC stimulation effects, and review computational models of this data, where available. For a review on the effects of tACS in human studies please refer to (Antal and Paulus, 2013; Herrmann et al., 2013; Marshall and Binder, 2013).

DC vs. AC STIMULATION

Transcranial electrical stimulation in humans has been predominantly applied using constant electric currents (often called direct current (DC)) to transiently modulate cognitive and behavioral function (Nitsche and Paulus, 2000; Nitsche et al., 2005; Stagg and Nitsche, 2011). The changes in neural excitability leading to the modulation of brain function have been extensively studied under controlled situations using animal models of DC stimulation, both *in vivo* and *in vitro* (Bindman et al., 1964; Purpura and Mcmurtry, 1965; Chan et al., 1988; Bikson et al., 2004; Rahman

et al., 2013). During subthreshold DC stimulation, the current flowing in the brain modulates the cellular excitability of resting neurons by changing the membrane voltage (transmembrane polarization). The induced polarization of the soma is at most 0.2 mV for each 1 V/m of applied field (Bikson et al., 2004; Radman et al., 2009). Given that conventional protocols (1 mA stimulation intensity) produce electric fields of 1 V/m maximum (Datta et al., 2009), the expected maximum polarization is only 0.2 mV at pyramidal somas. This resulting somatic polarization, albeit small, can affect firing rate for a large number of neurons (Fröhlich and McCormick, 2010; Reato et al., 2010).

Recently, an increasing number of human studies have employed time-varying current stimulation to influence cortical excitability (Marshall et al., 2006; Antal et al., 2008; Kirov et al., 2009; Kar and Krekelberg, 2012; Moliadze et al., 2012; Brignani et al., 2013). tACS refers to electrical stimulation where current is not constant (DC) but alternates between the anode and the cathode (switching polarity) with a sinusoidal waveform. Clinically, tACS may be applied using a wide range of stimulation frequencies and intensities, including with a DC offset (Marshall et al., 2006). While it has been shown that tACS can modulate cortical excitability, electroencephalogram (EEG) oscillations, and cognitive processes (for review see Antal and Paulus, 2013; Herrmann et al., 2013; Marshall and Binder, 2013), there is also evidence for a failure to produce such effects under some circumstances (Brignani et al., 2013). The predominant hypothesis of tACS action is that alternating fields can increase or decrease power of oscillatory rhythms in the brain in a frequency-dependent manner by synchronizing or desynchronizing neuronal networks—this generic hypothesis, applied across brain regions and frequencies, warrants analysis for mechanistic feasibility.

tACS SINUSOIDALLY MODULATES THE NEURONAL MEMBRANE POTENTIAL

At the cellular level sinusoidal AC electric fields applied extracellularly, when directed across pyramidal neurons (along the somatodendritic axis), will sinusoidally alter the transmembrane potential (Chan and Nicholson, 1986). Neurons polarize proportionally with field intensity during AC (Deans et al., 2007) and DC stimulation (Bikson et al., 2004; Fröhlich and McCormick, 2010) with no obvious lower threshold. Small polarization of the membrane can then lead to modulation of firing rate for active neurons (Chan and Nicholson, 1986; Ozen et al., 2010; Reato et al., 2010). However, as first reported in Deans et al. (2007) the cell susceptibility to polarization (mV of polarization per V/m applied electric field) of hippocampal pyramidal neurons (in CA3 is approximately inversely proportional to the applied field frequency (DC: 0.18 mV per V/m, 50 Hz AC: 0.07 mV per V/m) indicating a decrease in membrane response to increasing stimulation frequency. The efficacy of AC field frequency derives from the passive properties of biological membranes (that acts like a low-pass filter with a time constant of 5–20 ms, **Figure 1A**). While the effects of AC fields on single neurons are then expected to be smaller than the effects of DC fields, there are a few studies indicating that networks of neurons can exhibit a higher sensitivity to AC fields.

AC STIMULATION CAN ENTRAIN NEURONAL OSCILLATIONS

Kainic acid in rat hippocampal slices can induce high-beta/gamma oscillations (15 Hz–100 Hz) in the CA3 region. Deans et al. (2007) showed that the frequency and power of these gamma oscillations were modulated by the application of AC fields (< 8 V/m, at 20 or 50 Hz). More specifically, the authors showed that AC fields shift the original peak frequency of the oscillations to the stimulation frequency or a subharmonic (f/2, f/3...) of the stimulation. Fields as low as 0.25 V/m (peak amplitude) were able to modulate the oscillations in 20% of slices, while 0.5 V/m modulated gamma rhythms in 50% of slices (the effects were amplitude-dependent). These results provide evidence of an important effect of AC stimulation, specifically, entrainment of gamma oscillations to the applied field (**Figure 1B**). Note that while the frequency of the oscillatory rhythm spanned across two different physiological bands (high beta/gamma), the mechanisms that generate oscillations are probably the same. Previous studies (for a review see Bartos et al., 2007) suggest that kainic acid induce gamma-like oscillations (not beta).

Other experiments have shown that gamma oscillations in cell cultures can be driven electrically if frequency is carefully adjusted (Fujisawa et al., 2004). Perfusion of brain slices with high potassium solution can induce bursting firing that can also be entrained with very weak pulsed stimulation (0.3 V/m peak amplitude, Francis et al., 2003). Low-intensity pulsed stimulation can also modulate spike and wave seizures (Berenyi et al., 2012).

Entrainment of ongoing neuronal activity to AC stimulation at frequencies mimicking the frequency of cortical slow oscillations (0.8–1.7 Hz) was demonstrated across multiple cortical areas by Ozen et al. (2010) in anesthetized rats. Ozen et al. (2010) reported that membrane potential and unit activity were modulated by AC stimulation in cortical and hippocampal areas (20% and 16% of units were entrained in cortex and hippocampus, respectively). Postmortem calibration suggested that 1 V/m in the extracellular space was sufficient to phase-lock units. Intracellular recordings indicated that the intensities that effectively phase-locked induced 2–3 mV polarization. Increasing stimulation intensity recruited an increasingly larger population of spiking neurons without an evident threshold for this effect, consistent with previous *in vitro* work. Importantly, the modulation with applied AC fields was more effective when the brain endogenously exhibited slow-wave oscillations suggesting a form of resonance.

NEURONAL NETWORKS CAN AMPLIFY THE EFFECTS OF AC STIMULATION

Additional support for the hypothesis that active networks could be more sensitive than single cell to electric fields was presented for slow-wave oscillations in ferret cortical slices (Fröhlich and McCormick, 2010). When perfused with *in vivo*-like artificial cerebro-spinal fluid (ACSF) ferret slices exhibit such slow-wave oscillations. During DC stimulation in the range of 0.5–4.0 V/m, this study reported a higher frequency of these slow oscillations

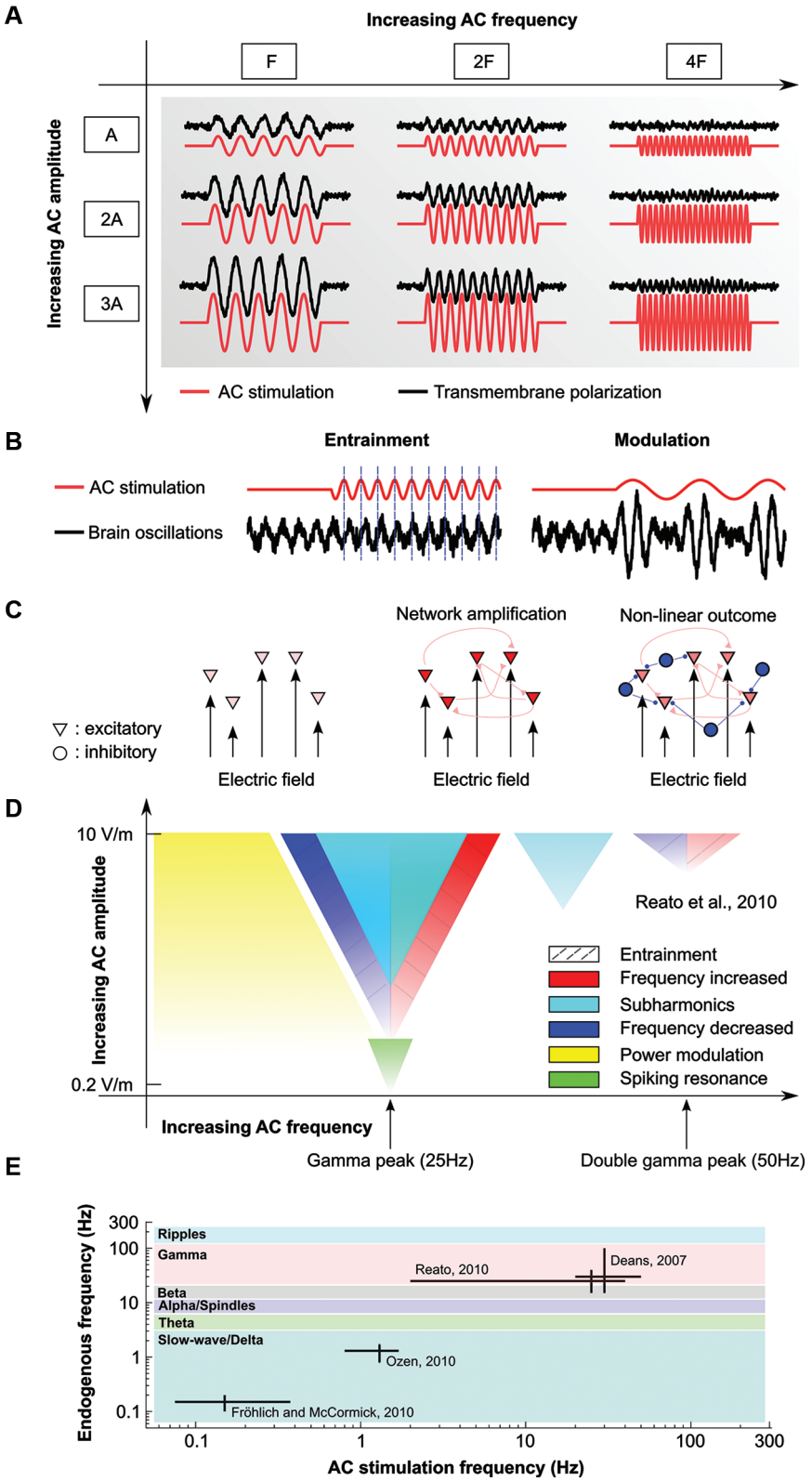

FIGURE 1 | Effects of AC stimulation on single and network of neurons. **(A)** Schematic of the effects of AC stimulation on resting neurons. Sinusoidal electrical stimulation (AC, red lines) sinusoidally modulates the membrane voltage (black lines). The membrane polarization increases with increasing stimulation amplitude (A, 2A, 3A) but decreases with increasing stimulation frequency (F, 2F, 4F). **(B)** Examples of possible effects of weak AC stimulation on oscillations. AC stimulation can entrain the oscillations by shifting their phase (*left*) or modulate its power at the stimulation frequency (*right*).

FIGURE 1 | (*Continued*) **(C)** Schematics of the effects of AC stimulation on network of neurons. While the effects of electrical stimulation on single neurons are small (*left*), synaptically connected neurons can provide feedback that amplifies the effects of stimulation (*center*). However, active neurons create network oscillations, usually set by the level of activity of excitatory and inhibitory neurons (triangle and circles, respectively). In this case, the effects of stimulation cannot *a priori* always be determined (*right*). **(D)** Summary of the known effects of weak AC stimulation on gamma oscillations. AC fields can entrain spiking activity at very low intensities (green), while low-frequency stimulation modulates the power of gamma oscillations (yellow). Gamma oscillations can be entrained (dashed lines) by using frequencies close to the endogenous one or double that frequency (increase in frequency, red, or decrease in frequency, blue). Frequencies close to the stimulation frequency but higher intensity induce pacing at half of the stimulation frequency (cyan). Color gradients indicate size of the effects. Frequencies that do not match the endogenous frequency, for example, can still affect the oscillations if the stimulation amplitude is increased. The figure is adapted from Reato et al. (2010). **(E)** Schematics of the *in vitro* and *in vivo* animal studies applying AC (sinusoidal) stimulation on oscillatory rhythms. The main frequency of the endogenous oscillations of interest (vertical axis) and the stimulation frequencies applied in the different studies (horizontal axis) demonstrate the limited range of neural rhythms that have been described in the animal literature. Colors indicate frequency bands. Also note the log-scale axes.

and determined that this effect was due to a reduced duration of the DOWN state (see below). AC stimulation entrained slow wave oscillations in an amplitude and frequency-dependent manner. In particular, AC fields with frequency matched to the endogenous oscillation led to more periodic up states at a rate that matched the stimulus frequency. By combining these experimental findings with a computational model of slow-wave oscillations, Fröhlich and McCormick (2010) showed that these effects could be explained by the weak polarization of the membrane acting simultaneously on many synaptically connected neurons (**Figure 1C**). Recently, the same group has shown frequency-specific entrainment of multi-unity activity also *in vivo* (Ali et al., 2013).

In a previous study, we analyzed the effects of weak electrical stimulation on carbachol-induced gamma oscillations in the CA3 region of rat hippocampal slices (Reato et al., 2010). The frequency of the stimulation was varied from constant DC to 40 Hz AC stimulation with effects observed at field-intensities as low as 0.2 V/m. DC stimulation modulated the power of the oscillations, with soma-depolarizing fields increasing the power and soma-hyperpolarizing field decreasing it. The effects of AC stimulation varied qualitatively for different frequencies. Low-frequency AC stimulation (2–7 Hz) strongly modulated the gamma power at the stimulation frequency (**Figure 1B**). Interestingly, at stimulation frequency close to the endogenous rhythm, we saw an increase of power at half of the stimulation frequency (sub-harmonic). Moreover, very low-amplitude stimulation (0.2 V/m) entrained firing activity only when the frequency of the endogenous rhythm was matched by the stimulation (resonance). Despite the complexity of the experimental results, we were able to fully account for all the measured effects with a computational model (**Figure 1D**). The model suggested that the effects derived from modulation of firing rate, spike timing and the balance between excitation and inhibition. Recurrent feedback between excitatory and inhibitory neurons leads to a compensatory increase of inhibition whenever excitation is increased, e.g., by field-induced depolarization. Such balanced networks are often invoked to explain normal physiological rhythms (Shu et al., 2003; Haider et al., 2006; Atallah and Scanziani, 2009). Although inhibitory neurons are less sensitive to extracellular electrical stimulation because of their symmetric geometry (Radman et al., 2009), it is also evident that since inhibitory neurons are in general more depolarized, they are likely more sensitive to small voltage fluctuations than excitatory neurons. Thus, even assuming no direct polarization of inhibitory neurons, networks in the brain are always active, and modulation of excitatory neurons may affect (indirectly) inhibitory neurons leading to non-trivial effects (Moliadze et al., 2012; Krause et al., 2013). Importantly, our study showed that the effects of AC stimulation cannot be reduced to a simple increase or decrease in power or frequency of the network oscillations (Reato et al., 2010).

THE EFFECTS OF AC STIMULATION DEPENDS ON BRAIN ACTIVITY

The combined results from the previous studies suggest some general principles regulating the effects of AC stimulation on network of neurons. AC stimulation of inactive neurons induces a simple sinusoidal modulation of neuronal membrane voltage that exhibits low-pass filtering properties. In the context of tACS, this would lead to the conclusion that high frequency stimulation (hundreds of hertz) may be ineffective in modulating brain activity (almost zero induced polarization, **Figure 1A**). However, the studies discussed above showed that network activity and the coherent stimulation of many neurons can amplify the effects of otherwise very small membrane polarizations. AC fields can modulate rate and timing of spiking neurons (Chan and Nicholson, 1986; Fröhlich and McCormick, 2010; Reato et al., 2010) and thus modulate recurrent interaction between neurons. Neurons whose activity is modulated by electrical stimulation will in turn modulate the activity of other neurons, generating a feedback loop that can amplify the effects of stimulation on single neurons (**Figure 1C**). When neurons are in an excitable state, oscillatory rhythms can emerge. Such networks are often characterized by a tight dynamical balance between excitation and inhibition that determines the firing rate and timing of excitatory and inhibitory neurons. When altering firing rate or timing in some neurons the network can "react" to compensate or magnify the effects in a non-trivial way.

For instance, as one might expect, AC fields can entrain network oscillations when stimulating with the frequency of the networks' own rhythm. This was observed for a variety of preparations (Francis et al., 2003; Fujisawa et al., 2004; Deans et al., 2007; Fröhlich and McCormick, 2010; Reato et al., 2010). Yet, in some circumstances the network is paced at half of the stimulation frequency instead. When the stimulation frequency is much lower than the network rhythm some oscillations remain unaffected (slow waves) while others are strongly modulated in power (gamma, **Figure 1B**). Even a form of stochastic resonance was observed in high-potassium slice preparation with a combination of AC and random noise stimulation (Gluckman et al., 1996).

These results suggest that the effects of AC stimulation are not always readily predicted and are certainly not a simple modulation on a one-dimensional scale of oscillation power (**Figure 1D**) as often assumed.

A key factor to consider when trying to understand and anticipate the effects of AC stimulation are the exact mechanisms underlying different endogenous rhythms. For example, slow-wave oscillations (0.5–4 Hz), typical oscillatory activity during sleep (Sejnowski and Destexhe, 2000; Huber et al., 2004), represent a succession of active states of neurons (UP state), characterized by high spiking activity and strong synaptic interaction with inactive states (DOWN states) with almost no firing (Steriade et al., 1993). The high level of activity of the UP state depletes the cellular resources and the self-sustained excitatory activity collapses (think of a group of children playing past their bed-time) thus transitioning to the DOWN state. This transition follows its internal dynamic and cannot be readily modulated. On the other hand, the transition from DOWN to UP state can be driven by even a single spike. Essentially the cellular resources have recovered during the quiescent phase and the network is ready to start up again. A small "kick" can get the avalanche of activity up again (the first kid waking up will get the group going again). Naturally, this DOWN-UP transition could be easily driven by any well-timed external stimulus. The results of Fröhlich and McCormick (2010) indeed suggest that neurons can be quickly driven with small polarization to the UP state. AC stimulation can then more easily entrain oscillations when the stimulus frequency matches the endogenous frequency by shortening the DOWN states (Reato et al., 2013).

In contrast, gamma oscillations are generated by the interplay of excitatory and inhibitory neurons, where excitatory neurons provide the excitation necessary for inhibitory neurons to set the timing of the network (like a clock, Fisahn et al., 1998; Bartos et al., 2007). The generation of half-harmonics when stimulating with the endogenous frequency results from increased temporal alignment of firing of excitatory neurons; this increased synchrony causes a stronger excitatory volley to inhibitory neurons which are thus more strongly activated forcing the network to suppress the next "beat"—thus the network "skips a beat" resulting in half as many cycles, i.e., half harmonic (Reato et al., 2010). The strong modulation of gamma oscillations with slow AC stimulation is a result of an overshoot of the dynamic balance between excitation and inhibition, akin to periodically hitting the break in a standing car with automatic drive.

In summary, the effects of stimulation cannot be established *a priori* without understanding the specific mechanisms underlying neuronal network dynamic.

FUTURE DIRECTIONS

tACS is currently being explored as a tool to modulate brain rhythms in a number of human experiments. We have reviewed here the few *in vitro* and *in vivo* studies of mechanisms underlying the effects of tACS. These studies have shown that active networks are very sensitive to electrical stimulation and in particular to AC stimulation. The effects are mediated by a small polarization of the neuronal membrane potential that lead to changes in spike rate and timing, which are then magnified by the network dynamic.

However, the effects of stimulation depend strongly on the specific network dynamics and in this sense there are still wide gaps in our understanding of AC stimulation. Specifically, alpha (8–12 Hz), beta (13–30 Hz) and theta (4–7 Hz) oscillations as well as spindle activity and sharp wave ripples are all important physiological oscillatory rhythms that have been extensively linked to cognitive phenomena such as attention, motor control, memory retrieval and memory consolidation. Yet, there is no electrophysiological data from cellular or network level studies on the effects of weak electric stimulation on any of these rhythms (**Figure 1E**). Several tACS studies involved stimulation using alpha/beta frequencies (Kanai et al., 2008; Pogosyan et al., 2009; Zaehle et al., 2010; Feurra et al., 2011; Neuling et al., 2012) or combining different stimulation frequencies, including theta (4–7 Hz) and beta (13–30 Hz) over the primary motor cortex (Schutter and Hortensius, 2011). The hope is to facilitate endogenous oscillations at these frequencies, but the lack of experimental evidence for this makes the study of the cellular and network effects of stimulation on these rhythms particularly important.There are *in vitro* preparations that generate beta rhythms (Shimono et al., 2000) and thalamo-cortical spindles (Von Krosigk et al., 1993; Tancredi et al., 2000), while to our knowledge, there are currently no *in vitro* models of alpha oscillations. Theta oscillations (Cappaert et al., 2009; Goutagny et al., 2009) and ripples (Behrens et al., 2005; Nimmrich et al., 2005) can also be pharmacologically induced. Rodent brain slice preparations are obviously a poor model for human brain rhythms; nevertheless they have proven to be a useful tool to study the cellular substrate of tACS particularly because stimulation may be applied in a controlled setting and specific interactions between networks of oscillating neurons can be systematically probed. We also note that transcranial stimulation in humans is thought to generate weaker fields (< 1 V/m) than what is used in slices models ($= 1$ V/m), combined with cortical folding which leads to uncontrolled field orientations, it is hard to predict the outcome of any one human experiment based on slice experiments alone. Animal *in vivo* experiments offer a more physiological environment to test stimulation effects. However, presently they offer limited control over the direction and intensity of current flow; a technical limitation that can be addressed through quantitative models of current flow in animals (Datta et al., 2009; Marquez-Ruiz et al., 2012).

The results shown here suggest that tACS may go beyond frequency coupling of the stimulation and endogenous activity (for instance alpha-modulated alpha) and could perhaps be used for cross frequency coupling. For example, recent studies have demonstrated that low-frequency oscillations can modulate the amplitude of higher frequency oscillations (like theta-modulated gamma) and that the effects are functionally and behaviorally relevant, including for working and spatial memory. However, to our knowledge, stimulation of brain rhythms with lower frequencies to modulate the amplitude of higher frequency oscillations has not been explored yet in human brain stimulation. In Reato et al. (2010) we demonstrated that gamma oscillations were strongly modulated by lower-frequency stimulation (including theta fre-

quencies), raising the possibility that such modulation may also be possible in humans. Practically, cross frequency coupling of stimulation and endogenous activity has the additional technical benefit that tACS would not produce stimulation artifacts at the frequency of interest (Neuling et al., 2012).

The *in vivo* and *in vitro* studies reviewed here provide evidence for the acute effects of stimulation on gamma and slow-wave oscillations. Yet, it is important to note that none of the animal studies reviewed above report lasting effects, i.e., as soon as the AC fields are turned off, the observed effects seemingly disappear. Admittedly, these studies did not apply long-duration stimulation (minutes) and thus long-term effects were not expected or noted. Clearly, long-term effects at the cellular level must mediate the long-term effects observed in human studies, thus, there is an urgent need to clarify the underlying mechanisms. Additionally, stimulation dosage including duration, intensity (Moliadze et al., 2012; Neuling et al., 2013), frequency (Zaehle et al., 2010; Struber et al., 2013), and electrode montage may interact synergistically to influence the post-stimulation effects. For DC stimulation, several studies have shown long-lasting synaptic effects after stimulation *in vitro* and *in vivo* (Bindman et al., 1962; Gartside, 1968a,b; Fritsch et al., 2010; Ranieri et al., 2012). Specifically, Brain-derived neurotrophic factor (BDNF; Fritsch et al., 2010), adenosine (Marquez-Ruiz et al., 2012), N-methyl-D-aspartate receptor (NMDA-receptors; Liebetanz et al., 2002), regulation of gene expression (Ranieri et al., 2012), and protein synthesis (Gartside, 1968b) have all been implicated in synaptic changes induced by weak DC stimulation. However, it's unclear how DC-induced long-term plasticity relates to AC stimulation. Bawin et al. (1984) have shown that AC stimulation can induce lasting effects on evoked responses (Bawin et al., 1984), but these results could not be readily reproduced (Deans et al., 2007). The *in vitro* preparations we cited in this review may be a good tool to test the effects of long-duration AC stimulation on neuronal networks. Understanding the acute and long-lasting effects of tACS at the cellular and network level along with physiological insights from human experiments may help to rationally design clinical stimulation protocols that aim to augment cognitive and behavioral function.

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REFERENCES

Ali, M. M., Sellers, K. K., and Frohlich, F. (2013). Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. *J. Neurosci.* 33, 11262–11275. doi: 10.1523/jneurosci.5867-12.2013

Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., and Paulus, W. (2008). Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimul.* 1, 97–105. doi: 10.1016/j.brs.2007.10.001

Antal, A., and Paulus, W. (2013). Transcranial alternating current stimulation (tACS). *Front. Hum. Neurosci.* 7:317. doi: 10.3389/fnhum.2013.00317

Atallah, B. V., and Scanziani, M. (2009). Instantaneous modulation of gamma oscillation frequency by balancing excitation with inhibition. *Neuron* 62, 566–577. doi: 10.1016/j.neuron.2009.04.027

Bartos, M., Vida, I., and Jonas, P. (2007). Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat. Rev. Neurosci.* 8, 45–56. doi: 10.1038/nrn2044

Bawin, S. M., Sheppard, A. R., Mahoney, M. D., and Adey, W. R. (1984). Influences of sinusoidal electric fields on excitability in the rat hippocampal slice. *Brain Res.* 323, 227–237. doi: 10.1016/0006-8993(84)90293-2

Behrens, C. J., van Den Boom, L. P., de Hoz, L., Friedman, A., and Heinemann, U. (2005). Induction of sharp wave-ripple complexes in vitro and reorganization of hippocampal networks. *Nat. Neurosci.* 8, 1560–1567. doi: 10.1038/nn1571

Berenyi, A., Belluscio, M., Mao, D., and Buzsaki, G. (2012). Closed-loop control of epilepsy by transcranial electrical stimulation. *Science* 337, 735–737. doi: 10.1126/science.1223154

Bikson, M., Inoue, M., Akiyama, H., Deans, J. K., Fox, J. E., Miyakawa, H., et al. (2004). Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *J. Physiol.* 557, 175–190. doi: 10.1113/jphysiol.2003.055772

Bindman, L. J., Lippold, O. C., and Redfearn, J. W. (1962). Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. *Nature* 196, 584–585. doi: 10.1038/196584a0

Bindman, L. J., Lippold, O. C., and Redfearn, J. W. (1964). The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *J. Physiol.* 172, 369–382.

Brignani, D., Ruzzoli, M., Mauri, P., and Miniussi, C. (2013). Is transcranial alternating current stimulation effective in modulating brain oscillations? *PLoS One* 8:e56589. doi: 10.1371/journal.pone.0056589

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., and Di Lazzaro, V. (2001). Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J. Neurosci.* 21, 1033–1038.

Buzsaki, G., and Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science* 304, 1926–1929. doi: 10.1126/science.1099745

Buzsaki, G., and Wang, X. J. (2012). Mechanisms of gamma oscillations. *Annu. Rev. Neurosci.* 35, 203–225. doi: 10.1146/annurev-neuro-062111-150444

Cappaert, N. L., Lopes da Silva, F. H., and Wadman, W. J. (2009). Spatio-temporal dynamics of theta oscillations in hippocampal-entorhinal slices. *Hippocampus* 19, 1065–1077. doi: 10.1002/hipo.20570

Chan, C. Y., Hounsgaard, J., and Nicholson, C. (1988). Effects of electric fields on transmembrane potential and excitability of turtle cerebellar Purkinje cells in vitro. *J. Physiol.* 402, 751–771.

Chan, C. Y., and Nicholson, C. (1986). Modulation by applied electric fields of Purkinje and stellate cell activity in the isolated turtle cerebellum. *J. Physiol.* 371, 89–114.

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., and Bikson, M. (2009). Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimul.* 2, 201–207. doi: 10.1016/j.brs.2009.03.005

Deans, J. K., Powell, A. D., and Jefferys, J. G. (2007). Sensitivity of coherent oscillations in rat hippocampus to AC electric fields. *J. Physiol.* 583, 555–565. doi: 10.1113/jphysiol.2007.137711

Feurra, M., Bianco, G., Santarnecchi, E., Del Testa, M., Rossi, A., and Rossi, S. (2011). Frequency-dependent tuning of the human motor system induced by transcranial oscillatory potentials. *J. Neurosci.* 31, 12165–12170. doi: 10.1016/s1388-2457(11)60449-5

Fisahn, A., Pike, F. G., Buhl, E. H., and Paulsen, O. (1998). Cholinergic induction of network oscillations at 40 Hz in the hippocampus in vitro. *Nature* 394, 186–189. doi: 10.1038/28179

Francis, J. T., Gluckman, B. J., and Schiff, S. J. (2003). Sensitivity of neurons to weak electric fields. *J. Neurosci.* 23, 7255–7261.

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., et al. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron* 66, 198–204. doi: 10.1016/j.neuron.2010.03.035

Fröhlich, F., and McCormick, D. A. (2010). Endogenous electric fields may guide neocortical network activity. *Neuron* 67, 129–143. doi: 10.1016/j.neuron.2010.06.005

Fujisawa, S., Matsuki, N., and Ikegaya, Y. (2004). Chronometric readout from a memory trace: gamma-frequency field stimulation recruits timed recurrent activity in the rat CA3 network. *J. Physiol.* 561, 123–131. doi: 10.1113/jphysiol.2004.066639

Gartside, I. B. (1968a). Mechanisms of sustained increases of firing rate of neurones in the rat cerebral cortex after polarization: reverberating circuits or modification of synaptic conductance? *Nature* 220, 382–383. doi: 10.1038/220382a0

Gartside, I. B. (1968b). Mechanisms of sustained increases of firing rate of neurones in the rat cerebral cortex after polarization: role of protein synthesis. *Nature* 220, 383–384. doi: 10.1038/220383a0

Gluckman, B. J., Neel, E. J., Netoff, T. I., Ditto, W. L., Spano, M. L., and Schiff, S. J. (1996). Electric field suppression of epileptiform activity in hippocampal slices. *J. Neurophysiol.* 76, 4202–4205.

Goutagny, R., Jackson, J., and Williams, S. (2009). Self-generated theta oscillations in the hippocampus. *Nat. Neurosci.* 12, 1491–1493. doi: 10.1038/nn.2440

Haider, B., Duque, A., Hasenstaub, A. R., and Mccormick, D. A. (2006). Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. *J. Neurosci.* 26, 4535–4545. doi: 10.1523/jneurosci.5297-05.2006

Herrmann, C. S., Rach, S., Neuling, T., and Struber, D. (2013). Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Front. Hum. Neurosci.* 7:279. doi: 10.3389/fnhum.2013.00279

Huber, R., Ghilardi, M. F., Massimini, M., and Tononi, G. (2004). Local sleep and learning. *Nature* 430, 78–81. doi: 10.1038/nature02663

Kanai, R., Chaieb, L., Antal, A., Walsh, V., and Paulus, W. (2008). Frequency-dependent electrical stimulation of the visual cortex. *Curr. Biol.* 18, 1839–1843. doi: 10.1016/j.cub.2008.10.027

Kar, K., and Krekelberg, B. (2012). Transcranial electrical stimulation over visual cortex evokes phosphenes with a retinal origin. *J. Neurophysiol.* 108, 2173–2178. doi: 10.1152/jn.00505.2012

Kirov, R., Weiss, C., Siebner, H. R., Born, J., and Marshall, L. (2009). Slow oscillation electrical brain stimulation during waking promotes EEG theta activity and memory encoding. *Proc. Natl. Acad. Sci. U S A* 106, 15460–15465. doi: 10.1073/pnas.0904438106

Krause, B., Márquez-Ruiz, J., and Cohen Kadosh, R. (2013). The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? *Front. Hum. Neurosci.* 7:602. doi: 10.3389/fnhum.2013.00602

Liebetanz, D., Nitsche, M. A., Tergau, F., and Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain* 125, 2238–2247. doi: 10.1093/brain/awf238

Marquez-Ruiz, J., Leal-Campanario, R., Sanchez-Campusano, R., Molaee-Ardekani, B., Wendling, F., Miranda, P. C., et al. (2012). Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. *Proc. Natl. Acad. Sci. U S A* 109, 6710–6715. doi: 10.1073/pnas.1121147109

Marshall, L., and Binder, S. (2013). Contribution of transcranial oscillatory stimulation to research on neural networks: an emphasis on hippocampo-neocortical rhythms. *Front. Hum. Neurosci.* 7:614. doi: 10.3389/fnhum.2013.00614

Marshall, L., Helgadottir, H., Molle, M., and Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature* 444, 610–613. doi: 10.1038/nature05278

Moliadze, V., Atalay, D., Antal, A., and Paulus, W. (2012). Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain Stimul.* 5, 505–511. doi: 10.1016/j.brs.2011.11.004

Montez, T., Poil, S. S., Jones, B. F., Manshanden, I., Verbunt, J. P., van Dijk, B. W., et al. (2009). Altered temporal correlations in parietal alpha and prefrontal theta oscillations in early-stage Alzheimer disease. *Proc. Natl. Acad. Sci. U S A* 106, 1614–1619. doi: 10.1073/pnas.0811699106

Neuling, T., Rach, S., and Herrmann, C. S. (2013). Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Front. Hum. Neurosci.* 7:161. doi: 10.3389/fnhum.2013.00161

Neuling, T., Rach, S., Wagner, S., Wolters, C. H., and Herrmann, C. S. (2012). Good vibrations: oscillatory phase shapes perception. *Neuroimage* 63, 771–778. doi: 10.1016/j.neuroimage.2012.07.024

Nimmrich, V., Maier, N., Schmitz, D., and Draguhn, A. (2005). Induced sharp wave-ripple complexes in the absence of synaptic inhibition in mouse hippocampal slices. *J. Physiol.* 563, 663–670. doi: 10.1113/jphysiol.2004.079558

Nitsche, M. A., and Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol.* 527 Pt 3, 633–639. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, M. A., Seeber, A., Frommann, K., Klein, C. C., Rochford, C., Nitsche, M. S., et al. (2005). Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J. Physiol.* 568, 291–303. doi: 10.1113/jphysiol.2005.092429

Ozen, S., Sirota, A., Belluscio, M. A., Anastassiou, C. A., Stark, E., Koch, C., et al. (2010). Transcranial electric stimulation entrains cortical neuronal populations in rats. *J. Neurosci.* 30, 11476–11485. doi: 10.1523/jneurosci.5252-09.2010

Pogosyan, A., Gaynor, L. D., Eusebio, A., and Brown, P. (2009). Boosting cortical activity at beta-band frequencies slows movement in humans. *Curr. Biol.* 19, 1637–1641. doi: 10.1016/j.cub.2009.07.074

Purpura, D. P., and Mcmurtry, J. G. (1965). Intracellular activities and evoked potential changes during polarization of motor cortex. *J. Neurophysiol.* 28, 166–185. doi: 10.1055/s-0029-1216188

Radman, T., Ramos, R. L., Brumberg, J. C., and Bikson, M. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimul.* 2, 215–228. doi: 10.1016/j.brs.2009.03.007

Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L. C., et al. (2013). Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. *J. Physiol.* 591, 2563–2578. doi: 10.1113/jphysiol.2012.247171

Ranieri, F., Podda, M. V., Riccardi, E., Frisullo, G., Dileone, M., Profice, P., et al. (2012). Modulation of Ltp at rat hippocampal Ca3-Ca1 synapses by direct current stimulation. *J. Neurophysiol.* 107, 1868–1880. doi: 10.1152/jn.00319.2011

Reato, D., Gasca, F., Datta, A., Bikson, M., Marshall, L., and Parra, L. C. (2013). Transcranial electrical stimulation accelerates human sleep homeostasis. *PLoS Comput. Biol.* 9:e1002898. doi: 10.1371/journal.pcbi.1002898

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2010). Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J. Neurosci.* 30, 15067–15079. doi: 10.1523/jneurosci.2059-10.2010

Santarnecchi, E., Polizzotto, N. R., Godone, M., Giovannelli, F., Feurra, M., Matzen, L., et al. (2013). Frequency-dependent enhancement of fluid intelligence induced by transcranial oscillatory potentials. *Curr. Biol.* 23, 1449–1453. doi: 10.1016/j.cub.2013.06.022

Schroeder, C. E., and Lakatos, P. (2009). Low-frequency neuronal oscillations as instruments of sensory selection. *Trends Neurosci.* 32, 9–18. doi: 10.1016/j.tins.2008.09.012

Schutter, D. J., and Hortensius, R. (2011). Brain oscillations and frequency-dependent modulation of cortical excitability. *Brain Stimul.* 4, 97–103. doi: 10.1016/j.brs.2010.07.002

Sejnowski, T. J., and Destexhe, A. (2000). Why do we sleep? *Brain Res.* 886, 208–223. doi: 10.1016/S0006-8993(00)03007-9

Shimono, K., Brucher, F., Granger, R., Lynch, G., and Taketani, M. (2000). Origins and distribution of cholinergically induced beta rhythms in hippocampal slices. *J. Neurosci.* 20, 8462–8473.

Shu, Y., Hasenstaub, A., and Mccormick, D. A. (2003). Turning on and off recurrent balanced cortical activity. *Nature* 423, 288–293. doi: 10.1038/nature01616

Stagg, C. J., and Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist* 17, 37–53. doi: 10.1177/1073858410386614

Steriade, M., Nunez, A., and Amzica, F. (1993). A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *J. Neurosci.* 13, 3252–3265.

Struber, D., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., and Herrmann, C. S. (2013). Antiphasic 40 Hz oscillatory current stimulation affects bistable motion perception. *Brain Topogr.* doi: 10.1007/s10548-013-0294-x. [Epub ahead of print].

Tancredi, V., Biagini, G., D'antuono, M., Louvel, J., Pumain, R., and Avoli, M. (2000). Spindle-like thalamocortical synchronization in a rat brain slice preparation. *J. Neurophysiol.* 84, 1093–1097.

Von Krosigk, M., Bal, T., and Mccormick, D. A. (1993). Cellular mechanisms of a synchronized oscillation in the thalamus. *Science* 261, 361–364. doi: 10.1126/science.8392750

Ward, L. M. (2003). Synchronous neural oscillations and cognitive processes. *Trends Cogn. Sci.* 7, 553–559. doi: 10.1016/j.tics.2003.10.012

Worrell, G. A., Parish, L., Cranstoun, S. D., Jonas, R., Baltuch, G., and Litt, B. (2004). High-frequency oscillations and seizure generation in neocortical epilepsy. *Brain* 127, 1496–1506. doi: 10.1093/brain/awh149

Zaehle, T., Rach, S., and Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS One* 5:e13766. doi: 10.1371/journal.pone.0013766

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The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance?

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Transcranial direct current stimulation (tDCS) is a promising tool for cognitive enhancement and neurorehabilitation in clinical disorders in both cognitive and clinical domains (e.g., chronic pain, tinnitus). Here we suggest the potential role of tDCS in modulating cortical excitation/inhibition (E/I) balance and thereby inducing improvements. We suggest that part of the mechanism of action of tDCS can be explained by non-invasive modulations of the E/I balance.

Keywords: transcranial direct current stimulation (tDCS), excitation, inhibition, GABA, glutamate, cognition

INTRODUCTION

Cognitive enhancement is a popular topic in the neuroscience community. Non-invasive neuromodulation methods, such as transcranial direct current stimulation (tDCS) can either increase (e.g., anodal) or decrease (e.g., cathodal) cortical excitability (Nitsche and Paulus, 2001; Nitsche et al., 2003) and thereby modulate cortical activity levels.

At a cellular level, the applied external electric field modifies the transmembrane potential differences by forcing the displacement of intracellular ions which cancel the generated intracellular field and thereby modify the spike firing probability (Bikson et al., 2004; Ruffini et al., 2013). With sufficient tDCS duration, synaptically driven aftereffects are induced (Bindman et al., 1964). The final effects of tDCS depend on the individual neural morphology (Radman et al., 2009), the orientation of somato-dendritic axes, and the neural pathways with respect to the electric field (Bikson et al., 2004; Kabakov et al., 2012).

tDCS has positive effects in a variety of clinical conditions such as Parkinson's disease, tinnitus, chronic pain, stroke, and even childhood psychosis (e.g., Fregni et al., 2006; Song et al., 2012; David et al., 2013; Khedr et al., 2013; Moreno-Duarte et al., 2013), but also in healthy individuals (Jacobson et al., 2012; Kuo and Nitsche, 2012; Cohen Kadosh, 2013). It is therefore considered a promising neurorehabilitation tool. Moreover, tDCS has recently been suggested as a possible tool to improve learning disabilities in children (Krause and Cohen Kadosh, 2013; Vicario and Nitsche, 2013). A crucial question remains to be answered: how exactly does tDCS modify such diverse conditions in both the typical and atypical brain?

NEUROTRANSMITTERS AND tDCS

Magnetic resonance spectroscopy (MRS) studies have shown that anodal tDCS reduces local concentrations of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), whereas cathodal tDCS reduces excitatory glutamate levels (Stagg et al., 2009; Clark et al., 2011).

Others have suggested that local GABA reductions co-occur with learning and performance improvements (Floyer-Lea et al., 2006) and that the magnitude of regional GABAergic changes during anodal tDCS reflects the degree of learning (Stagg et al., 2011). Namely, the further GABA is decreased, the larger the observed learning effect. Such disinhibition may lead to the unmasking of hidden excitatory connections (Jacobs and Donoghue, 1991) and thereby allow for the induction of activity-dependent long-term potentiation (LTP). LTP in turn is capable of inducing cortical reorganization, most likely by increasing local synaptic effectiveness (Hess and Donoghue, 1994), which in turn might alter deficient network processing.

In addition, data coming from animal experiments have demonstrated the implication of N-methyl-D-aspartate (NMDA) receptors and brain-derived neurotrophic factor (BDNF) in the synaptic potentiation of the motor cortex after anodal tDCS (Fritsch et al., 2010). Moreover, local administration of the adenosine A1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DCPCX) in the somatosensory cortex of alert rabbits prevented long-term depression induced by cathodal tDCS (Marquez-Ruiz et al., 2012). These data suggest that beyond GABA and glutamate, other neurochemicals may be involved in the mechanisms underlying long-term tDCS effects.

EXCITATION/INHIBITION (E/I) BALANCE

Homeostatic control of cortical excitability and induction of plasticity are crucial for allowing efficient information transfer in the brain, (Turrigiano and Nelson, 2000). This means that while plastic changes occur, the network must still maintain a certain amount of stability in order to produce meaningful

output. The dysregulation of cortical excitability may thus lead to symptoms seen in various central nervous system disorders (Eichler and Meier, 2008), depending on the area(s) in which the imbalance occurs. For instance, regional abnormalities in GABA concentrations have been found in neuropsychiatric disorders, such as schizophrenia (Goto et al., 2009; Yoon et al., 2010; Yizhar et al., 2011; Rowland et al., 2013), autism (Kubas et al., 2012; Rojas et al., 2013), insomnia (Morgan et al., 2012), and panic disorder (Long et al., 2013).

However, GABA concentrations alone may not fully explain different kinds of cognitive deficits. For instance, if glutamatergic excitation is increased as well, we would not expect to observe performance abnormalities. Most studies so far have only looked at glutamate and GABA in isolation (e.g., Goto et al., 2009; Yoon et al., 2010; Kubas et al., 2012; Rojas et al., 2013).

We suggest that the regional cortical excitation/inhibition (E/I) balance, measured by ratios of glutamate/GABA, may provide more meaningful interpretations of individual cognitive performance and deficits than glutamate or GABA alone. GABA and glutamate contribute in a complementary fashion to high-level prefrontal cognitive performance in healthy adults (Jocham et al., 2012). Furthermore, individuals with autism or schizophrenia show higher E/I ratios compared to healthy controls (Rubenstein and Merzenich, 2003), and this has been suggested to be related to behavioral and cognitive deficits (Yizhar et al., 2011). Similarly, regional increases in glutamate (Carrey et al., 2007; Arcos-Burgos et al., 2012) and reduced levels of GABA (Edden et al., 2012) have been found in several different brain areas of individuals with Attention-deficit hyperactivity disorder (ADHD). These findings lend support to the view that E/I balance plays a major role in normal cognition, as well as the symptomatic patterns of a variety of clinical conditions.

Using cathodal tDCS to artificially decrease E/I in ADHD for example could be beneficial. Cathodal stimulation may restore the elevated E/I balance towards a more typical level in targeted regions, which require greater baseline inhibition, in order to reduce irrelevant output. For instance, in healthy adults, applying cathodal stimulation to prefrontal regions has been shown to lead to improved attentional processing. This likely enhances prefrontal filtering of irrelevant information (Weiss and Lavidor, 2012).

The direction of the E/I imbalance may determine the behavioral outcome depending on the particular brain area and appears to be different in different clinical populations. Therefore, a fundamental understanding of individual differences in E/I ratio would allow for optimization of the choice of tDCS parameters for each individual in terms of polarity, intensity, duration, etc. (**Figure 1**).

DISCUSSION

This simple, but elegant model explains individual differences in cognitive performance and cognitive deficits, as well as the polarity-specific effects of tDCS on cognition, and can be extended to non-cognitive domains, as well (e.g., pain: Harris and

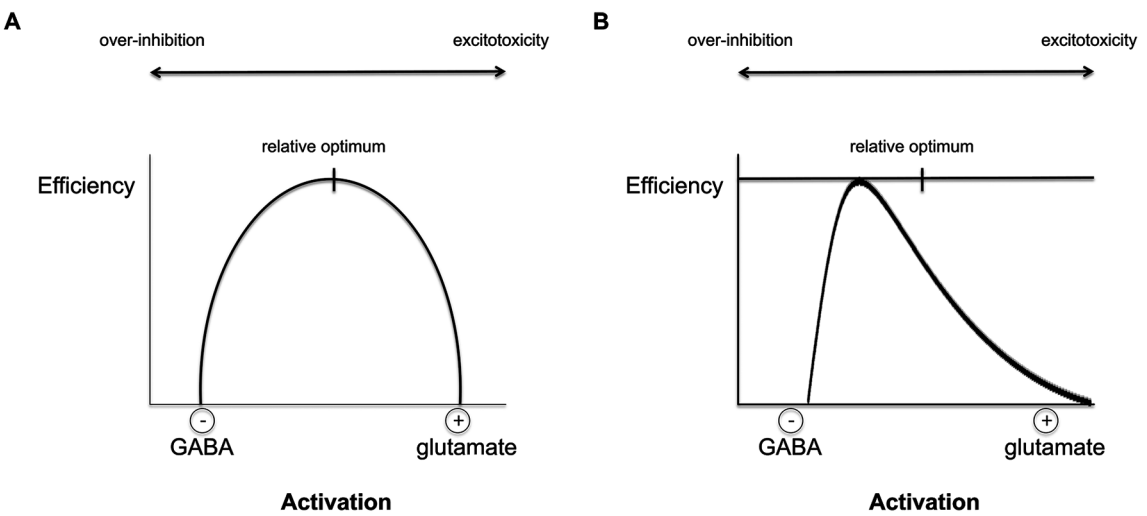

FIGURE 1 | The relationship between excitation/inhibition (E/I) balance and efficiency of a given cortical region. **(A)** According to the current hypothesis, E/I balance within a brain area can be viewed as an inverted-U shape in which the optimal performance is achieved when excitation and inhibition interact efficiently, allowing for both plasticity and stability. The degree of baseline E/I might, however, differ per brain region and individual. If the optimal balance is achieved, homeostatic control of activity-dependent plasticity and synaptic efficiency are possible and can lead to meaningful behavioral output. Deviations from the ideal balance are associated with atypical behavior and the severity of the deficit may vary with the degree of imbalance. tDCS can be used to target and restore the individual abnormalities in E/I imbalance in different neurological conditions. Only a moderate level of activation, i.e., balanced E/I levels, can reach the optimal level of processing efficiency and allow for homeostatic plasticity. High levels of GABA can lead to cortical over-inhibition that will reduce network output, whereas hyperactive glutamatergic activity can lead to excessive output and eventually to excitotoxicity and cell death (Faden et al., 1989; Belousov, 2012). **(B)** An example of the distribution of E/I balance in the healthy population: the finding that most anodal tDCS studies report behavioral improvements suggests that the distribution may be skewed with the majority showing non-optimal E/I ratio. However, for some individuals with increased E/I ratios, anodal tDCS will shift the non-pathological imbalance even further towards over-activation and therefore reduce behavioral outcomes.

Clauw, 2012). Nevertheless, the effects of tDCS on neural network dynamics, more specifically at neurotransmitters concentrations, are largely unknown.

At a microscopic level, glutamate is released by pyramidal cell synapses and thalamic synaptic inputs, whereas GABA is mainly released by a variety of interneurons (Nicoll et al., 1990; McCormick, 1992). Animal experiments using brain slices suggest that pyramidal cells in layer V are the most sensitive to the effects of weak electric fields applied over the skull surface (Radman et al., 2009). Thus, anodal and cathodal tDCS are expected to increase or decrease, respectively, the membrane potential of pyramidal cells and thereby alter the glutamatergic tone in the cortex.

Nevertheless, glutamate levels not only depend on pyramidal cells but also on input from thalamic projections. It has been recently shown in both humans (Polania et al., 2012) and alert rabbits (Marquez-Ruiz et al., 2012) that tDCS also modifies thalamocortical synapses by means of glutamate release from sensory afferents. As pyramidal cells project to different types of interneurons, it is expected that the modulation of glutamate levels correlates with GABA release. However, a recent computational modeling study based on in-vivo experimental data proposed that tDCS may induce opposing effects on different types of interneurons (Molaee-Ardekani et al., 2013), suggesting a more complex scenario. Finally, in order to fully understand the mechanism underlying E/I balance, other factors, such as levels of BDNF or cortical adenosine and cortical oscillations must also be taken into consideration. For example, it has been shown in brain slices that weak direct current (DC) stimulation may modulate slow-wave (Frohlich and McCormick, 2010) and gamma oscillations (Reato et al., 2010) related with E/I balance in the cortex (Shu et al., 2003; Haider et al., 2006; Atallah and Scanziani, 2009).

According to the current evidence, tDCS is likely to reinstate an optimal E/I balance that allows for optimal homeostatic plasticity in learning and cognition, if applied adequately to each individual's predispositions. If this consistently proves to be the case, a variety of cortex-based clinical conditions including atypical brain development may be successfully treated using tDCS. So far, there is little research investigating the relationship between E/I balance and cognition. The assessment of this balance in different clinical, neurological and neuro-developmental disorders will help refine tDCS strategies for treatment in the future. Whether electrical stimulation can also modulate E/I balance in the case of transcranial random noise stimulation (tRNS) and transcranial alternating current stimulation (tACS) is currently unknown and requires further exploration.

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REFERENCES

Arcos-Burgos, M., Londono, A. C., Pineda, D. A., Lopera, F., Palacio, J. D., Arbelaez, A., et al. (2012). Analysis of brain metabolism by proton magnetic resonance spectroscopy (1H-MRS) in attention-deficit/hyperactivity disorder suggests a generalized differential ontogenic pattern from controls. *Atten. Defic. Hyperact. Disord.* 4, 205–212. doi: 10.1007/s12402-012-0088-0

Atallah, B. V., and Scanziani, M. (2009). Instantaneous modulation of gamma oscillation frequency by balancing excitation with inhibition. *Neuron* 62, 566–577. doi: 10.1016/j.neuron.2009.04.027

Belousov, A. B. (2012). Novel model for the mechanisms of glutamate-dependent excitotoxicity: role of neuronal gap junctions. *Brain Res.* 1487, 123–130. doi: 10.1016/j.brainres.2012.05.063

Bikson, M., Inoue, M., Akiyama, H., Deans, J. K., Fox, J. E., Miyakawa, H., et al. (2004). Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *J. Physiol.* 557, 175–190. doi: 10.1113/jphysiol.2003.055772

Bindman, L. J., Lippold, O. C., and Redfearn, J. W. (1964). The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *J. Physiol.* 172, 369–382.

Carrey, N. J., Macmaster, F. P., Gaudet, L., and Schmidt, M. H. (2007). Striatal creatine and glutamate/glutamine in attention-deficit/hyperactivity disorder. *J. Child Adolesc. Psychopharmacol.* 17, 11–17. doi: 10.1089/cap.2006.0008

Clark, V. P., Coffman, B. A., Trumbo, M. C., and Gasparovic, C. (2011). Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: a (1)H magnetic resonance spectroscopy study. *Neurosci. Lett.* 500, 67–71. doi: 10.1016/j.neulet.2011.05.244

Cohen Kadosh, R. (2013). Using transcranial electrical stimulation to enhance cognitive functions in the typical and atypical brain. *Transl. Neurosci.* 4, 20–33. doi: 10.2478/s13380-013-0104-7

David, C. N., Rapoport, J. L., and Gogtay, N. (2013). Treatments in context: transcranial direct current brain stimulation as a potential treatment in pediatric psychosis. *Expert Rev. Neurother.* 13, 447–458. doi: 10.1586/ern.13.29

Edden, R. A., Crocetti, D., Zhu, H., Gilbert, D. L., and Mostofsky, S. H. (2012). Reduced GABA concentration in attention-deficit/hyperactivity disorder. *Arch. Gen. Psychiatry* 69, 750–753. doi: 10.1001/archgenpsychiatry.2011.2280

Eichler, S. A., and Meier, J. C. (2008). E-I balance and human diseases - from molecules to networking. *Front. Mol. Neurosci.* 1:2. doi: 10.3389/neuro.02.002.2008

Faden, A. I., Demediuk, P., Panter, S. S., and Vink, R. (1989). The role of excitatory amino acids and NMDA receptors in traumatic brain injury. *Science* 244, 798–800. doi: 10.1126/science.2567056

Floyer-Lea, A., Wylezinska, M., Kincses, T., and Matthews, P. M. (2006). Rapid modulation of GABA concentration in human sensorimotor cortex during motor learning. *J. Neurophysiol.* 95, 1639–1644. doi: 10.1152/jn.00346.2005

Fregni, F., Boggio, P. S., Santos, M. C., Lima, M., Vieira, A. L., Rigonatti, S. P., et al. (2006). Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. *Mov. Disord.* 21, 1693–1702. doi: 10.1002/mds.21012

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., et al. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron* 66, 198–204. doi: 10.1016/j.neuron.2010.03.035

Frohlich, F., and McCormick, D. A. (2010). Endogenous electric fields may guide neocortical network activity. *Neuron* 67, 129–143. doi: 10.1016/j.neuron.2010.06.005

Goto, N., Yoshimura, R., Moriya, J., Kakeda, S., Ueda, N., Ikenouchi-Sugita, A., et al. (2009). Reduction of brain gamma-aminobutyric acid (GABA) concentrations in early-stage schizophrenia patients: 3T Proton MRS study. *Schizophr. Res.* 112, 192–193. doi: 10.1016/j.schres.2009.04.026

Haider, B., Duque, A., Hasenstaub, A. R., and McCormick, D. A. (2006). Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. *J. Neurosci.* 26, 4535–4545. doi: 10.1523/jneurosci.5297-05.2006

Harris, R. E., and Clauw, D. J. (2012). Imaging central neurochemical alterations in chronic pain with proton magnetic resonance spectroscopy. *Neurosci. Lett.* 520, 192–196. doi: 10.1016/j.neulet.2012.03.042

Hess, G., and Donoghue, J. P. (1994). Long-term potentiation of horizontal connections provides a mechanism to reorganize cortical motor maps. *J. Neurophysiol.* 71, 2543–2547.

Jacobs, K. M., and Donoghue, J. P. (1991). Reshaping the cortical motor map by unmasking latent intracortical connections. *Science* 251, 944–947. doi: 10.2307/2874910

Jacobson, L., Koslowsky, M., and Lavidor, M. (2012). tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Exp. Brain Res.* 216, 1–10. doi: 10.1007/s00221-011-2891-9

Jocham, G., Hunt, L. T., Near, J., and Behrens, T. E. (2012). A mechanism for value-guided choice based on the excitation-inhibition balance in prefrontal cortex. *Nat. Neurosci.* 15, 960–961. doi: 10.1038/nn.3140

Kabakov, A. Y., Muller, P. A., Pascual-Leone, A., Jensen, F. E., and Rotenberg, A. (2012). Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. *J. Neurophysiol.* 107, 1881–1889. doi: 10.1152/jn.00715.2011

Khedr, E. M., Shawky, O. A., El-Hammady, D. H., Rothwell, J. C., Darwish, E. S., Mostafa, O. M., et al. (2013). Effect of anodal versus cathodal transcranial direct current stimulation on stroke rehabilitation: a pilot randomized controlled trial. *Neurorehabil. Neural Repair* 27, 592–601. doi: 10.1177/1545968313484808

Krause, B., and Cohen Kadosh, R. (2013). Can transcranial electrical stimulation improve learning difficulties in atypical brain development? A future possibility for cognitive training. *Dev. Cogn. Neurosci.* doi: 10.1016/j.dcn.2013.04.001. [Epub ahead of print].

Kubas, B., Kulak, W., Sobaniec, W., Tarasow, E., Lebkowska, U., and Walecki, J. (2012). Metabolite alterations in autistic children: a 1H MR spectroscopy study. *Adv. Med. Sci.* 57, 152–156. doi: 10.2478/v10039-012-0014-x

Kuo, M.-F., and Nitsche, M. A. (2012). Effects of transcranial electrical stimulation on cognition. *Clin. EEG Neurosci.* 43, 192–199. doi: 10.1177/1550059412444975

Long, Z., Medlock, C., Dzemidzic, M., Shin, Y. W., Goddard, A. W., and Dydak, U. (2013). Decreased GABA levels in anterior cingulate cortex/medial prefrontal cortex in panic disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 44, 131–135. doi: 10.1016/j.pnpbp.2013.01.020

Marquez-Ruiz, J., Leal-Campanario, R., Sanchez-Campusano, R., Molaee-Ardekani, B., Wendling, F., Miranda, P. C., et al. (2012). Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. *Proc. Natl. Acad. Sci. U S A* 109, 6710–6715. doi: 10.1073/pnas.1121147109

McCormick, D. A. (1992). Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Prog. Neurobiol.* 39, 337–388. doi: 10.1016/0301-0082(92)90012-4

Molaee-Ardekani, B., Marquez-Ruiz, J., Merlet, I., Leal-Campanario, R., Gruart, A., Sanchez-Campusano, R., et al. (2013). Effects of transcranial Direct Current Stimulation (tDCS) on cortical activity: a computational modeling study. *Brain Stimul.* 6, 25–39. doi: 10.1016/j.brs.2011.12.006

Moreno-Duarte, I., Morse, L., Alam, M., Bikson, M., Zafonte, R., and Fregni, F. (2013). Targeted therapies using electrical and magnetic neural stimulation for the treatment of chronic pain in spinal cord injury. *Neuroimage* doi: 10.1016/j.neuroimage.2013.05.097. [Epub ahead of print].

Morgan, P. T., Pace-Schott, E. F., Mason, G. F., Forselius, E., Fasula, M., Valentine, G. W., et al. (2012). Cortical GABA levels in primary insomnia. *Sleep* 35, 807–814. doi: 10.5665/sleep.1880

Nicoll, R. A., Malenka, R. C., and Kauer, J. A. (1990). Functional comparison of neurotransmitter receptor subtypes in mammalian central nervous system. *Physiol. Rev.* 70, 513–565.

Nitsche, M. A., and Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* 57, 1899–1901. doi: 10.1212/wnl.57.10.1899

Nitsche, M. A., Nitsche, M. S., Klein, C. C., Tergau, F., Rothwell, J. C., and Paulus, W. (2003). Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clin. Neurophysiol.* 114, 600–604. doi: 10.1016/s1388-2457(02)00412-1

Polania, R., Paulus, W., and Nitsche, M. A. (2012). Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Hum. Brain Mapp.* 33, 2499–2508. doi: 10.1002/hbm.21380

Radman, T., Ramos, R. L., Brumberg, J. C., and Bikson, M. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimul.* 2, 215–228, 228.e1–3. doi: 10.1016/j.brs.2009.03.007

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2010). Low-Intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J. Neurosci.* 30, 15067–15079. doi: 10.1523/jneurosci.2059-10.2010

Rojas, D. C., Singel, D., Steinmetz, S., Hepburn, S., and Brown, M. S. (2013). Decreased left perisylvian GABA concentration in children with autism and unaffected siblings. *Neuroimage* doi: 10.1016/j.neuroimage.2013.01.045. [Epub ahead of print].

Rowland, L. M., Kontson, K., West, J., Edden, R. A., Zhu, H., Wijtenburg, S. A., et al. (2013). In vivo measurements of Glutamate, GABA, and NAAG in Schizophrenia. *Schizophr. Bull.* 39, 1096–1104. doi: 10.1093/schbul/sbs092

Rubenstein, J. L., and Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav.* 2, 255–267.

Ruffini, G., Wendling, F., Merlet, I., Molaee-Ardekani, B., Mekonnen, A., Salvador, R., et al. (2013). Transcranial current brain stimulation (tCS): models and technologies. *IEEE Trans. Neural Syst. Rehabil. Eng.* 21, 333–345. doi: 10.1109/tnsre.2012.2200046

Shu, Y., Hasenstaub, A., and McCormick, D. A. (2003). Turning on and off recurrent balanced cortical activity. *Nature* 423, 288–293. doi: 10.1038/nature01616

Song, J. J., Vanneste, S., Van De Heyning, P., and De Ridder, D. (2012). Transcranial direct current stimulation in tinnitus patients: a systemic review and meta-analysis. *ScientificWorldJournal* 2012:427941. doi: 10.1100/2012/427941

Stagg, C. J., Bachtiar, V., and Johansen-Berg, H. (2011). The role of GABA in human motor learning. *Curr. Biol.* 21, 480–484. doi: 10.1016/j.cub.2011.01.069

Stagg, C. J., Best, J. G., Stephenson, M. C., O'shea, J., Wylezinska, M., Kincses, Z. T., et al. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *J. Neurosci.* 29, 5202–5206. doi: 10.1523/JNEUROSCI.4432-08.2009

Turrigiano, G. G., and Nelson, S. B. (2000). Hebb and homeostasis in neuronal plasticity. *Curr. Opin. Neurobiol.* 10, 358–364. doi: 10.1016/s0959-4388(00)00091-x

Vicario, C. M., and Nitsche, M. A. (2013). Transcranial direct current stimulation: a remediation tool for the treatment of childhood congenital dyslexia? *Front. Hum. Neurosci.* 7:139. doi: 10.3389/fnhum.2013.00139

Weiss, M., and Lavidor, M. (2012). When less is more: evidence for a facilitative cathodal tDCS effect in attentional abilities. *J. Cogn. Neurosci.* 24, 1826–1833. doi: 10.1162/jocn_a_00248

Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O'shea, D. J., et al. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature* 477, 171–178. doi: 10.1038/nature10360

Yoon, J. H., Maddock, R. J., Rokem, A., Silver, M. A., Minzenberg, M. J., Ragland, J. D., et al. (2010). GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *J. Neurosci.* 30, 3777–3781. doi: 10.1523/jneurosci.6158-09.2010

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Tracking the neuroplastic changes associated with transcranial direct current stimulation: a push for multimodal imaging

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INTRODUCTION

The human brain operates through an intricate balance of *excitatory* and *inhibitory* processes. Transcranial direct current stimulation (tDCS) is a non-invasive technique that is generally assumed to work by increasing the level of brain activity near the anode (positive polarity), while decreasing it near the cathode (negative polarity). However, this is based in part on untested assumptions: the exact (cellular and synaptic) inhibitory or excitatory processes that are targeted preferentially using either polarity is still an open area of research. Furthermore, the relationship between electrode polarity and membrane excitability is highly contingent upon stimulation parameters (e.g., montage, intensity, cognitive task, etc.). Although neuroimaging has been utilized to verify these general effects in the brain, further development is needed to advance our understanding of the mechanisms by which tDCS produces changes across different levels of the nervous system. To date, tDCS has produced reliable changes in neurometabolite concentration using magnetic resonance spectroscopy (MRS; Rango et al., 2008; Stagg et al., 2009; Clark et al., 2011); whole-brain functional connectivity using functional magnetic resonance imaging (fMRI; Baudewig et al., 2001; Kwon et al., 2008; Polanía et al., 2011a, 2012; Peña-Gómez et al., 2012; Sehm et al., 2012, 2013; Park et al., 2013; see Turi et al., 2012 for review); and neural oscillations and event-related potentials using electroencephalography (EEG; Keeser et al., 2011; Polanía et al., 2011b; Jacobson et al., 2012) or magnetoencephalography (MEG; Venkatakrishnan et al., 2011). While each of these imaging techniques provides information at specific levels within the brain's neural architecture, from the micro-scales (e.g., neuro-metabolites) to the macro-scales (e.g., population-level neural synchronization), no study has combined more than one imaging modality with tDCS in order to track neuroplastic changes across these different scales.

In this Opinion Article, we briefly summarize the progress made on tracking tDCS-induced neuroplastic changes using single imaging modalities (specifically MRS, fMRI, and EEG). We then demonstrate the need for multimodal imaging, with the goal of establishing a more comprehensive examination of both local and global neuroplastic changes due to tDCS. Such a design would enable measurements of brain chemistry and large-scale functional connectivity within the same subject and tDCS session, thus capturing interactions of these measures that may account for significant variability in cognition and behavior.

NEUROCHEMICAL MARKERS OF NEURAL PLASTICITY

Given that anodal tDCS leads to lasting changes in behaviors related to learning and memory (Brasil-Neto, 2012; Clark et al., 2012). It is hypothesized that its effects may interact with long-term synaptic potentiation (LTP) through changes in specific neurotransmitter levels. Proton magnetic resonance spectroscopy (^{1}H-MRS) allows for accurate quantification of certain neurotransmitters within a localized region of the brain. To date, there have been few published MRS-tDCS studies where data were acquired immediately before and after tDCS. For instance, Rango et al. (2008) demonstrated that anodal stimulation over right M1 resulted in increased myoinositol concentration beneath the stimulating electrode. Given that myoinositol is linked to membrane phospholipid metabolism and is associated with the LTP second messenger system (Rango et al., 2008), this supports the hypothesis that tDCS operates in part via an LTP-like mechanism. Along these lines, the NMDA antagonist dextromethorphane has been shown to prevent lasting effects of tDCS on motor-evoked potentials (MEPs), suggesting that the mechanisms affected by tDCS may be dependent on the NMDA glutamate receptor subtype (Liebetanz et al., 2002; Nitsche et al., 2003).

Further research using ^{1}H-MRS has demonstrated an increase in Glx (combined glutamate and glutamine) and NAA (N acetyl aspartate) under the anodal electrode (located near P4), compared to the opposite hemisphere (Clark et al., 2011), further supporting the hypothesis of increased metabolism and increased glutamatergic activity interacting with LTP mechanisms. Stagg et al. (2009) found that GABAergic and glutamatergic activity was increased after anodal stimulation (over left M1) and was reduced after cathodal stimulation. Moreover, changes in GABA concentration were inversely related to the amount of motor learning. Furthermore, Fritsch et al. (2010) found that genetic polymorphisms in the gene that codes for brain-derived neurotropic factor (BDNF) mediate the neuroplastic effects of direct current stimulation: Val66Val polymorphism of the BDNF gene was found to be beneficial to motor skill learning through training in humans, while Met66Met knockin mice showed decreased effects of local felid stimulation in M1 slices in mice.

While results differ to some degree under various stimulation and MRS parameters, ^{1}H-MRS has proven to be a useful tool for the assessment of the neurochemical changes due to tDCS. Together, the observed effects of stimulation are consistent with the modulation of LTP and/or LTD mechanisms, with changes in myoinositol, Glx, GABA, NAA, and BDNF consistent with LTP-type processes.

TDCS-INDUCED CHANGES IN BRAIN DYNAMICS: LARGE-SCALE FUNCTIONAL CONNECTIVITY

Functional connectivity is a statistical measure of the relationship between multiple brain regions. This measure provides information about whole-brain information integration, and can predict individual variability in cognitive performance in both healthy controls and patients (Friston, 1994; Bullmore and Sporns, 2009). TDCS may modify the threshold for LTP and LTD within and across structurally connected brain regions that comprise a functional network (Venkatakrishnan and Sandrini, 2012). Indeed, previous studies have shown that tDCS produces alterations across widespread distributed brain networks that extend far from the area of stimulation (Lang et al., 2005; Roche et al., 2011; Polanía et al., 2012).

Co-variation of resting-state fluctuations in blood oxygen level-dependent (BOLD) fMRI have been interpreted as measures of the *intrinsic* functional connectivity within the brain (Raichle et al., 2001; Fox et al., 2005). A recent investigation of the dynamic interactions within and across intrinsic resting-state networks before and after the application of anodal tDCS over the dorsal lateral prefrontal cortex (DLPFC; cathode over contralateral supraorbital area) revealed a redistribution of activity across resting-state networks (Peña-Gómez et al., 2012). Active tDCS resulted in site-specific increases in *synchronous* activity between lateral frontal and parietal areas and *asynchronous* activity between brain regions comprising the default-mode network (i.e., medial prefrontal and medial posterior areas; Peña-Gómez et al., 2012). In related work, a graph theory analysis of resting-state fMRI data found that anodal stimulation over left M1 combined with cathodal stimulation over the contralateral frontopolar cortex resulted in a global *decrease* in the long-distance topological functional coupling of the left M1 with the rest of the brain (Polanía et al., 2011a). It was hypothesized that the local increase of spontaneous activity due to anodal stimulation over M1 may have decreased the neuronal signal-to-noise ratio and consequently decreased the synchronization with other brain regions.

Other fMRI studies have investigated network connectivity changes induced by tDCS (e.g., Polanía et al., 2012; Sehm et al., 2012, 2013; Park et al., 2013), with all of them suggesting that tDCS over important network hubs (including DLPFC and M1) both increases local spontaneous activity and modulates functional connectivity across brain regions. Thus, network-level changes associated with tDCS may allow for the characterization of neuroplastic changes at the level of whole-brain functional connectivity.

CORTICAL OSCILLATIONS AND EVENT-RELATED POTENTIALS

EEG has provided information about changes in neural oscillations associated with tDCS. For instance, Keeser et al. (2011) found that anodal stimulation over left DLPFC with the cathode over right frontopolar cortex decreased delta power and marginally increased beta power. Likewise, Jacobson et al. (2012) demonstrated a selective reduction in theta-band power following anodal stimulation over the right inferior frontal gyrus (cathodal stimulation over left orbitofrontal cortex) compared to sham.

Together, these findings are consistent with the hypothesis that anodal stimulation leads to a shift from lower to higher oscillatory frequencies (Keeser et al., 2011). Indeed, it is possible that tDCS differentially modulates cortical oscillatory frequencies, and may potentially influence mental states and behavioral performance. However, it is important to note that there is limited mechanistic evidence (from both animal and human studies) that can explain the effects of direct current stimulation on the shift from higher to lower frequency oscillations in humans. Nonetheless, Fröhlich and McCormick (2010) showed that weak constant and sine-wave electric fields enhance and entrain slow oscillations, which was hypothesized to represent dynamic feedback mechanisms that modulate and guide network-wide synchronization at different frequency bands. To this end, electric fields may have functional implications on the interplay between different cortical areas, local processing and oscillations at specific frequencies. Additionally, using a computational network model, (Reato et al., 2010) showed that incremental polarization by weak currents lead to a small increase in firing rate, with excitatory spike times broadly distributed across the theta cycle, resembling *in vivo* recordings of theta-modulated gamma activity. Altogether, EEG measures provide precise information on the timing of brain activity, allowing for a temporally-accurate account of tDCS alterations of brain dynamics, which may elucidate the mechanisms by which tDCS operates.

COMBINING MARKERS OF THE MECHANISMS AFFECTED BY tDCS

When taken together, the neuroimaging methods reviewed so far provide a complex spatiotemporal description of the functional effects of tDCS and depict changes in brain function resulting from

stimulation. However, stimulation protocols (e.g., duration, intensity, cognitive paradigm, electrode size and montage) vary across studies and therefore introduce another layer of complexity when trying to compare and interpret results from multiple studies. These parameters can have complex effects on experimental results—for instance, increasing stimulation intensity can have non-linear effects on motor evoked-potential amplitudes (Batsikadze et al., 2013). Additionally, differences in individual subject characteristics (e.g., sex, handedness, age, etc), and other factors may lead to discrepancies between studies. It is proposed that these imaging methods must be combined in a more coordinated way in order to better identify and characterize markers of neuroplasticity induced by tDCS. For instance, a combined MRS-fMRI-EEG study using the same participants and tDCS protocol could utilize measures of specific neurometabolites (e.g., Glx, GABA, BDNF and myoinositol) to be compared with network-level functional connectivity with fMRI and changes in frequency bands (e.g., delta, theta and gamma) with EEG. While still imperfect, and constrained by the limits of each method, a combination of neuroimaging methods could still provide a deeper understanding of the mechanisms by which tDCS influences brain function and behavior.

A recently published study demonstrated the feasibility of combined EEG-fMRI with transcranial magnetic stimulation (Peters et al., 2013), which suggests that such a protocol could be implemented with a tDCS unit and an added MRS sequence. Furthermore, multi-site collaborations, meta-analyses and replication studies can be fostered with standardized stimulation protocols (e.g., size of electrode sponges, duration and intensity of stimulation) and image acquisitions.

In summary, it has been shown that tDCS is well-poised as a novel intervention to alter learning and memory (Clark et al., 2012), attention (Coffman et al., 2012), and a variety of other cognitive functions in healthy and clinical populations (see Kuo et al., 2013 and Floel, 2013 for reviews). Understanding the mechanisms by which these changes occur could help to increase its effectiveness and help us to understand the neural architecture and dynamics of the human brain. For instance, increasing both the glutamatergic transmission and functional connectivity that is otherwise impaired in schizophrenia (Friston, 1998; Szulc et al., 2013) could lead to effective therapies that combine both pharmacology and stimulation (Brunelin et al., 2012) protocols. Thus, the importance of investigating potential interactions across these levels of analyses could inform future hypotheses for the most optimal cortical targets and specific methods of brain stimulation for neurological and psychiatric disorders. With continued multimodal imaging work akin to that conducted by Peters et al. (2013), we can further our understanding of the neuroplastic effects of tDCS that will ultimately translate to clinical applications, resulting in more effective and well-controlled therapeutic interventions.

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REFERENCES

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.-F., and Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J. Physiol.* 591(Pt 7), 1987–2000. doi: 10.1113/jphysiol.2012.249730

Baudewig, J., Nitsche, M. A., Paulus, W., and Frahm, J. (2001). Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. *Magn. Reson. Med.* 45, 196–201.

Brasil-Neto, J. P. (2012). Learning, memory, and transcranial direct current stimulation. *Front. Psychiatry* 3:80. doi: 10.3389/fpsyt.2012.00080

Brunelin, J., Mondino, M., Gassab, L., Haesebaert, F., Gaha, L., Suaud-Chagny, M.-F., et al. (2012). Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *Am. J. Psychiatry* 169, 719–724. doi: 10.1176/appi.ajp.2012.11071091

Bullmore, E., and Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat. Rev. Neurosci.* 10, 186–198. doi: 10.1038/nrn2575

Clark, V. P., Coffman, B. A., Mayer, A. R., Weisend, M. P., Lane, T. D. R., Calhoun, V. D., et al. (2012). TDCS guided using fMRI significantly accelerates learning to identify concealed objects. *Neuroimage* 59, 117–128. doi: 10.1016/j.neuroimage.2010.11.036

Clark, V. P., Coffman, B. A., Trumbo, M. C., and Gasparovic, C. (2011). Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: a ^{1}H magnetic resonance spectroscopy study. *Neurosci. Lett.* 500, 67–71. doi: 10.1016/j.neulet.2011.05.244

Coffman, B. A., Trumbo, M. C., and Clark, V. P. (2012). Enhancement of object detection with transcranial direct current stimulation is associated with increased attention. *BMC Neurosci.* 13:108. doi: 10.1186/1471-2202-13-108

Floel, A. (2013). tDCS-enhanced motor and cognitive function in neurological diseases. *Neuroimage.* doi: 10.1016/j.neuroimage.2013.05.098. [Epub ahead of print].

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., and Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc. Natl. Acad. Sci. U.S.A.* 102, 9673–9678. doi: 10.1073/pnas.0504136102

Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: a synthesis. *Hum. Brain Mapp.* 2, 56–78. doi: 10.1002/hbm.460020107

Friston, K. J. (1998). The disconnection hypothesis. *Schizophr. Res.* 30, 115–125. doi: 10.1016/S0920-9964(97)00140-0

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., et al. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron* 66, 198–204. doi: 10.1016/j.neuron.2010.03.035

Fröhlich, F., and McCormick, D. A. (2010). Endogenous electric fields may guide neocortical network activity. *Neuron* 67, 129–143. doi: 10.1016/j.neuron.2010.06.005

Jacobson, L., Ezra, A., Berger, U., and Lavidor, M. (2012). Modulating oscillatory brain activity correlates of behavioral inhibition using transcranial direct current stimulation. *Clin. Neurophysiol.* 123, 979–984. doi: 10.1016/j.clinph.2011.09.016

Keeser, D., Padberg, F., Reisinger, E., Pogarell, O., Kirsch, V., Palm, U., et al. (2011). Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study. *Neuroimage* 55, 644–657. doi: 10.1016/j.neuroimage.2010.12.004

Kuo, M. F., Paulus, W., and Nitsche, M. A. (2013). Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage.* doi: 10.1016/j.neuroimage.2013.05.117. [Epub ahead of print].

Kwon, Y. H., Ko, M. H., Ahn, S. H., Kim, Y., Song, J. C., Lee, C., et al. (2008). Primary motor cortex activation by transcranial direct current stimulation in the human brain. *Neurosci. Lett.* 435, 56–59. doi: 10.1016/j.neulet.2008.02.012

Lang, N., Siebner, H. R., Ward, N. S., Lee, L., Nitsche, M. A., Paulus, W., et al. (2005). How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur. J. Neurosci.* 22, 495–504. doi: 10.1111/j.1460-9568.2005.04233.x

Liebetanz, D., Nitsche, M. A., Tergau, F., and Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain* 125, 2238–2247. doi: 10.1093/brain/awf238

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., et al. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J. Physiol.* 553, 293–301. doi: 10.1113/jphysiol.2003.049916

Park, C.-H., Chang, W. H., Park, J.-Y., Shin, Y.-I., Kim, S. T., and Kim, Y.-H. (2013). Transcranial direct current stimulation increases resting state interhemispheric connectivity. *Neurosci. Lett.* 539, 7–10. doi: 10.1016/j.neulet.2013.01.047

Peña-Gómez, C., Sala-Lonch, R., Junqué, C., Clemente, I. C., Vidal, D., Bargalló, N., et al. (2012). Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. *Brain Stimul.* 5, 252–263. doi: 10.1016/j.brs.2011.08.006

Peters, J. C., Reithler, J., Schuhmann, T., Graaf, T. D., Uludağ, K., Goebel, R., et al. (2013). On the feasibility of concurrent human TMS-EEG-fMRI measurements. *J. Neurophysiol.* 109, 1214–1227. doi: 10.1152/jn.00071.2012

Polanía, R., Paulus, W., Antal, A., and Nitsche, M. A. (2011a). Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. *Neuroimage* 54, 2287–2296. doi: 10.1016/j.neuroimage.2010.09.085

Polanía, R., Nitsche, M. A., and Paulus, W. (2011b). Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. *Hum. Brain Mapp.* 32, 1236–1249. doi: 10.1002/hbm.21104

Polanía, R., Paulus, W., and Nitsche, M. A. (2012). Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Hum. Brain Mapp.* 33, 2499–2508. doi: 10.1002/hbm.21380

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., and Shulman, G. L. (2001). A default mode of brain function. *Proc. Natl. Acad. Sci. U.S.A.* 98, 676–682. doi: 10.1073/pnas.98.2.676

Rango, M., Cogiamanian, F., Marceglia, S., Barberis, B., Arighi, A., Biondetti, P., et al. (2008). Myoinositol content in the human brain is modified by transcranial direct current stimulation in a matter of minutes: a 1H-MRS study. *Magn. Reson. Med.* 60, 782–789. doi: 10.1002/mrm.21709

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2010). Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J. Neurosci.* 30, 15067–15079. doi: 10.1523/JNEUROSCI.2059-10.2010

Roche, N., Lackmy, A., Achache, V., Bussel, B., and Katz, R. (2011). Effects of anodal tDCS on lumbar propriospinal system in healthy subjects. *Clin. Neurophysiol.* 589, 2813–2826.

Sehm, B., Kipping, J., Schäfer, A., Villringer, A., and Ragert, P. (2013). A Comparison between uni- and bilateral tDCS effects on functional connectivity of the human motor cortex. *Front. Hum. Neurosci.* 7:183. doi: 10.3389/fnhum.2013.00183

Sehm, B., Schäfer, A., Kipping, J., Margulies, D., Conde, V., Taubert, M., et al. (2012). Dynamic modulation of intrinsic functional connectivity by transcranial direct current stimulation. *J. Neurophysiol.* 108, 3253–3263. doi: 10.1152/jn.00606.2012

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., et al. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *J. Neurosci.* 29, 5202–5206. doi: 10.1523/JNEUROSCI.4432-08.2009

Szulc, A., Galinska-Skok, B., Waszkiewicz, N., Bibulowicz, D., Konarzewska, B., and Tarasow, E. (2013). Proton magnetic resonance spectroscopy changes after antipsychotic treatment. *Curr. Med. Chem.* 20, 414–427.

Turi, Z., Paulus, W., and Antal, A. (2012). Functional neuroimaging and transcranial electrical stimulation. *Clin. EEG Neurosci.* 43, 200–208. doi: 10.1177/1550059412444978

Venkatakrishnan, A., Contreras-Vidal, J. L., Sandrini, M., and Cohen, L. G. (2011). Independent component analysis of resting brain activity reveals transient modulation of local cortical processing by transcranial direct current stimulation. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2011, 8102–8105.

Venkatakrishnan, A., and Sandrini, M. (2012). Combining transcranial direct current stimulation and neuroimaging: novel insights in understanding neuroplasticity. *J. Neurophysiol.* 107, 1–4. doi: 10.1152/jn.00557.2011

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Modulation of cortical-subcortical networks in Parkinson's disease by applied field effects

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Studies suggest that endogenous field effects may play a role in neuronal oscillations and communication. Non-invasive transcranial electrical stimulation with low-intensity currents can also have direct effects on the underlying cortex as well as distant network effects. While Parkinson's disease (PD) is amenable to invasive neuromodulation in the basal ganglia by deep brain stimulation (DBS), techniques of non-invasive neuromodulation like transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) are being investigated as possible therapies. tDCS and tACS have the potential to influence the abnormal cortical-subcortical network activity that occurs in PD through sub-threshold changes in cortical excitability or through entrainment or disruption of ongoing rhythmic cortical activity. This may allow for the targeting of specific features of the disease involving abnormal oscillatory activity, as well as the enhancement of potential cortical compensation for basal ganglia dysfunction and modulation of cortical plasticity in neurorehabilitation. However, little is currently known about how cortical stimulation will affect subcortical structures, the size of any effect, and the factors of stimulation that will influence these effects.

Keywords: Parkinson's disease, transcranial direct current stimulation, transcranial alternating current stimulation, transcranial electrical stimulation, field effects

INTRODUCTION

Are transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) potential treatment modalities for Parkinson's disease (PD)?

While the foremost treatment for PD continues to be dopaminergic medications, invasive neuromodulation through deep brain stimulation (DBS) has become a mainstay of therapy in selected patients (Okun, 2012). As in a variety of other neurological disorders (Rothwell, 2012; Schulz et al., 2013), techniques of non-invasive neuromodulation are also being investigated as possible treatment options for PD (Cantello, 2002; Fregni et al., 2005; Edwards et al., 2008; Wu et al., 2008; Lefaucheur, 2009). However, PD is relatively unique amongst these diseases in that the targeted network involves cortical-subcortical activity rather than just cortical activity. This mini-review discusses the use of non-invasive applied electrical fields in PD and considers their potential to influence cortical oscillations and modulate dysfunctional cortical-subcortical networks through the application of weak exogenous fields.

A RATIONALE FOR TRANSCRANIAL ELECTRICAL STIMULATION IN THE TREATMENT OF PARKINSON'S DISEASE

Although classically considered a disease of the basal ganglia, functional imaging and EEG studies have shown altered cortical activity in the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), and primary motor cortex (M1) in patients with PD (Priori and Lefaucheur, 2007). Moreover, synchronization of oscillatory activity in the motor cortices at specific frequencies is believed to be important in normal motor control (Joundi et al., 2012), and excessive oscillatory activity and abnormal synchronization in the beta band may play a role in the manifestation of PD symptoms (Eusebio and Brown, 2009; Shimamoto et al., 2013). Though the relationship between beta oscillations and PD remains poorly understood, it is rooted in the observations of enhanced beta frequency oscillations in the basal ganglia in PD that are correlated with clinical symptoms and improvement from dopaminergic medications, as well as a worsening of motor symptoms that can be seen by inducing beta oscillations in subthalamic nucleus (STN) using DBS (Stein and Bar-Gad, 2013). Recent studies have suggested that this activity might be cortical in origin, with hyperactivity of the STN occurring secondary to abnormal motor cortical activity transmitted via the hyperdirect pathway (Litvak et al., 2011; Crowell et al., 2012). Further, the clinical efficacy of STN DBS in PD may involve antidromic effects upon the motor cortex (Gradinaru et al., 2009), and high frequency DBS has been shown to decrease beta frequency power in the cortical origin of the hyperdirect pathway that is coherent with beta frequency activity in the STN (Whitmer et al., 2012).

Techniques of non-invasive neuromodulation such as tDCS and tACS have the potential to influence the abnormal cortical-subcortical network activity that occurs in PD (**Figure 1**). tDCS is believed to exert its primary influence on the CNS

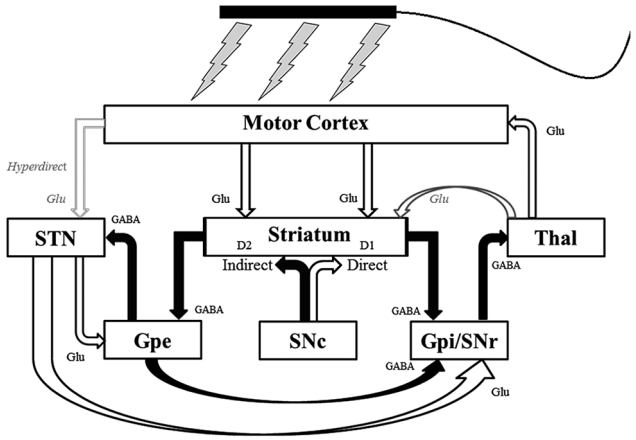

FIGURE 1 | Schematic of the pathways of the basal ganglia-thalamocortical network that non-invasive transcranial electrical stimulation could potentially influence. Unfilled arrows are excitatory connections. Filled arrows are inhibitory connections. D1 = D1 dopaminergic receptors; D2 = D2 dopaminergic receptors; GABA = γ-Aminobutyric acid (GABA)-ergic; Glu = glutaminergic; Gpe = external segment of the globus pallidus; Gpi = internal segment of the globus pallidus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; Thal = thalamus. Modified with permission from Hess et al. (2013).

through extracellular field effects upon membrane potentials (Paulus, 2011) in both a site and polarity specific manner (Zaghi et al., 2010). In general, anodal stimulation increases cortical excitability, while cathodal stimulation decreases it (Nitsche and Paulus, 2000, 2001). Longer-acting effects are likely mediated by separate polarity-specific effects on synaptic plasticity (Liebetanz et al., 2002; Fritsch et al., 2010; Stagg and Nitsche, 2011). In addition to modulating local cortical excitability, neuroimaging studies have demonstrated the ability of tDCS to influence regional cerebral blood flow (rCBF) and resting-state functional connectivity in distant but anatomically and/or functionally connected areas (Lang et al., 2005; Zaghi et al., 2010; Keeser et al., 2011). Thus tDCS could potentially ameliorate PD symptomatology through the induction of sub-threshold changes in excitability in key cortical nodes of the basal ganglia-thalamocortical pathway or produce long-term effects on synaptic plasticity. The putative mechanism of action of tACS is less clear, but may include entrainment or disruption of ongoing rhythmic cortical activity (Zaghi et al., 2010). This could make tACS an ideal modality to interfere with the abnormal oscillatory activity that occurs in the basal ganglia-thalamocortical network in PD (Brittain et al., 2013).

tDCS IN PARKINSON'S DISEASE

The study of the therapeutic potential of tDCS in PD is still largely preliminary, yet with some promising findings (Rothwell, 2012). In animal models, cathodal tDCS increased extracellular dopamine levels as measured by striatal microdialysis in healthy rats (Tanaka et al., 2013), and anodal tDCS of M1 improved motor function in the 6-hydroxydopamine rat model of PD (Li et al., 2011). In patients with PD, a single session of sham-controlled anodal tDCS of M1 yielded improvements in motor function that were different from sham stimulation (Fregni et al., 2006). One randomized, double-blind, sham-controlled trial examined the effects of tDCS in PD (Benninger et al., 2010). Subjects underwent eight sessions of tDCS ($n = 13$) or sham stimulation ($n = 12$) while on medication, with stimulation in the tDCS group alternating between the premotor/motor area and prefrontal cortex stimulation. tDCS decreased walking time (the primary outcome) compared to sham one day after stimulation, but only when tested off medications and after exclusion of an outlier in the sham group. Though motor Unified Parkinson's Disease Rating Scale (UPDRS) and reaction time changes did not differ between groups, upper extremity bradykinesia was significantly improved at all evaluations periods up to three months after stimulation. In addition to motor symptoms, a wide variety of non-motor symptoms occur in PD that are not responsive to levodopa therapy and could potentially be treated with tDCS (Wu et al., 2008). Left DLPFC anodal stimulation has been shown to improve working memory in PD patients (Boggio et al., 2006), and anodal DLPFC tDCS improved phonemic fluency and enhanced fMRI measures of functional connectivity in verbal fluency related networks (Pereira et al., 2013).

tACS IN PARKINSON'S DISEASE

As in tDCS, the literature related to PD using tACS is sparse, though intriguing. tACS at varying frequencies was shown to modulate the rate of force development and peak force in hand-grip response to a go/no-go task (Joundi et al., 2012), and tACS administered in the beta band (20 Hz) to M1 slowed voluntary movement speed in healthy subjects (Pogosyan et al., 2009). While in one study (Shill et al., 2011) tACS over the forehead and mastoids did not significantly influence off medication UPDRS scores in early PD patients, a recent study achieved a reduction in tremor amplitude of up to 53% using tACS over the contralateral M1 in patients with tremor-dominant PD (Brittain et al., 2013). In this study, tACS at tremor frequency, double tremor frequency, and sham (30 seconds of stimulation) was applied in random order to 12 patients over the transcranial magnetic simulation (TMS)-demonstrated motor hot spot for the muscles most involved with tremor. Stimulation was first allowed to drift in and out of phase with tremor to determine the most effective phase relationship in reducing tremor. In a subset of five patients, stimulation at tremor frequency was given for 30 seconds, during which tremor frequency and the phase relationship between tremor and stimulation was monitored and adjusted in real time. Resting tremor amplitude was reduced by an average of 42%. Further, stimulation did not interfere with performance on pegboard tasks, suggesting that normal motor activity would likely not be affected.

CONCLUSIONS

The application of non-invasive applied electric fields provides a potential window through which the dysfunctional subcortical-cortical networks in PD can be accessed and influenced. However, it remains largely speculative how cortical stimulation will affect subcortical structures, what the effect size will be, and the factors of stimulation that will influence these effects. Given the progressive neurodegenerative nature of the disease and the increasing

recognition of the full range of symptoms associated with it, the utility of these techniques may be more as adjuncts to other therapies (Chen, 2010). This being said, the ease of use and low cost of transcranial electrical stimulation makes its development for possible clinical uses appealing (Brunoni et al., 2013). In addition to modulating basal ganglia-thalamocortical network activity, tDCS and tACs may also be useful in promoting cortical compensation for basal ganglia network dysfunction (Fregni et al., 2006) and amplifying cortical plasticity during physical therapy and neurorehabilitation (Chen, 2010; Block and Celnik, 2012). tDCS has also already shown promise in the treatment of non-motor cognitive symptoms in PD, for which current therapies are quite limited when compared to therapies for motor symptoms (Boggio et al., 2006; Wu et al., 2008; Pereira et al., 2013).

A better understanding of the mechanisms by which non-invasive electrical stimulation affect neural networks would likely streamline the discovery of any potential therapeutic applications in PD. Yet as we have seen with DBS in PD, our mechanistic understanding can sometimes lag behind successful therapeutic implementation. Further studies will help to clarify factors such as the optimal montages, sites, and intervals of stimulation (Paulus, 2011), as well as potential interactions with levodopa and other pharmacologic agents (Chaieb et al., 2012).

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REFERENCES

Benninger, D. H., Lomarev, M., Lopez, G., Wassermann, E. M., Li, X., Considine, E., et al. (2010). Transcranial direct current stimulation for the treatment of Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 81, 1105–1111. doi: 10.1136/jnnp.2009.202556

Block, H. J., and Celnik, P. (2012). Can cerebellar transcranial direct current stimulation become a valuable neurorehabilitation intervention? *Expert Rev. Neurother.* 12, 1275–1277. doi: 10.1586/ern.12.121

Boggio, P. S., Ferrucci, R., Rigonatti, S. P., Covre, P., Nitsche, M., Pascual-Leone, A., et al. (2006). Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *J. Neurol. Sci.* 249, 31–38. doi: 10.1016/j.jns.2006.05.062

Brittain, J. S., Probert-Smith, P., Aziz, T. Z., and Brown, P. (2013). Tremor suppression by rhythmic transcranial current stimulation. *Curr. Biol.* 23, 436–440. doi: 10.1016/j.cub.2013.01.068

Brunoni, A. R., Boggio, P. S., Ferrucci, R., Priori, A., and Fregni, F. (2013). Transcranial direct current stimulation: challenges, opportunities, and impact on psychiatry and neurorehabilitation. *Front. Psychiatry* 4:19. doi: 10.3389/fpsyt.2013.00019

Cantello, R. (2002). Applications of transcranial magnetic stimulation in movement disorders. *J. Clin. Neurophysiol.* 19, 272–293.

Chaieb, L., Antal, A., Terney, D., and Paulus, W. (2012). Pharmacological modulation of the short-lasting effects of antagonistic direct current-stimulation over the human motor cortex. *Front. Psychiatry* 3:67. doi: 10.3389/fpsyt.2012.00067

Chen, R. (2010). Transcranial direct current stimulation as a treatment for Parkinson's disease—interesting, but not ready for prime time. *J. Neurol. Neurosurg. Psychiatry* 81:1061. doi: 10.1136/jnnp.2010.205112

Crowell, A. L., Ryapolova-Webb, E. S., Ostrem, J. L., Galifianakis, N. B., Shimamoto, S., Lim, D. A., et al. (2012). Oscillations in sensorimotor cortex in movement disorders: an electrocorticography study. *Brain* 135, 615–630. doi: 10.1093/brain/awr332

Edwards, M. J., Talelli, P., and Rothwell, J. C. (2008). Clinical applications of transcranial magnetic stimulation in patients with movement disorders. *Lancet Neurol.* 7, 827–840. doi: 10.1016/S1474-4422(08)70190-X

Eusebio, A., and Brown, P. (2009). Synchronisation in the beta frequency-band–the bad boy of parkinsonism or an innocent bystander? *Exp. Neurol.* 217, 1–3. doi: 10.1016/j.expneurol.2009.02.003

Fregni, F., Boggio, P. S., Santos, M. C., Lima, M., Vieira, A. L., Rigonatti, S. P., et al. (2006). Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. *Mov. Disord.* 21, 1693–1702. doi: 10.1002/mds.21012

Fregni, F., Simon, D. K., Wu, A., and Pascual-Leone, A. (2005). Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. *J. Neurol. Neurosurg. Psychiatry* 76, 1614–1623. doi: 10.1136/jnnp.2005.069849

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., et al. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron* 66, 198–204. doi: 10.1016/j.neuron.2010.03.035

Gradinaru, V., Mogri, M., Thompson, K. R., Henderson, J. M., and Deisseroth, K. (2009). Optical deconstruction of parkinsonian neural circuitry. *Science* 324, 354–359. doi: 10.1126/science.1167093

Hess, C. W., Vaillancourt, D. E., and Okun, M. S. (2013). The temporal pattern of stimulation may be important to the mechanism of deep brain stimulation. *Exp. Neurol.* 247, 296–302. doi: 10.1016/j.expneurol.2013.02.001

Joundi, R. A., Jenkinson, N., Brittain, J. S., Aziz, T. Z., and Brown, P. (2012). Driving oscillatory activity in the human cortex enhances motor performance. *Curr. Biol.* 22, 403–407. doi: 10.1016/j.cub.2012.01.024

Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., et al. (2011). Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. *J. Neurosci.* 31, 15284–15293. doi: 10.1523/JNEUROSCI.0542-11.2011

Lang, N., Siebner, H. R., Ward, N. S., Lee, L., Nitsche, M. A., Paulus, W., et al. (2005). How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur. J. Neurosci.* 22, 495–504. doi: 10.1111/j.1460-9568.2005.04233.x

Lefaucheur, J. P. (2009). Treatment of Parkinson's disease by cortical stimulation. *Expert Rev. Neurother.* 9, 1755–1771. doi: 10.1586/ern.09.132

Li, Y., Tian, X., Qian, L., Yu, X., and Jiang, W. (2011). Anodal transcranial direct current stimulation relieves the unilateral bias of a rat model of Parkinson's disease. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2011, 765–768. doi: 10.1109/IEMBS.2011.6090175

Liebetanz, D., Nitsche, M. A., Tergau, F., and Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain* 125, 2238–2247. doi: 10.1093/brain/awf238

Litvak, V., Jha, A., Eusebio, A., Oostenveld, R., Foltynie, T., Limousin, P., et al. (2011). Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. *Brain* 134, 359–374. doi: 10.1093/brain/awq332

Nitsche, M. A., and Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol.* 527 Pt 3, 633–639. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, M. A., and Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* 57, 1899–1901. doi: 10.1212/wnl.57.10.1899

Okun, M. S. (2012). Deep-brain stimulation for Parkinson's disease. *N. Engl. J. Med.* 367, 1529–1538. doi: 10.1056/NEJMct1208070

Paulus, W. (2011). Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. *Neuropsychol. Rehabil.* 21, 602–617. doi: 10.1080/09602011.2011.557292

Pereira, J. B., Junque, C., Bartres-Faz, D., Marti, M. J., Sala-Llonch, R., Compta, Y., et al. (2013). Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease. *Brain Stimul.* 6, 16–24. doi: 10.1016/j.brs.2012.01.006

Pogosyan, A., Gaynor, L. D., Eusebio, A., and Brown, P. (2009). Boosting cortical activity at beta-band frequencies slows movement in humans. *Curr. Biol.* 19, 1637–1641. doi: 10.1016/j.cub.2009.07.074

Priori, A., and Lefaucheur, J. P. (2007). Chronic epidural motor cortical

stimulation for movement disorders. *Lancet Neurol.* 6, 279–286. doi: 10.1016/s1474-4422(07)70056-x

Rothwell, J. C. (2012). Clinical applications of noninvasive electrical stimulation: problems and potential. *Clin. EEG Neurosci.* 43, 209–214. doi: 10.1177/1550059412444973

Schulz, R., Gerloff, C., and Hummel, F. C. (2013). Non-invasive brain stimulation in neurological diseases. *Neuropharmacology* 64, 579–587. doi: 10.1016/j.neuropharm.2012.05.016

Shill, H. A., Obradov, S., Katsnelson, Y., and Pizinger, R. (2011). A randomized, double-blind trial of transcranial electrostimulation in early Parkinson's disease. *Mov. Disord.* 26, 1477–1480. doi: 10.1002/mds.23591

Shimamoto, S. A., Ryapolova-Webb, E. S., Ostrem, J. L., Galifianakis, N. B., Miller, K. J., and Starr, P. A. (2013). Subthalamic nucleus neurons are synchronized to primary motor cortex local field potentials in Parkinson's disease. *J. Neurosci.* 33, 7220–7233. doi: 10.1523/jneurosci.4676-12.2013

Stagg, C. J., and Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist* 17, 37–53. doi: 10.1177/1073858410386614

Stein, E., and Bar-Gad, I. (2013). Beta oscillations in the cortico-basal ganglia loop during parkinsonism. *Exp. Neurol.* 245, 52–59. doi: 10.1016/j.expneurol.2012.07.023

Tanaka, T., Takano, Y., Tanaka, S., Hironaka, N., Kobayashi, K., Hanakawa, T., et al. (2013). Transcranial direct-current stimulation increases extracellular dopamine levels in the rat striatum. *Front. Syst. Neurosci.* 7:6. doi: 10.3389/fnsys.2013.00006

Whitmer, D., De Solages, C., Hill, B., Yu, H., Henderson, J. M., and Bronte-Stewart, H. (2012). High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. *Front. Hum. Neurosci.* 6:155. doi: 10.3389/fnhum.2012.00155

Wu, A. D., Fregni, F., Simon, D. K., Deblieck, C., and Pascual-Leone, A. (2008). Noninvasive brain stimulation for Parkinson's disease and dystonia. *Neurotherapeutics* 5, 345–361. doi: 10.1016/j.nurt.2008.02.002

Zaghi, S., Acar, M., Hultgren, B., Boggio, P. S., and Fregni, F. (2010). Noninvasive brain stimulation with low-intensity electrical currents: putative mechanisms of action for direct and alternating current stimulation. *Neuroscientist* 16, 285–307. doi: 10.1177/1073858409336227

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Translating tDCS into the field of obesity: mechanism-driven approaches

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Transcranial direct current stimulation (tDCS) is emerging as a promising technique for neuromodulation in a variety of clinical conditions. Recent neuroimaging studies suggest that modifying the activity of brain circuits involved in eating behavior could provide therapeutic benefits in obesity. One session of tDCS over the dorsolateral prefrontal cortex can induce an acute decrease in food craving, according to three small clinical trials, but the extension of these findings into the field of obesity remains unexplored. Importantly, there has been little/no interaction of our current understanding of tDCS and its mechanisms with obesity-related research. How can we start closing this gap and rationally guide the translation of tDCS into the field of obesity? In this mini-review I summarize some of the challenges and questions ahead, related to basic science and technical aspects, and suggest future directions.

Keywords: transcranial direct current stimulation, obesity, weight loss, inhibitory control, prefrontal cortex

Obesity is an unmet global medical need. Modification of lifestyle behaviors, i.e., limiting food intake and increasing physical activity, remains the cornerstone treatment in the vast majority of cases, but it is often ineffective (Fabricatore and Wadden, 2006). There is need for innovative approaches to facilitate behavioral changes leading to a successful weight loss.

Recent data from obesity neuroimaging studies point to an imbalance in prefrontal and limbic brain circuits that support cognition- and reward-related aspects of eating behavior (Carnell et al., 2012; Brooks et al., 2013; Vainik et al., 2013). Manipulating brain activity could help rebalance these circuits and translate into beneficial behavioral changes. Three small proof-of-concept studies have reported an acute decrease in food craving following one session of transcranial direct current stimulation (tDCS) aimed at enhancing the activity of the dorsolateral prefrontal cortex (Fregni et al., 2008; Goldman et al., 2011; Montenegro et al., 2012). The gap between the effects reported in these studies and the efficacy standards expected for clinical trials related to weight management (FDA, 2007) seems large at this time. *How can we start closing the gap and rationally guide the translation of tDCS into the field of obesity?*

Obesity is a heterogeneous condition that can result from a variety of behavioral and non-behavioral phenotypes, ranging from purely metabolic causes to extreme cases of compulsive overeating. In this scenario, tailored interventions may be more appropriate than a one-size-fits-all approach. However, we do not know yet what subtypes of obesity could benefit from tDCS. A reasonable starting point for exploratory trials can be the use of tDCS to facilitate changes in eating behavior, and a focus on obesity cases that share certain characteristics, e.g., high levels of eating disinhibition or binge eating.

Where in the brain should tDCS be applied in obesity? Candidate targets include brain regions supporting eating behavior at three key levels of integration: homeostasis, reward and cognition. The first challenge is that, except for cognition, these regions are subcortical, e.g., hypothalamus, insula and nucleus accumbens. It is unclear whether conventional or high-definition tDCS approaches can provide adequate reliability, sensitivity and specificity for such deep targets, which can be better reached via deep brain stimulation (DBS; Halpern et al., 2011). tDCS seems to be more suited for cortical targets, specifically lateral and dorsomedial sectors of the prefrontal cortex that contribute to cognitive control. Neuroimaging studies have shown that successful long-term weight loss maintainers have a pattern of increased activation in the lateral prefrontal cortex during satiation or in response to food cues (DelParigi et al., 2007; McCaffery et al., 2009). This activation is stronger than in control (non-obese) subjects, suggesting that lateral prefrontal hyperactivity may be a compensatory mechanism to overcome obesity in these individuals. Future studies should examine in detail the specific prefrontal-related processes that may underlie success in these subjects and, based on this information, design tDCS interventions to induce similar brain patterns in refractory obese subjects. This will likely require multiple sessions and high-intensity stimulation schemes, as long as safety is not compromised.

A mechanistic approach to the use of tDCS in obesity requires both a brain and a cognitive target, if the intention is to enhance cognitive regulation of food intake. An emerging

cognitive target in obesity is inhibitory control, a core component of executive functions that supports self-regulatory processes and goal-oriented eating behavior (Appelhans, 2009; Houben, 2011; Yokum et al., 2012; Vainik et al., 2013). Prior studies have mapped inhibitory control capacity (indexed by performance in response inhibition tasks) to a basic set of brain regions that include inferior frontal gyrus, pre-supplementary motor area, and subthalamic nucleus (Chambers et al., 2009). tDCS is well suited to reach this target according to preliminary computational models (Truong et al., 2013) and experimental data (Juan and Muggleton, 2012). Given that tDCS enhances synaptic plasticity processes related to learning (Stagg and Nitsche, 2011), the combination of tDCS with computerized training of inhibitory control is a good strategy. This can narrow down tDCS-induced plasticity effects to the cognitive process and brain circuit being targeted. A recent study supports the feasibility and efficacy of pairing tDCS with inhibitory control training (Ditye et al., 2012) and two preliminary clinical trials are underway in obesity based on this approach (Clinical trials.gov website; study numbers: NCT01632280, NCT01793766).

Most of what has been learned to date about tDCS as a technique can be extended into obesity, but there are largely unexplored factors that could modify the impact of tDCS on the brain, particularly in obese subjects. First, the potential influence of metabolic/physiological state: being in a weight-reduced or weight-stable state as well as prandial status (fasting/fed) are associated with different underlying brain activity (Tataranni et al., 1999; Rosenbaum et al., 2008). This source of variability may change the predicted effect of tDCS on obesity-related brain networks, as initial brain activation state has an important role in determining the behavioral outcome of brain stimulation (state-dependency; Silvanto et al., 2008). Additionally, weight-loss diets may influence tDCS-induced plasticity mechanisms. Intake of high-fat, low-carbohydrate, ketogenic diets (e.g., Atkins) enhances GABA-A-receptor-mediated intracortical inhibition (Cantello et al., 2007)—an outcome that might alter the dynamics of tDCS after-effects (Nitsche et al., 2004).

There are still significant gaps of knowledge in obesity pathophysiology that make decisions on tDCS study design difficult at this point. One of them is regarding the best time to apply tDCS to maximize benefits: *prior, during*, or *after* weight loss. Is it better to strengthen brain circuits in preparation for a subsequent weight loss challenge or, rather, guide brain remodeling as weight loss takes place and/or transitions into a weight maintenance phase? To be able to answer these questions there is need for fundamental research examining the time course of neurocognitive changes throughout weight loss. The contribution of brain regions will likely vary over time.

Aside from behavioral effects, there may be additional advantages for the use of tDCS in obesity via metabolism. Anodal tDCS applied over the motor cortex promotes brain energy consumption and causes systemic glucose uptake (Binkofski et al., 2011). The origin of these changes is uncertain; they could occur through a depletion of energy in the brain, the activation of hypothalamic energy sensing mechanisms, and/or via effects on the neurohormonal stress systems. More research is needed, but these findings are encouraging, because glucose intolerance and diabetes are common complications of obesity.

Last, from a more technical angle, it is necessary to define optimal tDCS parameters in obesity. Prior studies with tDCS in food craving have used empirically determined protocols (typically pad size: 35 cm^2, intensity: 2 mA, duration: 20 minutes, montage: bilateral dorsolateral prefrontal cortex). Moving forward there is need for computational models to make a rational selection of parameters and guide future refinements of tDCS protocols. As an example, we have recently examined the impact of head fat variability on current density distribution (Truong et al., 2012, 2013).

In conclusion, the translation of tDCS into the field of obesity is still at a very early stage, with many challenges and open question ahead. There is need for foundational studies that generate an adequate knowledge base and principles to guide the development of this emerging field.

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REFERENCES

Appelhans, B. M. (2009). Neurobehavioral inhibition of reward-driven feeding: implications for dieting and obesity. *Obesity (Silver Spring)* 17, 640–647. doi: 10.1038/oby.2008.638

Binkofski, F., Loebig, M., Jauch-Chara, K., Bergmann, S., Melchert, U. H., Scholand-Engler, H. G., et al. (2011). Brain energy consumption induced by electrical stimulation promotes systemic glucose uptake. *Biol. Psychiatry* 70, 690–695. doi: 10.1016/j.biopsych.2011.05.009

Brooks, S. J., Cedernaes, J., and Schioth, H. B. (2013). Increased prefrontal and parahippocampal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: a meta-analysis of fMRI studies. *PLoS One* 8:e60393. doi: 10.1371/journal.pone.0060393

Cantello, R., Varrasi, C., Tarletti, R., Cecchin, M., D'andrea, F., Veggiotti, P., et al. (2007). Ketogenic diet: electrophysiological effects on the normal human cortex. *Epilepsia* 48, 1756–1763. doi: 10.1111/j.1528-1167.2007.01156.x

Carnell, S., Gibson, C., Benson, L., Ochner, C. N., and Geliebter, A. (2012). Neuroimaging and obesity: current knowledge and future directions. *Obes. Rev.* 13, 43–56. doi: 10.1111/j.1467-789x.2011.00927.x

Chambers, C. D., Garavan, H., and Bellgrove, M. A. (2009). Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci. Biobehav. Rev.* 33, 631–646. doi: 10.1016/j.neubiorev.2008.08.016

DelParigi, A., Chen, K., Salbe, A. D., Hill, J. O., Wing, R. R., Reiman, E. M., et al. (2007). Successful dieters have increased neural activity in cortical areas involved in the control of behavior. *Int. J. Obes. (Lond)* 31, 440–448. doi: 10.1038/sj.ijo.0803431

Ditye, T., Jacobson, L., Walsh, V., and Lavidor, M. (2012). Modulating behavioral inhibition by tDCS combined with cognitive training. *Exp. Brain Res.* 219, 363–368. doi: 10.1007/s00221-012-3098-4

Fabricatore, A. N., and Wadden, T. A. (2006). Obesity. *Annu. Rev. Clin. Psychol.* 2, 357–377.

FDA (2007). Guidance for industry developing products for weight management: draft guidance. *Fed. Reg.* 72, 7441–7442.

Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F. A., Nitsche, M. A., et al. (2008). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite* 51, 34–41. doi: 10.1016/j.appet.2007.09.016

Goldman, R. L., Borckardt, J. J., Frohman, H. A., O'neil, P. M., Madan, A., Campbell, L. K., et al. (2011). Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. *Appetite* 56, 741–746. doi: 10.1016/j.appet.2011.02.013

Halpern, C. H., Torres, N., Hurtig, H. I., Wolf, J. A., Stephen, J., Oh, M. Y., et al. (2011). Expanding applications of deep brain stimulation: a potential therapeutic role in obesity and addiction management. *Acta Neurochir. (Wien)* 153, 2293–2306. doi: 10.1007/s00701-011-1166-3

Houben, K. (2011). Overcoming the urge to splurge: influencing eating behavior by manipulating inhibitory control. *J. Behav. Ther. Exp. Psychiatry* 42, 384–388. doi: 10.1016/j.jbtep.2011.02.008

Juan, C. H., and Muggleton, N. G. (2012). Brain stimulation and inhibitory control. *Brain Stimul.* 5, 63–69. doi: 10.1016/j.brs.2012.03.012

McCaffery, J. M., Haley, A. P., Sweet, L. H., Phelan, S., Raynor, H. A., Del Parigi, A., et al. (2009). Differential functional magnetic resonance imaging response to food pictures in successful weight-loss maintainers relative to normal-weight and obese controls. *Am. J. Clin. Nutr.* 90, 928–934. doi: 10.3945/ajcn.2009.27924

Montenegro, R. A., Okano, A. H., Cunha, F. A., Gurgel, J. L., Fontes, E. B., and Farinatti, P. T. (2012). Prefrontal cortex transcranial direct current stimulation associated with aerobic exercise change aspects of appetite sensation in overweight adults. *Appetite* 58, 333–338. doi: 10.1016/j.appet.2011.11.008

Nitsche, M. A., Liebetanz, D., Schlitterlau, A., Henschke, U., Fricke, K., Frommann, K., et al. (2004). GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. *Eur. J. Neurosci.* 19, 2720–2726. doi: 10.1111/j.0953-816x.2004.03398.x

Rosenbaum, M., Sy, M., Pavlovich, K., Leibel, R. L., and Hirsch, J. (2008). Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J. Clin. Invest.* 118, 2583–2591. doi: 10.1172/jci35055

Silvanto, J., Muggleton, N., and Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends Cogn. Sci.* 12, 447–454. doi: 10.1016/j.tics.2008.09.004

Stagg, C. J., and Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist* 17, 37–53. doi: 10.1177/1073858410386614

Tataranni, P. A., Gautier, J. F., Chen, K., Uecker, A., Bandy, D., Salbe, A. D., et al. (1999). Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. *Proc. Natl. Acad. Sci. U S A* 96, 4569–4574. doi: 10.1073/pnas.96.8.4569

Truong, D. Q., Magerowski, G., Blackburn, G. L., Bikson, M., and Alonso-Alonso, M. (2013). Computational modeling of transcranial direct current stimulation (tDCS) in obesity: impact of head fat and dose guidelines. *Neuroimage (Amst)* 2, 759–766. doi: 10.1016/j.nicl.2013.05.011

Truong, D. Q., Magerowski, G., Pascual-Leone, A., Alonso-Alonso, M., and Bikson, M. (2012). Finite element study of skin and fat delineation in an obese subject for transcranial direct current stimulation. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2012, 6587–6590. doi: 10.1109/embc.2012.6347504

Vainik, U., Dagher, A., Dube, L., and Fellows, L. K. (2013). Neurobehavioural correlates of body mass index and eating behaviours in adults: a systematic review. *Neurosci. Biobehav. Rev.* 37, 279–299. doi: 10.1016/j.neubiorev.2012.11.008

Yokum, S., Ng, J., and Stice, E. (2012). Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. *Int. J. Obes. (Lond)* 36, 656–664. doi: 10.1038/ijo.2011.175

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Putative physiological mechanisms underlying tDCS analgesic effects

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Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that induces changes in excitability, and activation of brain neurons and neuronal circuits. It has been observed that beyond regional effects under the electrodes, tDCS also alters activity of remote interconnected cortical and subcortical areas. This makes the tDCS stimulation technique potentially promising for modulation of pain syndromes. Indeed, utilizing specific montages, tDCS resulted in analgesic effects in experimental settings, as well as in post-operative acute pain and chronic pain syndromes. The promising evidence of tDCS-induced analgesic effects raises the challenging and complex question of potential physiologic mechanisms that underlie/mediate the accomplished pain relief. Here we present hypotheses on how the specific montages and targets for stimulation may affect the pain processing network.

Keywords: transcranial direct current stimulation (tDCS), pain, analgesia, mechanisms, neuromodulation

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique (Nitsche and Paulus, 2000) that delivers electrical current of relatively low intensity (1 or 2 miliamperes over an area of about 20 to 35 cm^2) painlessly through the skull to selected areas of the brain, and induce changes in excitability and activation of brain neurons and neuronal circuits. An important, and perhaps primary, mechanism of tDCS is a subthreshold modulation of neuronal resting membrane potential. Stimulation of several-minute duration results in a polarity-dependent induction of glutamatergic calcium-dependent neuroplasticity, which shares some aspects with long-term potentiation, and depression (Nitsche et al., 2003, 2008). The effects of tDCS on cortical excitability are polarity-dependent. Anodal tDCS enhances, while cathodal tDCS diminishes excitability, within certain parameters of stimulation duration and strength (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003). Too long, or strong stimulation, however, may have an opposite effect, resulting in diminished excitability after the anodal stimulation and enhanced excitability after the cathodal tDCS (Batsikadze et al., 2013; Monte-Silva et al., 2013). In addition, recent evidence suggests that tDCS interacts with various cerebral neurotransmitter systems, and is mediated by dopamine, acetylcholine, serotonin or GABA (Nitsche et al., 2004a,b,c, 2006, 2009; Kuo et al., 2007; Terney et al., 2008). Moreover, tDCS has been shown to facilitate changes in brain-derived neurotrophic factor (BDNF; Fritsch et al., 2010) that is a distinct marker of neuronal plasticity and notably has been associated with pain processing (Stefani et al., 2012).

The effects and outcome of tDCS depend on the area of the brain that is stimulated (e.g., Nitsche et al., 2007). Beyond regional effects under the electrodes, activity alterations of interconnected remote cortical and subcortical areas have also been described (Polania et al., 2011; DaSilva et al., 2012). This makes the tDCS stimulation technique potentially promising for modulation of pain syndromes, which include pathological alterations of activity, and excitability of a multitude of interconnected areas. Different interwoven cortico-subcortical pain-related networks, so-called Pain Matrix, cover sensory-discriminative, affective, and vegetative aspects of pain processing. The main components of the sensory-discriminative pain processing network are the spinothalamic tract, the lateral thalamus, somatosensory areas, and the posterior insula (Moisset and Bouhassira, 2007). The affective component of pain has been related to anterior insular, and cingulate cortices, as well as prefrontal areas. Vegetative, and neuroendocrine effects of pain perception are closely linked to various subcortical regions, such as amygdala, hypothalamus ventral tegmental area and others (Hsieh et al., 1995; Zaghi et al., 2009). Neuroplastic alterations of connectivity between these areas might contribute to chronification of pain.

Several specific tDCS montages have been probed, which resulted in analgesic effects: (a) excitability-enhancing (anodal) tDCS delivered over the primary motor cortex (e.g., Fregni et al., 2006a,b; Fenton et al., 2008; Kuhnl et al., 2008; Knotkova et al., 2013), typically with the anode positioned over M1 contralateral to the affected side and cathode over the ipsilateral supraorbital region in case of unilateral pain; or the anode over M1 of the

dominant hemisphere and the cathode over the supraorbital region contralateral to the anode in case of bilateral pain; (b) excitability-diminishing (cathodal) tDCS over the somatosensory cortex (Antal et al., 2008; Knotkova et al., 2009) [the cathode over S1, the anode over the contralateral supraorbital region, with the same consideration of pain localization as described above]; (c) anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC; Riberto et al., 2011; Valle et al., 2009) [the anode over DLPFC corresponding with the F3 electrode position of the 10–20 international EEG system, the cathode over the contralateral supraorbital region]; (d) combined anodal left DLPFC and cathodal tDCS of contralateral somatosensory cortex [the cathode over the gut representation area of the right S1] (Borckardt et al., 2011).

In the available studies, the assessment of analgesic effects elicited with these montages in subjects with bilateral pain has not systematically compared the pain intensity separately at each side, and thus it is unclear if the effect of the stimulation was unilateral or bilateral. However, as noted by Antal et al. (2010), there is evidence that tDCS of M1 induces widespread changes in cortical activity and can induce changes in activity of the contralateral hemisphere.

Analgesic effects have been explored in experimental settings (experimentally induced pain in healthy subjects), as well as in post-operative acute pain and chronic pain syndromes in clinical settings. The analgesic effects have been shown to be cumulative, and therefore a majority of clinical trials of tDCS encompassed the stimulation on several (usually 5, rarely 10) consecutive days. For example, anodal M1 tDCS over five consecutive days resulted in a significant decrease of pain intensity after spinal cord injury (Fregni et al., 2006a), and similar results were observed in chronic neuropathic pain due to multiple sclerosis (Mori et al., 2010), chronic pelvic pain (Fenton et al., 2009) and pain of various origin (Antal et al., 2010; Knotkova et al., 2013). Stimulation over the prefrontal cortex resulted in significant pain relief after 10 but not 5 sessions (Valle et al., 2009). Meta-analysis of analgesic effects in the existing studies is thoroughly discussed in a Cochrane systematic review by O'Connell et al. (2011). Overall, a significant heterogeneity among studies was noted, and a sub-group evaluation of tDCS applied to the motor cortex suggested superiority of active stimulation over sham (SMD −0.59, 95% CI −1.10 to −0.08).

The evidence of tDCS-induced analgesic effects raises the challenging and complex question of potential physiologic mechanisms that underlie/mediate the accomplished pain relief. Here we develop hypotheses on how the specific montages and targets for stimulation may affect the pain processing network.

MODULATION OF THE SENSORY-DISCRIMINATIVE PAIN PROCESSING

CHANGES IN THALAMIC ACTIVITY

Thalamic activity is crucial for processing and filtering of nociceptive signals on the pathways ascending to the cortical part of the pain matrix, and the thalamus also receives direct input from descending cortico-thalamic pathways originating in the primary motor cortex. Notably, anodal tDCS over M1 has been shown to increase functional coupling between ipsilateral M1 and thalamus (Polania et al., 2011) and therefore it is likely that the analgesic effects observed after the facilitatory motor cortex stimulation are at least partially attributable to modulation of thalamic activity. Indeed, changes in regional cerebral blood flow following epidural motor cortex stimulation (Peyron et al., 1995; Garcia-Larrea et al., 1999; Garcia-Larrea and Peyron, 2007) indicated that stimulation of the motor cortex may trigger rapid and phasic activation in the lateral thalamus (which receives direct input from the motor area), followed by parallel or secondary activation of medial thalamic regions, and the anterior cingulate gyrus, the insula and the upper brain stem. (Garcia-Larrea et al., 1999). Interestingly, the blood flow change in the lateral thalamus has not significantly correlated with patient's perceived pain relief and although important as a trigger of further events, the activation of the lateral thalamus is not a sufficient condition for clinical pain-relieving effects (Garcia-Larrea et al., 1999). However, neuronal inactivation in response to motor cortex stimulation was detected in thalamic *sensory* neurons, specifically in ventral posterolateral nuclei and centromedian-parafascicular thalamic complex, and the inactivating effect was particularly observed for neurons responsive to nociceptive peripheral stimulation (Pagano et al., 2012). It can be speculated that the inhibition of the sensory thalamic nuclei and the activation of the lateral (motoric) thalamic area after the motor cortex stimulation may be functionally related, the lateral thalamus receiving the input from the motor cortex and inhibiting the thalamic sensory neurons that are involved in the transmission of nociceptive signals from the periphery.

MOTOR-CORTEX-DRIVEN INHIBITION OF THE SOMATOSENSORY CORTEX

As there is a direct connection between the primary motor cortex and primary somatosensory cortex via cortico-cortical pathways in the human brain, it is possible that stimulation of the motor cortex directly inhibits the activity in the somatosensory cortex. By these means, recent work by Chiou et al. (2012) on animal models demonstrated that motor cortex stimulation blocked the transmission of somatosensory information to the primary somatosensory cortex. In the experiment, epidural motor cortex stimulation, but not stimulation outside of the motor cortex, lead to suppression of the ipsilateral somatosensory evoked potentials. However, these findings have to be interpreted with caution as the stimulation was delivered at suprathreshold level, and therefore the effects cannot be directly extrapolated to the subthreshold tDCS stimulation. Interestingly, a study of the somatosensory cortex in rats (Choi and Callaway, 2011) has shown the existence of inhibitory neurons in the somatosensory cortex that receive direct monosynaptic input not only from distant areas such as thalamus, but also from the ipsilateral motor cortex.

DIRECT INHIBITION OF THE SOMATOSENSORY CORTEX

Cathodal tDCS is thought to have a direct excitability-reducing effect on the S1 area. Since hyperexcitability within S1 in chronic pain syndromes, such as facial neuropathic pain or carpal tunnel syndrome has been clearly documented in recent neuroimaging studies, tDCS-generated reduction of this pathological excitability alteration should be beneficial. Moreover, thickening of neuronal

layers in the somatosensory cortex has been observed in chronic migraineurs (DaSilva et al., 2007), which might be a hint for structural neuroplastic alterations of the respective area due to its pain-related hyperactivity of this area. It has been suggested that repeated/long-term down-regulation of nociceptive activity in S1, which could be also induced by tDCS, may result in normalization of this maladaptive change.

MODULATION OF THE EMOTIONAL/AFFECTIVE COMPONENT OF PAIN

ACTIVATION OF THE PREFRONTAL CORTEX

Stimulation of the prefrontal cortex has been associated with a modulation of a large neuronal network related to the limbic system, including the cingulate gyrus and parahippocampal areas (Mottaghy et al., 2000; Catafu et al., 2001). The dopaminergic and serotoninergic circuits of the frontal and prefrontal cortex and related subcortical areas mediate attentional control, impulsivity, working memory, decision-making, as well as mood regulation and emotional processing. Notably, activation of the brain structures associated with emotional appraisal of pain in condition of the epidural motor cortex stimulation correlated with subjectively reported pain relief (Peyron et al., 1995; Garcia-Larrea et al., 1999) and it is thought that neuromodulation modifying emotional appraisal of pain and pain experience is directly related to clinical analgesic effects of the neuromodulatory interventions (Garcia-Larrea et al., 1999). Indeed, tDCS stimulation of the prefrontal dorsolateral cortex increased pain thresholds in healthy subjects (Boggio et al., 2008) and relieved chronic pain (Valle et al., 2009).

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Interestingly, a recent work by DosSantos et al. (2012) has shown that a single session of anodal tDCS over the motor cortex results in reduction of mu opioid receptor binding of an exogenous receptor ligand in the pain matrix, suggesting that the analgesic effect of M1-tDCS may possibly be due to a direct increase of endogenous opioid release (DosSantos et al., 2012). The authors suggest that the decreased binding of the exogenous ligand was possibly due to receptor occupancy by enhanced release of endogenous opioids. The reduction was detected in numerous cortical and subcortical structures of the pain matrix, such as nucleus accumbens, anterior cingulate cortex, insula and thalamus, and was accompanied by an increased threshold for experimentally induced cold pain. Although opioid analgesic effects are known to relate to both the emotional- as well as sensory dimension of pain, no significant changes in clinical pain levels were elicited after a single tDCS session, suggesting that the immediate opiodergic effects of a single tDCS application are subclinical, and repeated application might be necessary to get clinically meaningful results.

CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

The findings suggest that multiple physiologic mechanisms mediate the analgesic effects of tDCS, involving changes in both the perceptual processing of pain and the emotional component of pain experience. However, the mechanisms and their translation into predicable clinical outcomes are far from being fully understood. Future studies are needed to expand understanding of tDCS-induced analgesic mechanisms and to address the presented hypotheses of tDCS effects on the pain-processing network. Extrapolating from studies of the epidural motor cortex stimulation, changes of the thalamic activation after tDCS may be determined via the regional cerebral blood flow evaluation in the thalamus and related regions after a single- and multiple tDCS stimulation of the motor cortex, including explorations of the association between the thalamic activation changes and pain relief. Future studies addressing the hypothesis of the tDCS-generated analgesic effects due to motor-cortex-driven inhibition of the somatosensory cortex may utilize evaluations of the somatosensory potentials, exploring suppression of the somatosensory evoked potentials after the anodal tDCS stimulation of the ipsilateral motor cortex. Moreover, studies of tDCS combined with functional imaging (fMRI) with regard to the inhibitory (cathodal) stimulation of the somatosensory cortex as well as the anodal tDCS in both the experimentally induced- and spontaneous chronic pain may provide further insight into the tDCS effects on the pain matrix. Beyond the exploration of regional effects, functional imaging data might also be helpful to explore stimulation-dependent alterations of the pain-related cerebral network, via functional connectivity analysis. The latter approach will be also relevant to explore specific effects of different stimulation paradigms on the above-mentioned discernable components of the pain matrix.

Further, future studies are needed to systematically elucidate the impact of the stimulation parameters on the analgesic outcomes, including aspects related to stimulation intensity, strength, repetition rate and timing, as well as electrode positions and stimulation polarity, because a critical aspect of the future impact of tDCS in pain management is the optimization of the stimulation protocols with regard to specific patient populations.

REFERENCES

Antal, A., Brepohl, N., Poreisz, C., Boros, K., Csifcsak, G., and Paulus, W. (2008). Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *Clin. J. Pain* 24, 56–63. doi: 10.1097/ajp.0b013e318157233b

Antal, A., Terney, D., Kuhnl, S., and Paulus, W. (2010). Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. *J. Pain Symptom Manage.* 39, 890–903. doi: 10.1016/j.jpainsymman.2009.09.023

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., and Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J. Physiol.* 591, 1987–2000. doi: 10.1113/jphysiol.2012.249730

Boggio, P. S., Zaghi, S., Lopes, M., and Fregni, F. (2008). Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. *Eur. J. Neurol.* 15, 1124–1130. doi: 10.1111/j.1468-1331.2008.02270.x

Borckardt, J. J., Romagnuolo, J., Reeves, S. T., Madan, A., Frohman, H., Beam, W., et al. (2011). Feasibility, safety, and effectiveness of transcranial direct current stimulation for decreasing post-ERCP pain: a randomized, sham-controlled, pilot study. *Gastrointest. Endosc.* 73, 1158–1164. doi: 10.1016/j.gie.2011.01.050

Catafu, A. M., Perez, V., Gironell, A., Martin, J. C., Kulisevsky, J., Estorch, M., et al. (2001). SPECT mapping of cerebral activity changes induced

by repetitive transcranial magnetic stimulation in depressed patients. *Psychiatry Res.* 106, 151–160. doi: 10.1016/s0925-4927(01)00079-8

Chiou, R. J., Lee, H. Y., Chang, C. W., Lin, K. H., and Kuo, C. C. (2012). Epidural motor cortex stimulation suppresses somatosensory evoked potentials in the primary somatosensory cortex of the rat. *Brain Res.* 1463, 42–50. doi: 10.1016/j.brainres.2012.04.027

Choi, J., and Callaway, E. M. (2011). Monosynaptic inputs to ErbB4-expressing inhibitory neurons in mouse primary somatosensory cortex. *J. Comp. Neurol.* 519, 3402–3414. doi: 10.1002/cne.22680

DaSilva, A. F., Granziera, C., Snyder, J., and Hadjikhani, N. (2007). Thickening in the somatosensory cortex of patients with migraine. *Neurology* 69, 1990–1995. doi: 10.1212/01.wnl.0000291618.32247.2d

DaSilva, A. F., Mendonca, M. E., Zaghi, S., Lopes, M., DosSantos, M. F., Spierings, E. L., et al. (2012). tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. *Headache* 52, 1283–1295. doi: 10.1111/j.1526-4610.2012.02141.x

DosSantos, M. F., Love, T. M., Martikainen, I. K., Nascimento, T. D., Fregni, F., Cummiford, C., et al. (2012). Immediate effects of tDCS on the mu-opioid system of a chronic patient. *Front. Psychiatry* 3:93. doi: 10.3389/fpsyt.2012.00093

Fenton, B., Fanning, J., Boggio, P., and Fregni, F. (2008). A pilot efficacy trial of tDCS for the treatment of refractory chronic pelvic pain. *Brain Stimul.* 1, 260. doi: 10.1016/j.brs.2008.06.044

Fenton, B. W., Palmieri, P. A., Boggio, P., Fanning, J., and Fregni, F. (2009). A preliminary study of transcranial direct current stimulation for the treatment of refractory chronic pelvic pain. *Brain Stimul.* 2, 103–107. doi: 10.1016/j.brs.2008.09.009

Fregni, F., Boggio, P. S., Lima, M. C., Ferreira, M. J., Wagner, T., and Rigonatti, S. P. (2006a). A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* 122, 197–209. doi: 10.1016/j.pain.2006.02.023

Fregni, F., Gimenes, R., Valle, A. S., Ferreira, M. J., Rocha, R. R., Natalle, L., et al. (2006b). A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. *Arthritis Rheum.* 54, 3988–3998.

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., and Cohen, L. G. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron* 66, 198–204. doi: 10.1016/j.neuron.2010.03.035

Garcia-Larrea, L., and Peyron, R. (2007). Motor cortex stimulation for neuropathic pain: from phenomenology to mechanisms. *Neuroimage* 37, S71–S79. doi: 10.1016/j.neuroimage.2007.05.062

Garcia-Larrea, L., Peyron, R., Mentens, P., Gregoire, M. C., Lavenne, F., Le Bars, D., et al. (1999). Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. *Pain* 259–273. doi: 10.1016/s0304-3959(99)00114-1

Hsieh, J. C., Belfrage, M., Stone-Elander, M., Hansson, P., and Ingvar, M. (1995). Central representation of chronic ongoing neuropathic pain studies by positron emission tomography. *Pain* 63, 225–236. doi: 10.1016/0304-3959(95)00048-w

Knotkova, H., Homel, P., and Cruciani, R. A. (2009). Cathodal tDCS over the somatosensory cortex relieved chronic neuropathic pain in a patient with complex regional pain syndrome (CRPS/RSD). Case Report. *J. Pain Manag.* 2, 365–368. doi: 10.1016/j.jpain.2009.01.164

Knotkova, H., Leuschner, Z., Soto, E., Greenberg, A., and Cruciani, R. A. (2013). Evaluation of outcomes from Transcranial Direct Current Stimulation (tDCS) for the treatment of chronic pain. *J. Pain* 14, S64.

Kuhnl, S., Terney, D., Paulus, W., and Antal, A. (2008). The effect of daily sessions of anodal tDCS on chronic pain. *Brain Stimul.* 1, 281. doi: 10.1016/j.brs.2008.06.249

Kuo, M. F., Grosch, J., Fregni, F., Paulus, W., and Nitsche, M. A. (2007). Focusing effect of acetylcholine on neuroplasticity in the human motor cortex. *J. Neurosci.* 27, 14442–14447. doi: 10.1523/jneurosci.4104-07.2007

Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., et al. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimul.* 6, 424–432. doi: 10.1016/j.brs.2012.04.011

Moisset, X., and Bouhassira, D. (2007). Brain imaging of neuropathic pain. *Neuroimage* 37(Suppl. 1), S80–S88. doi: 10.1016/j.neuroimage.2007.03.054

Mori, F., Codeca, C., Kusayanagi, H., Monteleone, F., Buttari, F., Fiore, S., et al. (2010). Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. *J. Pain* 11, 436–442. doi: 10.1016/j.jpain.2009.08.011

Mottaghy, F. M., Krause, B. J., Kemna, L. J., Topper, R., Tellmann, L., and Beu, M. (2000). Modulation of the neuronal circuitry subserving working memory in healthy human subjects by repetitive transcranial magnetic stimulation. *Neurosci. Lett.* 280, 167–170. doi: 10.1016/s0304-3940(00)00798-9

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., et al. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain Stimul.* 1, 206–223. doi: 10.1016/j.brs.2008.06.004

Nitsche, M. A., Doemkes, S., Karakose, T., Antal, A., Liebetanz, D., Lang, N., et al. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J. Neurophysiol.* 97, 3109–3117. doi: 10.1152/jn.01312.2006

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., et al. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J. Physiol.* 553, 293–301. doi: 10.1113/jphysiol.2003.049916

Nitsche, M. A., Grundey, J., Liebetanz, D., Lang, N., Tergau, F., and Paulus, W. (2004a). Catecholaminergic consolidation of motor cortical neuroplasticity in humans. *Cereb. Cortex* 14, 1240–1245. doi: 10.1093/cercor/bhh085

Nitsche, M. A., Jaussi, W., Liebetanz, D., Lang, N., Tergau, F., and Paulus, W. (2004b). Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology* 29, 1573–1578. doi: 10.1038/sj.npp.1300517

Nitsche, M. A., Kuo, M. F., Karrasch, R., Wächter, B., Liebetanz, D., and Paulus, W. (2009). Serotonin affects transcranial direct current-induced neuroplasticity in humans. *Biol. Psychiatry* 66, 503–508. doi: 10.1055/s-0029-1238466

Nitsche, M. A., Lampe, C., Antal, A., Liebetanz, D., Lang, N., Tergau, F., et al. (2006). Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. *Eur. J. Neurosci.* 23, 1651–1657. doi: 10.1111/j.1460-9568.2006.04676.x

Nitsche, M. A., Liebetanz, D., Antal, A., Lang, N., Tergau, F., and Paulus, W. (2003). Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects. *Suppl. Clin. Neurophysiol.* 56, 255–276. doi: 10.1016/S1567-424X(09)70230-2

Nitsche, M. A., Liebetanz, D., Schlitterlau, A., Henschke, U., Fricke, K., Frommann, K., et al. (2004c). GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. *Eur. J. Neurosci.* 19, 2720–2726. doi: 10.1111/j.0953-816X.2004.03398.x

Nitsche, M. A., and Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol.* 527, 633–639. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, M. A., and Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* 57, 1899–1901. doi: 10.1212/wnl.57.10.1899

O'Connell, N. E., Wand, B. M., Marston, L., Spencer, S., and Desouza, L. H. (2011). Non-invasive brain stimulation techniques for chronic pain. A report of a Cochrane systematic review and meta-analysis. *Eur. J. Phys. Rehabil. Med.* 47, 309–326.

Pagano, R. L., Fonoff, E. T., Dale, C. S., Ballester, G., Teixeira, M. J., and Britto, L. R. (2012). Motor cortex stimulation inhibits thalamic sensory neurons and enhances activity of PAG neurons: possible pathways for antinociception. *Pain* 153, 2359–2369. doi: 10.1016/j.pain.2012.08.002

Peyron, R., Garcia-Larrea, L., Deiber, M. P., Cinotti, L., Convers, P., Sindou, M., et al. (1995). Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. *Pain* 62, 275–286. doi: 10.1016/0304-3959(94)00211-v

Polania, R., Paulus, W., and Nitsche, M. A. (2011). Modulating cortico-striatal and thalamo-cortical func-

tional connectivity with transcranial direct current stimulation. *Hum. Brain Mapp.* 33, 2499–2508. doi: 10.1002/hbm.21380

Riberto, M., Marcon Alfieri, F., Monteiro de Benedetto Pacheco, K., Dini Leite, V., Nemoto Kaihami, H., Fregni, F., et al. (2011). Efficacy of transcranial direct current stimulation coupled with a multidisciplinary rehabilitation program for the treatment of fibromyalgia. *Open Rheumatol. J.* 5, 45–50. doi: 10.2174/1874312901105010045

Stefani, L. C., Torres, I. L., de Souza, I. C., Rozisky, J. R., Fregni, F., and Caumo, W. (2012). BDNF as an effect modifier for gender effects on pain thresholds in healthy subjects. *Neurosci. Lett.* 514, 62–66. doi: 10.1016/j.neulet.2012.02.057

Terney, D., Bergmann, I., Poreisz, C., Chaieb, L., Boros, K., Nitsche, M. A., et al. (2008). Pergolide increases the efficacy of cathodal direct current stimulation to reduce the amplitude of laser-evoked potentials in humans. *J. Pain Symptom Manage.* 36, 79–91. doi: 10.1016/j.jpainsymman.2007.08.014

Valle, A., Roizenblatt, S., Botte, S., Zaghi, S., Riberto, M., Tufik, S., et al. (2009). Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial. *J. Pain Manag.* 2, 353–361.

Zaghi, S., Heine, N., and Fregni, F. (2009). Brain stimulation for the treatment of pain: a review of costs, clinical effects, and mechanisms of treatment for three different central neuromodulatory approaches. *J. Pain Manag.* 2, 339–352.

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Inhibition among olfactory receptor neurons

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Often assumed to be epiphenomena of a cell's activity, extracellular currents and resulting potential changes are increasingly recognized to influence the function of other cells in the vicinity. Experimental evidence shows that even small electric fields can modulate spike timing in neurons. Moreover, when neurons are brought close together experimentally or in pathological conditions, activity in one neuron can excite its neighbors. Inhibitory ephaptic mechanisms, however, may depend on more specialized coupling among cells. Recent studies in the *Drosophila* olfactory system have shown that excitation of a sensory neuron can inhibit its neighbor, and it was speculated that this interaction was ephaptic. Here we give an overview of ephaptic interactions that effect changes in spike timing, excitation or inhibition in diverse systems with potential relevance to human neuroscience. We examine the mechanism of the inhibitory interaction in the *Drosophila* system and that of the well-studied ephaptic inhibition of the Mauthner cell in more detail. We note that both current towards and current away from the local extracellular environment of a neuron can inhibit it, but the mechanism depends on the specific architecture of each system.

Keywords: olfaction, inhibition, ephaptic, sensillum, sensory neurons, *Drosophila*

While chemical and electrical synapses are anatomically identifiable specialized contacts that mediate interactions among cells, electric fields and currents produced by cells in their local environment may also influence the activity of their neighbors (Jefferys, 1995; Anastassiou et al., 2011). The extent to which these ephaptic interactions contribute to information processing in the human nervous system is not yet clear. Our understanding of ephaptic mechanisms has been especially informed by investigating the communication among cells in several very tractable systems, including the Mauthner cells in fish (Furukawa and Furshpan, 1963; reviewed in Zottoli and Faber, 2000; Korn and Faber, 2005; Weiss and Faber, 2010). Recently, Su et al. (2012) showed that inhibitory interactions among grouped olfactory sensory neurons in the fruit fly *Drosophila melanogaster* modulate their responses to odors, suggesting that processing of olfactory information may already begin among neurons within the sensory organs. Blocking synaptic transmission by several experimental means did not remove the inhibition, which together with other considerations led the authors to hypothesize that an ephaptic mechanism underlies the interaction. Here we present a brief overview of ephaptic interactions in diverse systems and then focus on inhibitory ephaptic mechanisms in the Mauthner cell system and in the *Drosophila* olfactory system.

The transmembrane potential (V_m) of a cell is the difference between the electrical potential inside the cell (V_i) and the potential externally (V_e), which are both measured against the same (distant) reference point, such that $V_m = V_i - V_e$. The resting V_m in many neurons is approximately −70 mV. While V_e is often assumed to be constant and assigned a value of 0 V by convention, current flow to or from the local extracellular environment near the cell can change local V_e and thereby V_m. The direction of electric current is defined arbitrarily as if only positive charges are moving, so in the case of movement of anions the current is opposite in direction to the actual anionic flow. Current flow to the local extracellular environment may hyperpolarize the membrane by making V_e more positive, while current flow away may reduce the absolute potential difference between V_i and V_e. Current flow is the result of an electric field, which is defined as the force per unit positive charge acting on a charged particle and is expressed in newtons per coulomb or volts per meter (N/C = V/m). A field can act to drive current in the extracellular space and also across the membrane and intracellularly.

Even very small fields can change the timing of spikes generated by neurons, as was shown in rat cortical pyramidal neurons where changes under 0.2 mV in V_e induced by an external oscillating field could entrain spikes (Anastassiou et al., 2011). Small electric fields, when concurrent to other suprathreshold input, also had significant effects in rat hippocampal neurons on spike timing and these could be magnified by dynamic network activity (Radman et al., 2007; Reato et al., 2010). It is becoming increasingly clear that, in addition to the firing rate of an individual neuron, its precise spike timing in an ensemble of neurons in a circuit has an important role in relaying information (De Zeeuw et al., 2011). Moreover, the degree of phase-locking of hippocampal neurons to the theta-oscillation was shown to be predictive for the strength of human memory formation (Rutishauser et al., 2010), indicating a role for spike timing in information storage. The ability of electric fields to affect spike timing suggests ephaptic interactions may indeed contribute to information processing in the brain in combination with other intercellular mechanisms.

Ephaptic effects on spike timing may also play a role in the pathological transition from synchronous discharge into epileptic seizure in several brain areas (Jefferys, 1995; Vigmond et al., 1997; McCormick and Contreras, 2001).

In addition to modulating the timing of spikes, stronger fields can bring neurons to threshold, especially under experimental or pathological conditions. Indeed, early studies showed that action potentials could be transmitted between two experimentally apposed squid giant axon fibers (Arvanitaki, 1942; Ramón, and Moore, 1978) and it was Arvanitaki (1942) who first called the zone of contact or close vicinity, where the cells can influence each other's activity, an ephapse. Clinically, the sudden sharp pains experienced by patients with trigeminal neuralgia may in part be caused by ephaptic neurotransmission between apposed denuded axonal membranes of nociceptors near the trigeminal ganglion (Oaklander, 2008). Similarly, the involuntary contractions of facial muscles in hemi-facial spasm have been attributed to ephapsis among fibers in the facial nerve when it is chronically but often subclinically injured by pressure of a blood vessel, although mechanisms such as ectopic generation of muscle discharges may also contribute (Valls-Solé, 2013). Computational approaches suggest that close apposition, as occurs among the tightly packed fascicles of unmyelinated axons of olfactory receptor neurons, also allows an action potential in one fiber to elicit action potentials in its neighbors under normal physiological conditions through ephaptic coupling (Bokil et al., 2001), so even in the absence of gap junctions between them (Blinder et al., 2003).

In contrast to excitatory coupling, ephaptic inhibition among cells may require specialized anatomical, molecular and electrical features. In the retina, for example, connexin hemichannels may be involved in an ephaptic negative feedback mechanism whereby voltage changes in horizontal cells result in sign-inverted changes in the cone cells (Klaassen et al., 2012). In the cerebellum Purkinje cells receive inhibitory input from basket cells whose axons establish chemical synapses on the Purkinje soma but also ramify around the axon initial segment of Purkinje cells forming a highly organized structure, the pinceau. Electrophysiological investigation showed that a field effect inhibition is exerted on the axon initial segment (Korn and Axelrad, 1980). Indeed there are few direct chemical synapses from basket cell axons on the Purkinje cells within the pinceau (see e.g., Somogyi and Hámori, 1976), and several GABAergic signaling components show only low expression in it (Iwakura et al., 2012). The pinceau may therefore mediate ephaptic modulation by basket cells of Purkinje activity in a similar way as the well-studied axon cap that holds the terminals of interneurons around the initial segment of the Mauthner cell.

The Mauthner (or "M−") cells are a pair of neurons in the hindbrain of teleosts and amphibians that integrate auditory, visual and tactile sensory inputs to generate an escape reflex of the animal, the C-start (Zottoli and Faber, 2000; Korn and Faber, 2005). The descending axon of a Mauthner cell crosses over to the contralateral side. Sensory inputs collected on two main dendritic branches bring the Mauthner cell to threshold and an action potential, initiated at or near the axon hillock on a proximal unmyelinated axonal segment, propagates along the axon to contract the musculature on the contralateral side of the body (**Figure 1A**). Fast inhibitory feedback and feed forward through interneurons limits activation of the Mauthner cell to a single spike and stops simultaneous excitation of the other Mauthner cell, which together results in the characteristic C-shaped whipping movement of the body that displaces the animal away from the triggering stimuli. The fast inhibition arrives at the same time as the Mauthner cell receives excitatory input, suggesting that the inhibition contributes to setting the threshold of the startle response (Weiss et al., 2008). An ephaptic mechanism underlies the fast inhibition (Furukawa and Furshpan, 1963). The axons of specific interneurons terminate near the axon hillock of the Mauthner cell in a highly organized structure, the axon cap. The axon terminals are unmyelinated and, on excitation of the interneurons, inward currents at the last node of Ranvier cause current to flow out from the axon terminals into the local environment of the Mauthner cell. High electrical resistance in the axon cap causes the current flow into it to locally increase V_e around part of the Mauthner cell. While leakage across the Mauthner membrane also causes a slight increase in V_i, simultaneous measurements of V_e and V_i have shown that the increase in V_e is much larger suggesting that the potential increase is indeed due to current from an extrinsic source. In the Mauthner system, a current from the axon terminals of interneurons to the environment around part of the Mauthner cell thereby results in a local extrinsic hyperpolarizing potential (EHP) that inhibits the cell's activity. Reciprocal ephaptic inhibition also occurs. An action potential in the Mauthner cell leads to a passive hyperpolarizing potential (PHP) in the interneurons innervating the axon cap, which has been used experimentally to identify them, because the action current leaves the Mauthner cell at its soma and dendrites and its extracellular return path brings part of the current to the excitable region of these PHP interneurons (Faber and Korn, 1989); the momentary inhibition produced by the PHP is thought to be essential for subsequently synchronizing these interneurons for feedback inhibition.

In *Drosophila*, olfactory receptor neurons in the antennae group into units called sensilla (Shanbhag et al., 1999, 2000). The response to odorants can be excitatory, inhibitory or a sequential combination of excitation and inhibition. Recently it was found that the sustained action potential response of one neuron is inhibited by a transient excitation of a neighbor within the sensillum and, based on experiments which suggested the interaction was non-synaptic, an ephaptic mechanism was proposed (Su et al., 2012). The neurons in a sensillum have different odor specificities (De Bruyne et al., 2001). Neurons express one, or sometimes more than one (Goldman et al., 2005), odor receptor. Each receptor confers specificity to a narrow or a broader range of different food- and other environmental odors (Dobritsa et al., 2003; Hallem and Carlson, 2006; Benton et al., 2009; Ai et al., 2010; Stensmyr et al., 2012) or to fly odors that may act as pheromones (Van der Goes van Naters and Carlson, 2007). Sensilla are externally visible as hairs or pegs with many pores (**Figure 1B**) through which the odor molecules from the air can enter. The hair lumen forms a compartment that holds the dendrites of the olfactory receptor neurons. As is the case in other cells that are embedded in epithelia, the neurons contact a different milieu apically than basally. The dendritic processes of the olfactory neurons sharing a sensillum are bathed together

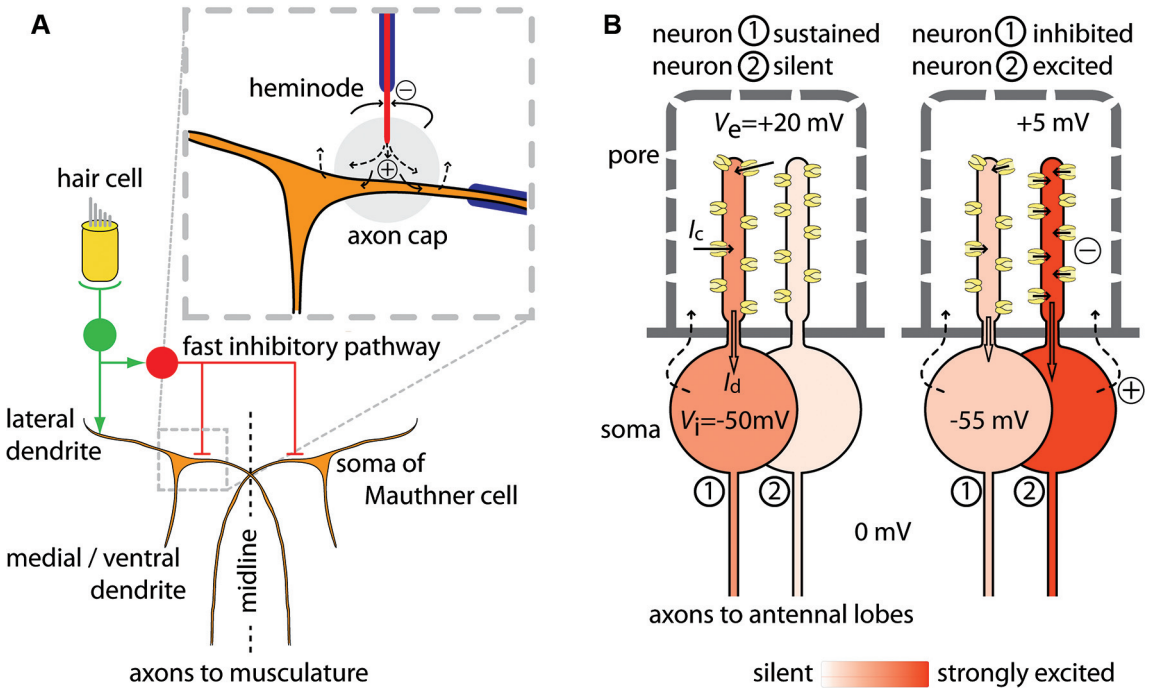

FIGURE 1 | Schematic of currents that mediate ephaptic inhibition in the Mauthner cell and in *Drosophila* olfactory receptor neurons. (**A**) A pair of Mauthner cells (in brown) project axons to the contralateral side of the body (redrawn and adapted from Korn and Faber, 2005; Weiss et al., 2008). Only the part of the circuit that mediates fast excitation and fast ephaptic inhibition from hair cell input is shown. Excitation of VIII nerves (in green) by hair cell input excites both the ipsilateral Mauthner cell and inhibitory interneurons (in red) through mixed electrical and chemical synapses. The fast inhibition by the interneurons acts on both Mauthner cells. Axons of these neurons terminate in the axon cap, a structure of high resistivity (enlarged inset, grey circle). Current influx at the heminode flows out at the unmyelinated axon terminal within the axon cap, thereby increasing the extracellular potential V_e and hyperpolarizing the zone of the Mauthner cell where impulse initiation occurs. (**B**) A *Drosophila* sensillum with two neurons. The sensillum hair has pores through which odor molecules enter. The hair lumen forms a compartment holding the dendrites of the two neurons. At left, neuron 1 shows a sustained response to odor and neuron 2 is silent. An odorant causes channels to open in neuron 1 and each open channel carries a current I_c, which sum to the dendritic current I_d (block arrow) that depolarizes the soma region. At right, neuron 1 is inhibited by the transient excitation of neuron 2. Opening of many channels in neuron 2 draws current from the extracellular dendritic space, which reduces V_e also for neuron 1. The per-channel current I_c decreases, so that I_d in neuron 1 also decreases and the soma becomes less depolarized. Illustrative values of potentials are given for V_i and V_e. The return source current (dashed arrows) follows a complex path, and also involves auxiliary cells (not shown). For both **(A)** and **(B)**: currents from sources are shown as dashed arrows; currents to sinks are shown as solid arrows; sources and sinks are defined as in Buzsáki et al. (2012).

in lymph that is high in $[K^+]$ and low in $[Na^+]$ (in moth sensilla: Kaissling and Thorson, 1980), reminiscent of the apical environment of hair cells in the inner ear, while their somata are surrounded by fluid resembling other extracellular fluids that are low in $[K^+]$ and high in $[Na^+]$. The external potential V_e around the dendrites is approximately 30–35 mV higher than the V_e of the soma. This external potential around the dendrites decreases during an odor stimulus, because channel opening allows current to flow from the lymph compartment into the dendrites. The current from the lymph into the dendrite is then conducted proximally and depolarizes the soma's membrane to generate action potentials. In this model, the rate at which the neuron generates action potentials is determined by the size of the current coming from the dendritic compartment into the soma region. The size of the inward dendritic current depends on the number of open channels, which is determined by the odor stimulus, and the amount of current per channel, which is affected by V_e. A transient decrease in V_e caused by an odor stimulus for a neighboring neuron will reduce the current through each open channel and also the dendritic current into the soma region. This decrease in the depolarizing current will then slow the generation of action potentials by the neuron. A straightforward test for this mechanism could be achieved by connecting two sensilla with a wire. In this configuration we would predict that the sustained response of a neuron in one sensillum could be inhibited by excitation of a neuron in the connected sensillum. Inhibition in this configuration would show that the interaction can be explained by current flow through the extracellular space.

In comparing one aspect of the Mauthner cell system and the *Drosophila* sensillum, we note that ephaptic inhibition of a neuron can occur both by current flow to and by current flow from its local environment. In the Mauthner cell system, current towards the axon hillock increases local V_e and thereby hyperpolarizes the excitable part of the membrane. In the *Drosophila* sensillum, by contrast, inhibition is caused by current flow out from the dendritic environment of a neuron showing a sustained response. While current flow from the local environment causes a decrease in V_e and thereby a depolarization of the dendritic membrane,

this local change in membrane potential does not affect the neuron's firing rate directly because the dendrite is presumably non-excitable. Rather, the drop in V_e causes a decrease in the per-channel current and thereby reduces the dendritic current into the soma region. This results in an inhibition of the neuron's action potential activity. The time course of inhibition appears to mirror the kinetics of excitation of its neighbor (data in Su et al., 2012). In both systems, the ephaptic interaction is dependent on compartmentalization of the extracellular space so that local current can significantly change V_e.

The function of the inhibition of a sustained response of one neuron in a *Drosophila* sensillum by transient activation of another neuron may be to increase salience of the odor transient (Su et al., 2012). Compartmentalization of groups of sensory cells, as occurs in the *Drosophila* olfactory sensillum, is found in a number of other systems including the mammalian taste bud. While the focus of much research has been on stimulus-response characteristics of individual sensory cells, it is not yet understood how the cells in a group modulate each other's output. The inhibitory interaction found in *Drosophila* suggests initial processing of information starts at the periphery, and that ephaptic interactions may play an important role.

It is becoming increasingly clear that ephaptic interactions make an essential contribution to information processing in the nervous system. The rapid kinetics by which cell function can be modulated through electric fields suggest ephaptic interactions may act especially in a short time domain to complement slower intercellular communication through chemical synapses. Elucidating the mechanisms that operate in small circuits, such as the Mauthner cell system and the *Drosophila* olfactory sensillum, will be essential to understand processing in more complex networks.

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REFERENCES

Ai, M., Min, S., Grosjean, Y., Leblanc, C., Bell, R., Benton, R., et al. (2010). Acid sensing by the *Drosophila* olfactory system. *Nature* 468, 691–695. doi: 10.1038/nature09537

Anastassiou, C. A., Perin, R., Markram, H., and Koch, C. (2011). Ephaptic coupling of cortical neurons. *Nat. Neurosci.* 14, 217–223. doi: 10.1038/nn.2727

Arvanitaki, A. (1942). Effects evoked in an axon by activity in a contiguous one. *J. Neurophysiol.* 5, 89–108.

Benton, R., Vannice, K. S., Gomez-Diaz, C., and Vosshall, L. B. (2009). Variant ionotropic glutamate receptors as chemosensory receptors in *Drosophila*. *Cell* 136, 149–162. doi: 10.1016/j.cell.2008.12.001

Blinder, K. J., Pumplin, D. W., Paul, D. L., and Keller, A. (2003). Intercellular interactions in the mammalian olfactory nerve. *J. Comp. Neurol.* 466, 230–239. doi: 10.1002/cne.10872

Bokil, H., Laaris, N., Blinder, K., Ennis, M., and Keller, A. (2001). Ephaptic interactions in the mammalian olfactory system. *J. Neurosci.* 21, RC173 (1–5).

Buzsáki, G., Anastassiou, C. A., and Koch, C. (2012). The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. *Nat. Rev. Neurosci.* 13, 407–420. doi: 10.1038/nrn3241

De Bruyne, M., Foster, K., and Carlson, J. R. (2001). Odor coding in the *Drosophila* antenna. *Neuron* 30, 537–552. doi: 10.1016/S0896-6273(01)00289-6

De Zeeuw, C. I., Hoebeek, F. E., Bosman, L. W. J., Schonewille, M., Witter, L., and Koekkoek, S. K. (2011). Spatiotemporal firing patterns in the cerebellum. *Nat. Rev. Neurosci.* 12, 327–344. doi: 10.1038/nrn3011

Dobritsa, A. A., Van der Goes van Naters, W., Warr, C. G., Steinbrecht, R. A., and Carlson, J. R. (2003). Integrating the molecular and cellular basis of odor coding in the *Drosophila* antenna. *Neuron* 37, 827–841. doi: 10.1016/s0896-6273(03)00094-1

Faber, D. S., and Korn, H. (1989). Electrical field effects: their relevance in central neural networks. *Physiol. Rev.* 69, 821–863.

Furukawa, T., and Furshpan, E. J. (1963). Two inhibitory mechanisms in the Mauthner neurons of goldfish. *J. Neurophysiol.* 26, 140–176.

Goldman, A. L., Van der Goes van Naters, W., Lessing, D., Warr, C. G., and Carlson, J. R. (2005). Coexpression of two functional odor receptors in one neuron. *Neuron* 45, 661–666. doi: 10.1016/j.neuron.2005.01.025

Hallem, E. A., and Carlson, J. R. (2006). Coding of odors by a receptor repertoire. *Cell* 125, 143–160. doi: 10.1016/j.cell.2006.01.050

Iwakura, A., Uchigashima, M., Miyazaki, T., Yamasaki, M., and Watanabe, M. (2012). Lack of molecular-anatomical evidence for GABAergic influence on axon initial segment of cerebellar Purkinje cells by the pinceau formation. *J. Neurosci.* 32, 9438–9448. doi: 10.1523/JNEUROSCI.1651-12.2012

Jefferys, J. G. R. (1995). Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. *Physiol. Rev.* 75, 689–723.

Kaissling, K.-E., and Thorson, J. (1980). "Insect olfactory sensilla: structural, chemical and electrical aspects of the functional organisation," in *Receptors for Transmitters, Hormones and Pheromones in Insects*, eds D. B. Satelle, L. M. Hall and J. G. Hildebrand (Amsterdam: Elsevier), 261–282.

Klaassen, L. J., Fahrenfort, I., and Kamermans, M. (2012). Connexin hemichannel mediated ephaptic inhibition in the retina. *Brain Res.* 1487, 25–38. doi: 10.1016/j.brainres.2012.04.059

Korn, H., and Axelrad, H. (1980). Electrical inhibition of Purkinje cells in the cerebellum of the rat. *Proc. Natl. Acad. Sci. U S A* 77, 6244–6247. doi: 10.1073/pnas.77.10.6244

Korn, H., and Faber, D. S. (2005). The Mauthner cell half a century later: a neurobiological model for decision-making? *Neuron* 47, 13–28. doi: 10.1016/j.neuron.2005.05.019

McCormick, D. A., and Contreras, D. (2001). On the cellular and network bases of epileptic seizures. *Annu. Rev. Physiol.* 63, 815–846. doi: 10.1146/annurev.physiol.63.1.815

Oaklander, A. L. (2008). Mechanisms of pain and itch caused by herpes zoster (shingles). *J. Pain* 9, S10–S18. doi: 10.1016/j.jpain.2007.10.003

Radman, T., Su, Y., An, J. H., Parra, L. C., and Bikson, M. (2007). Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. *J. Neurosci.* 27, 3030–3036. doi: 10.1523/JNEUROSCI.0095-07.2007

Ramón, F., and Moore, J. W. (1978). Ephaptic transmission in squid giant axons. *Am. J. Physiol.* 234, C162–C169.

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2010). Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J. Neurosci.* 30, 15067–15079. doi: 10.1523/JNEUROSCI.2059-10.2010

Rutishauser, U., Ross, I. B., Mamelak, A. N., and Schuman, E. M. (2010). Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature* 464, 903–907. doi: 10.1038/nature08860

Shanbhag, S. R., Müller, B., and Steinbrecht, A. (1999). Atlas of olfactory organs of *Drosophila melanogaster*. 1. Types, external organization, innervation and distribution of olfactory sensilla. *Int. J. Insect Morphol.* 28, 377–397. doi: 10.1016/S0020-7322(99)00039-2

Shanbhag, S. R., Müller, B., and Steinbrecht, A. (2000). Atlas of olfactory organs of *Drosophila melanogaster*. 2. Internal organization and cellular architecture of olfactory sensilla. *Arthropod Struct. Dev.* 29, 211–229. doi: 10.1016/S1467-8039(00)00028-1

Somogyi, P., and Hámori, J. (1976). A quantitative electron microscopic study of the Purkinje cell axon initial segment. *Neuroscience* 1, 361–365. doi: 10.1016/0306-4522(76)90127-5

Stensmyr, M. C., Dweck, H. K., Farhan, A., Ibba, I., Strutz, A., Mukunda, L., et al. (2012). A conserved dedicated olfactory circuit for detecting harmful microbes in *Drosophila*. *Cell* 151, 1345–1357. doi: 10.1016/j.cell.2012.09.046

Su, C. Y., Menuz, K., Reisert, J., and Carlson, J. R. (2012). Non-synaptic inhibition between grouped neurons in an olfactory circuit. *Nature* 492, 66–71. doi: 10.1038/nature11712

Valls-Solé, J. (2013). "Facial nerve palsy and hemifacial spasm," in *Handbook of Clinical Neurology, Vol. 115 (3rd series), Peripheral Nerve Disorders*, eds G. Said and C. Krarup (Amsterdam: Elsevier), 367–380.

Van der Goes van Naters, W., and Carlson, J. R. (2007). Receptors and neurons for fly odors in *Drosophila*. *Curr. Biol.* 17, 606–612. doi: 10.1016/j.cub.2007.02.043

Vigmond, E. J., Perez Velazquez, J. L., Valiante, T. A., Bardakjian, B. L., and Carlen, P. L. (1997). Mechanisms of electrical coupling between pyramidal cells. *J. Neurophysiol.* 78, 3107–3116.

Weiss, S. A., and Faber, D. S. (2010). Field effects in the CNS play functional roles. *Front. Neural Circuits* 4:15. doi: 10.3389/fncir.2010.00015

Weiss, S. A., Preuss, T., and Faber, D. S. (2008). A role of electrical inhibition in sensorimotor integration. *Proc. Natl. Acad. Sci. U S A* 105, 18047–18052. doi: 10.1073/pnas.0806145105

Zottoli, S. J., and Faber, D. S. (2000). The Mauthner cell: what has it taught us? *Neuroscientist* 6, 26–38. doi: 10.1177/107385840000600111

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Ephaptic communication in the vertebrate retina

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In the vertebrate retina, cones project to the horizontal cells (HCs) and bipolar cells (BCs). The communication between cones and HCs uses both chemical and ephaptic mechanisms. Cones release glutamate in a Ca^{2+}-dependent manner, while HCs feed back to cones via an ephaptic mechanism. Hyperpolarization of HCs leads to an increased current through connexin hemichannels located on the tips of HC dendrites invaginating the cone synaptic terminals. Due to the high resistance of the extracellular synaptic space, this current makes the synaptic cleft slightly negative. The result is that the Ca^{2+}-channels in the cone presynaptic membrane experience a slightly depolarized membrane potential and therefore more glutamate is released. This ephaptic mechanism forms a very fast and noise free negative feedback pathway. These characteristics are crucial, since the retina has to perform well in demanding conditions such as low light levels. In this mini-review we will discuss the critical components of such an ephaptic mechanism. Furthermore, we will address the question whether such communication appears in other systems as well and indicate some fundamental features to look for when attempting to identify an ephaptic mechanism.

Keywords: ephaptic communication, vertebrate retina, cones, horizontal cells, inhibition

Neuronal activity leads to both intracellular and extracellular potential changes. In this way the synchronized activity of multiple neurons may generate local field potentials (LFPs). LFPs are discussed extensively in the other contributions to the special issue. Here we will discuss a special form of neuronal communication that operates by modulating the extracellular potential: ephaptic communication.

Ephaptic communication differs from LFPs in that it is highly localized and requires a specialized structure, an ephapse. The term ephapse is derived from the Greek verb *ephaptein* which means *to closely touch*. An ephapse is a specialized structure that generates a high extracellular resistance, such that current flowing through the extracellular space produces a potential difference. This potential difference modifies the activity of voltage gated channels localized within the ephapse, leading to, for instance, changes in spike threshold or modulation of synaptic transmission. In principle, any synaptic structure should generate an ephaptic interaction. However, in most synapses the extracellular resistance of the synaptic cleft is not large enough to generate a significant effect (**Figure 1A**).

The retina's first synapse is a good example of a synapse where significant ephaptic interactions occur (**Figure 1B**). Cone photoreceptors project to horizontal cells (HCs) and bipolar cells (BCs) via Ca^{2+}-dependent glutamate release. Light stimulation hyperpolarizes cones, which leads to a reduction of glutamate release. Since HCs receive input from many cones and are strongly coupled electrically, they collect and average signals over a larger area. This information is fed back to the cones negatively, generating the center-surround organization of BCs. This inhibitory pathway from HCs to cones is mediated via an ephaptic mechanism.

Two key features of this synapse are crucial for the ephaptic interaction to occur. First, a high extracellular resistance is needed, which is generated by a highly specialized synaptic structure (**Figure 1C**). The dendrites of HCs and BCs invaginate the cone photoreceptor terminal thus creating a restricted synaptic space with a relatively high resistance (**Figure 1D**, white resistor). Secondly, connexin hemichannels are key players in this ephapse (**Figure 1D**, blue resistor; Kamermans et al., 2001; Klaassen et al., 2011). Connexins are proteins that can form electrical synapses or gap junctions. However, at the tips of the HC dendrites they form hemichannels, which are non-specific channels that are open at physiological membrane potentials. A constant inward current flows through these connexin hemichannels. This current passes through the synaptic space, which has a finite resistance (**Figure 1D**, white resistor), inducing a voltage drop and making the synaptic cleft slightly negative. L-type Ca^{2+}-channels located in the presynaptic membrane of the cones (**Figure 1D**, red circle) sense this negativity as a slight depolarization of the cone membrane potential. In a voltage clamp experiment, this will become visible as a shift of the activation potential of the Ca^{2+}-current towards more negative potentials. Note that this is an apparent shift, evoked by the change in extracellular potential. Light stimulation hyperpolarizes photoreceptors, leading to a *decrease* in glutamate release, which hyperpolarizes HCs. This hyperpolarization causes the inward current through connexin hemichannels to increase, making the synaptic cleft even more negative. Consequently, the activation potential of the Ca^{2+}-

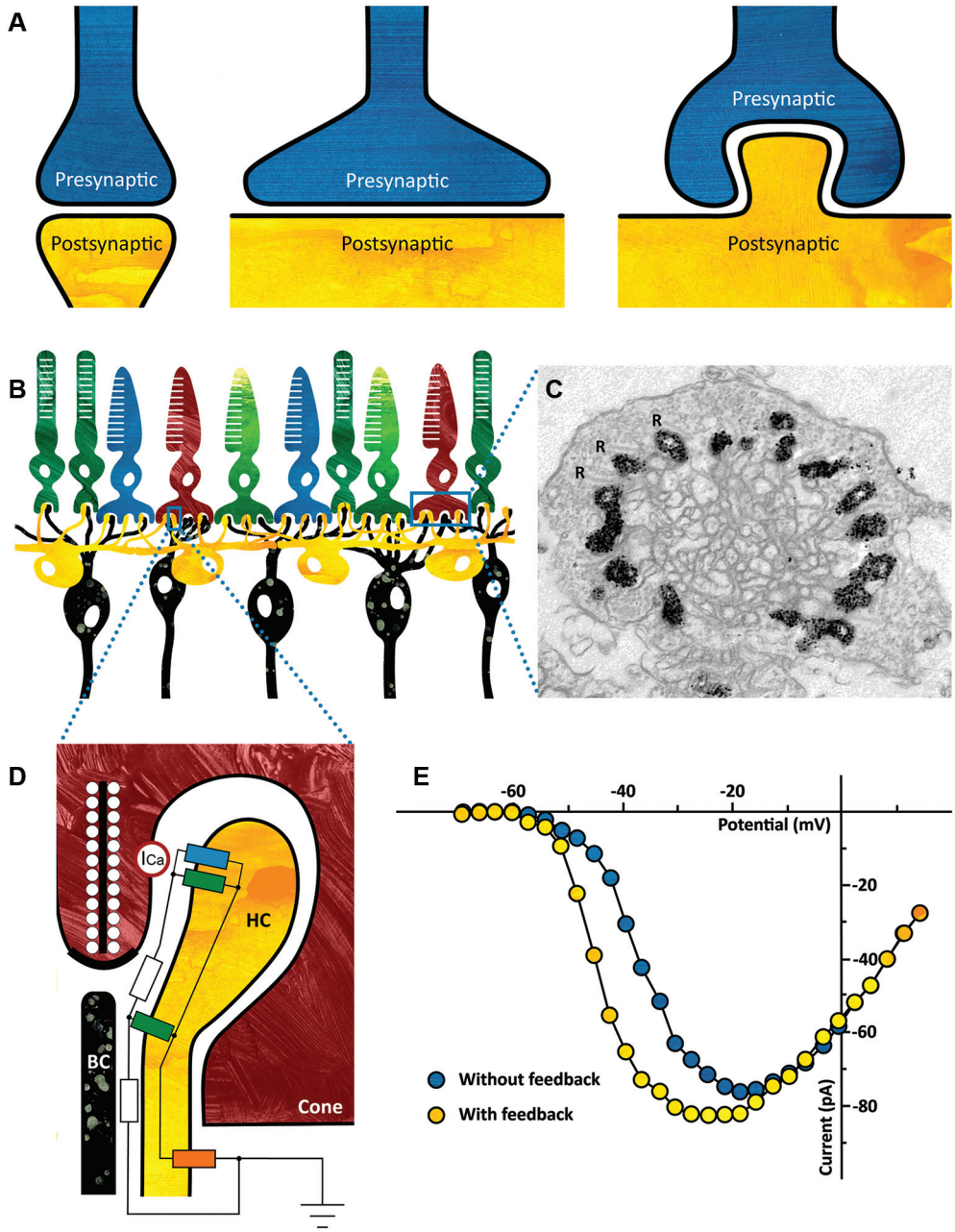

FIGURE 1 | (A) Ephaptic interactions will occur in every synapse. The strength of the ephaptic interaction will depend on the organization of the synapse. It will only become significant if the extracellular resistance is high enough. Left: synapse without significant ephaptic interaction. Middle and right: synapse with potentially significant ephaptic interactions. **(B)** Schematic drawing of the vertebrate outer retina. The photoreceptors are the light sensitive neurons in the retina (top layer). They are contacted by horizontal cells (HCs) (yellow) and bipolar cells (BCs) (black). The dendrites of both the HCs and the BCs invaginate the photoreceptor synaptic terminal. **(C)** Electron micrograph of a cone synaptic terminal. In this zebrafish HCs express Green Fluorescent Protein (GFP), which is visible as a black label in this image. Note that every ribbon is flanked by HC dendrites. R: synaptic ribbons. (Taken from: Klaassen et al., 2012) **(D)** Schematic drawing of the cone/HC synapse. In the dark, glutamate release is high and thus the glutamate receptors are activated (green resistors). A constant inward current flows through the connexin hemichannels (blue resistor) and because the resistance of the synaptic cleft is relatively high (white resistors), the synaptic space is slightly negative compared to the extrasynaptic space. When the retina receives a full field light stimulus, cones and consequently HCs hyperpolarize. This causes an increased inward current through the connexin hemichannels, resulting in an increased negativity of the synaptic cleft. The voltage sensitive Ca-channels on the cone (I_{Ca}, red circle) detect this as a slight depolarization of the membrane potential, effectively shifting the Ca-current activation potential towards more negative potentials (see Panel E). The influx of calcium increases and consequently the glutamate release. The current entering the HCs via the connexin hemichannels leaves the HCs via the potassium channel on the HC somata (orange resistor). **(E)** Feedback from HCs to cones modulates the Ca-current of cones. Ca-current of a cone in control condition (blue) and when HCs are hyperpolarized and feedback is active (yellow). (Modified from: Verweij et al., 1996).

current shifts even further, thereby *increasing* glutamate release (**Figure 1E**, yellow dots).

The ephaptic feedback mechanism has a number of very specific properties. Due to its electrical nature, feedback from HCs to cones is very fast and has no synaptic delay (Vroman et al., submitted). Conventional synaptic transmission depends on vesicular neurotransmitter release. The signal transmitted is noisy because each vesicle release-event causes a discrete postsynaptic potential change. Since ephaptic transmission does not depend on vesicles, it will hardly add noise to the input signal. These features are very well suited for the role of HCs in retinal signal processing. The HC/cone ephapse utilizes ephaptic transmission to generate the surround of BCs, which is the first step in reducing redundant visual information. This redundancy reduction only works if the feedback signal is fast. If this were not the case, the surround of BCs would lag the center response for moving stimuli, thus compromising the efficiency of redundancy reduction. The low noise characteristics of the ephaptic feedback mechanism are especially important at low light levels, when the photoreceptor responses barely exceed the noise level (Field et al., 2005; Ala-Laurila et al., 2011). Adding synaptic noise to the signal would strongly reduce the information content transmitted to BCs.

Are the key features, as we described for the HC/cone ephapse, general requirements for ephaptic communication? A high extracellular resistance is essential but can be achieved in many ways. For instance, it can be achieved by increasing the size of a synapse or by the presence of an invaginating synaptic structure (**Figure 1A**). However, the extracellular resistance can also be increased by the expression of extracellular matrix molecules such as proteoglycans (Bogdanik et al., 2008; Klaassen et al., 2012). A fundamental property of ephaptic transmission is that it depends on current flow, not on specific channel types. Current will flow through any open channel into the cell, the so-called current sink. While the current sink in the HC/cone ephapse is formed by connexin hemichannels, in other ephapses different channel types may play this role. In our example, L-type Ca^{2+}-channels convert the extracellular potential change into a cellular response, but in principle any voltage sensitive channel can play this role. Byzov and co-workers (Byzov et al., 1977; Byzov and Shura-Bura, 1986) were the first to propose an ephaptic interaction between HCs and cones. They suggested that postsynaptic glutamate receptors functioned as current sink. We have shown that, under certain conditions, glutamate receptors can indeed contribute as well (Fahrenfort et al., 2005). In addition, we have shown that pannexin 1 channels also contribute to the ephaptic interaction (Prochnow et al., 2009; Klaassen et al., 2011; Vroman et al., submitted), showing that the ephaptic feedback is mediated by a number of channel types. This large diversity of possible molecular compositions of an ephaptic mechanism might be one of the reasons why so few other ephaptic mechanisms have been described.

Is there evidence for ephaptic interactions in other synapses? For example, the mossy fibers in the hippocampus form large synapses with CA3 pyramidal cell dendrites. These synapses potentially have a high enough resistance to form an ephapse. This ephaptic interaction would depend on the current flowing through glutamate receptors. Activation of presynaptic Ca^{2+}-channels leads to glutamate release, which opens glutamate-gated channels in the postsynaptic membrane. The current through these channels makes the potential in the synaptic cleft slightly negative, leading to a depolarization of the presynaptic membrane and a further increase of glutamate release. This positive feedback loop enhances the output of the mossy fiber (Berretta et al., 2000; Kasyanov et al., 2000; Savtchenko, 2007). Interestingly, pannexin 1 channels have also been shown to function postsynaptically from pyramidal neurons (Thompson et al., 2008). Based on morphological arguments, an ephaptic mechanism has also been proposed for synaptic transmission between type I hair cells in the cochlea and the afferent calyx fiber (Hamilton, 1968; Gulley and Bagger-Sjoback, 1979; Yamashita and Ohmori, 1990; Goldberg, 1996). This synapse is also invaginating and thus creates the high resistance necessary for a functional ephapse. Recently, Su et al. (2012) presented evidence for an ephaptic interaction between insect olfactory receptor neurons, located within a sensillium with a high extracellular resistance. They showed that activation of one receptor neuron inhibited the neighboring neuron within the same sensillium, while evidence for synaptic transmission was missing.

An example of ephaptic communication outside the brain can be found in the heart. Action potential propagation between cardiac myocytes, necessary for heart muscle contraction, appears to be dependent on both gap junctional coupling and an ephaptic interaction (Sperelakis, 2002; Lin and Keener, 2013; Rhett et al., 2013). The ephaptic interaction is possible in the area surrounding the gap-junctions, because the space between membranes is narrow and the gap junctions increase the extracellular resistance. Moreover, both connexin hemichannels and sodium channels are present in the membrane to function as current sink. Interestingly, in this system sodium channels not only form the current sink, but also function as the voltage sensitive channels on the opposing cell.

These examples of ephaptic mechanisms are focused on modulation of transmission by extracellular potential differences. However, extracellular potential gradients could have additional influences on synaptic transmission as well. Sylantyev et al. (2008) have shown in hippocampal CA1 cells that the cation influx through postsynaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptors upon activation by presynaptic glutamate release affect the clearance of glutamate from the synaptic cleft. An increase in AMPA receptor density causes an increase in cation flux. Since glutamate is negatively charged and therefore experiences a force opposite to the cation flux, diffusion from the cleft is faster.

At first instance, it would seem that ephaptic communication is a rather energy intensive mechanism. A continuously open channel puts a high metabolic load on the cell. The cell needs to spend energy to maintain its ionic balance and membrane potential. On the other hand, conventional synaptic transmission is not cheap either. Neurotransmitters have to be synthesized and vesicles have to be generated and filled and require the presence of docking, fusion and recovery mechanisms. On the post-synaptic site, receptors have to be expressed and processes lowering the neurotransmitter content of the synaptic cleft, such as neurotransmitter re-uptake transporters, need to be in place.

While an ephaptic system puts a high metabolic load on the cell, it might very well be that conventional synaptic transmission is more costly.

In this mini-review we discussed ephaptic communication within a synapse. We described two main advantages for ephaptic communication: (1) it is very fast and has no synaptic delay, and (2) it has very low noise levels. In principle, such communication will occur in any synapse, but its influence will only become significant if the synapse has certain properties. The elements that are crucial for ephaptic neuronal communication are: (1) an ephapse with a large resistance to the extrasynaptic space, (2) a current sink and (3) voltage sensitive channels on the opposing membrane. Because the identity of the channels involved can be very variable, looking for convoluted or tight synaptic cleft may be a good starting point when searching for an ephapse in other systems.

REFERENCES

Ala-Laurila, P., Greschner, M., Chichilnisky, E. J., and Rieke, F. (2011). Cone photoreceptor contributions to noise and correlations in the retinal output. *Nat. Neurosci.* 14, 1309–1316. doi: 10.1038/nn.2927

Berretta, N., Rossokhin, A. V., Kasyanov, A. M., Sokolov, M. V., Cherubini, E., and Voronin, L. L. (2000). Postsynaptic hyperpolarization increases the strength of AMPA-mediated synaptic transmission at large synapses between mossy fibers and CA3 pyramidal cells. *Neuropharmacology* 39, 2288–2301. doi: 10.1016/s0028-3908(00)00076-9

Bogdanik, L., Framery, B., Frolich, A., Franco, B., Mornet, D., Bockaert, J., et al. (2008). Muscle dystroglycan organizes the postsynapse and regulates presynaptic neurotransmitter release at the Drosophila neuromuscular junction. *PLoS One* 3:e2084. doi: 10.1371/journal.pone.0002084

Byzov, A. L., Golubtzov, K. V., and Trifonov, J. A. (1977). "The model of mechanism of feedback between horizontal cells and photoreceptors in vertebrate retina," in *Vertebrate Photoreception*, eds H. B. Barlow and P. Fatt (London: Academic Press), 265–274.

Byzov, A. L., and Shura-Bura, T. M. (1986). Electrical feedback mechanism in the processing of signals in the outer plexiform layer of the retina. *Vision Res.* 26, 33–44. doi: 10.1016/0042-6989(86)90069-6

Fahrenfort, I., Klooster, J., Sjoerdsma, T., and Kamermans, M. (2005). The involvement of glutamate-gated channels in negative feedback from horizontal cells to cones. *Prog. Brain Res.* 147, 219–229. doi: 10.1016/s0079-6123(04)47017-4

Field, G. D., Sampath, A. P., and Rieke, F. (2005). Retinal processing near absolute threshold: from behavior to mechanism. *Annu. Rev. Physiol.* 67, 491–514. doi: 10.1146/annurev.physiol.67.031103.151256

Goldberg, J. M. (1996). Theoretical analysis of intercellular communication between the vestibular type I hair cell and its calyx ending. *J. Neurophysiol.* 76, 1942–1957.

Gulley, R. L., and Bagger-Sjoback, D. (1979). Freeze-fracture studies on the synapse between the type I hair cell and the calyceal terminal in the guinea-pig vestibular system. *J. Neurocytol.* 8, 591–603. doi: 10.1007/bf01208511

Hamilton, D. W. (1968). The calyceal synapse of type I vestibular hair cells. *J. Ultrastruct. Res.* 23, 98–114. doi: 10.1016/s0022-5320(68)80034-6

Kamermans, M., Fahrenfort, I., Schultz, K., Janssen-Bienhold, U., Sjoerdsma, T., and Weiler, R. (2001). Hemichannel-mediated inhibition in the outer retina. *Science* 292, 1178–1180. doi: 10.1126/science.1060101

Kasyanov, A. M., Maximov, V. V., Byzov, A. L., Berretta, N., Sokolov, M. V., Gasparini, S., et al. (2000). Differences in amplitude-voltage relations between minimal and composite mossy fibre responses of rat CA3 hippocampal neurons support the existence of intrasynaptic ephaptic feedback in large synapses. *Neuroscience* 101, 323–336. doi: 10.1016/s0306-4522(00)00366-3

Klaassen, J., Fahrenfort, I., and Kamermans, M. (2012). Connexin hemichannel mediated ephaptic inhibition in the retina. *Brain Res.* 1487, 25–38. doi: 10.1016/j.brainres.2012.04.059

Klaassen, L. J., Sun, Z., Steijaert, M. N., Bolte, P., Fahrenfort, I., Sjoerdsma, T., et al. (2011). Synaptic transmission from horizontal cells to cones is impaired by loss of connexin hemichannels. *PLoS Biol.* 9:e1001107. doi: 10.1371/journal.pbio.1001107

Lin, J., and Keener, J. P. (2013). Ephaptic coupling in cardiac myocytes. *IEEE Trans. Biomed. Eng.* 60, 576–582. doi: 10.1109/tbme.2012.2226720

Prochnow, N., Hoffmann, S., Vroman, R., Klooster, J., Bunse, S., Kamermans, M., et al. (2009). Pannexin1 in the outer retina of the zebrafish, Danio rerio. *Neuroscience* 162, 1039–1054. doi: 10.1016/j.neuroscience.2009.04.064

Rhett, J. M., Veeraraghavan, R., Poelzing, S., and Gourdie, R. G. (2013). The perinexus: sign-post on the path to a new model of cardiac conduction? *Trends Cardiovasc. Med.* 23, 222–228. doi: 10.1016/j.tcm.2012.12.005

Savtchenko, L. P. (2007). Bilateral processing in chemical synapses with electrical 'ephaptic' feedback: a theoretical model. *Math. Biosci.* 207, 113–137. doi: 10.1016/j.mbs.2006.09.016

Sperelakis, N. (2002). An electric field mechanism for transmission of excitation between myocardial cells. *Circ. Res.* 91, 985–987. doi: 10.1161/01.res.0000045656.34731.6d

Su, C. Y., Menuz, K., Reisert, J., and Carlson, J. R. (2012). Non-synaptic inhibition between grouped neurons in an olfactory circuit. *Nature* 492, 66–71. doi: 10.1038/nature11712

Sylantyev, S., Savtchenko, L. P., Niu, Y. P., Ivanov, A. I., Jensen, T. P., Kullmann, D. M., et al. (2008). Electric fields due to synaptic currents sharpen excitatory transmission. *Science* 319, 1845–1849. doi: 10.1126/science.1154330

Thompson, R. J., Jackson, M. F., Olah, M. E., Rungta, R. L., Hines, D. J., Beazely, M. A., et al. (2008). Activation of pannexin-1 hemichannels augments aberrant bursting in the hippocampus. *Science* 322, 1555–1559. doi: 10.1126/science.1165209

Verweij, J., Kamermans, M., and Spekreijse, H. (1996). Horizontal cells feed back to cones by shifting the cone calcium-current activation range. *Vision Res.* 36, 3943–3953. doi: 10.1016/s0042-6989(96)00142-3

Yamashita, M., and Ohmori, H. (1990). Synaptic responses to mechanical stimulation in calyceal and bouton type vestibular afferents studied in an isolated preparation of semicircular canal ampullae of chicken. *Exp. Brain Res.* 80, 475–488. doi: 10.1007/bf00227989

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Field effects and ictal synchronization: insights from in homine observations

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It has been well established in animal models that electrical fields generated during inter-ictal and ictal discharges are strong enough in intensity to influence action potential firing threshold and synchronization. We discuss recently published data from microelectrode array recordings of human neocortical seizures and speculate about the possible role of field effects in neuronal synchronization. We have identified two distinct seizure territories that cannot be easily distinguished by traditional EEG analysis. The ictal core exhibits synchronized neuronal burst firing, while the surrounding ictal penumbra exhibits asynchronous and relatively sparse neuronal activity. In the ictal core large amplitude rhythmic ictal discharges produce large electric fields that correspond with highly synchronous neuronal firing. In the penumbra rhythmic ictal discharges are smaller in amplitude, but large enough to influence spike timing, yet neuronal synchrony is not observed. These *in homine* observations are in accord with decades of animal studies supporting a role of field effects in neuronal synchronization during seizures, yet also highlight how field effects may be negated in the presence of strong synaptic inhibition in the penumbra.

Keywords: ephaptic conduction, field effect, seizures, epilepsy, synchrony

An electrical field effect occurs when currents associated with an extracellular field cross the cell membrane. If the current is significant the transmembrane potential ($V_m = V_{intracelullar} - V_{extracellular}$) will differ from the intracellular potential. If the transmembrane potential surpasses threshold it may initiate firing, or at reduced transmembrane polarization influence action potential timing (Radman et al., 2007a; Anastassiou et al., 2011), synaptic efficacy (Bikson et al., 2004), or other membrane processes (Faber and Korn, 1989; Jefferys, 1995; Weiss and Faber, 2010).

Field effects are thought to play a role in seizure initiation and propagation (Jefferys, 1995; Dudek et al., 1998). In the absence of synaptic transmission, non-synaptic mechanisms are sufficient to initiate and propagate seizure like activity in hippocampal slice models (Jefferys and Haas, 1982; Taylor and Dudek, 1982, 1984; Jiruska et al., 2010). Also, paired extra- and intracellular recordings of spontaneous paroxysmal events in cat neocortex *in vivo*, with synaptic transmission unaffected, have confirmed that fields associated with ictal discharges depolarize the neuronal membrane and can elicit action potentials (Grenier et al., 2003a,b).

These discharges are thought to be generated by large paroxysmal depolarizing shifts (Goldensohn and Purpura, 1963; Grenier et al., 2003a,b) mediated by glutamatergic synaptic transmission, high-voltage calcium spikes, and a persistent voltage-gated sodium current (Traub et al., 1993). The electric field associated with these currents ranges between 3–9 mV/mm (Pockberger et al., 1984; Jefferys, 1995). Early modeling studies found that the electric fields associated with ictal discharges can synchronize action potentials on a time scale of 1 ms (Traub et al., 1985). Moreover, in hippocampal slices neuronal synchrony during ictal discharges is modulated by changes in osmolality that can strengthen or weaken field effects (Bikson et al., 2003).

The mechanism by which field effects contribute to neural synchronization has been a subject of intense study. It is estimated that DC uniform fields alter the transmembrane potential in individual neurons at the soma (Radman et al., 2009) by 0.18 mV per mV/mm field strength (Deans et al., 2007). However, in hippocampal slices bathed in high K+ to elicit epileptiform activity exogenously pulsed uniform fields as small as 295 μV/mm could entrain neuronal firing (Francis et al., 2003). An explanation for the sensitivity of spike timing to weak electric fields may be that network interactions amplify small field effects experienced by all neurons across an extended territory (Parra and Bikson, 2004; Reato et al., 2010; Weiss and Faber, 2010) by modifying the spike timing of a significant portion of the population (Radman et al., 2007b; Anastassiou et al., 2011) and increasing the synchrony of chemical synaptic transmission in an auto-regenerative manner. Recordings from cortical neuronal ensembles, *in vitro* (Anastassiou et al., 2011), and *in vivo* (Ozen et al., 2010) confirm

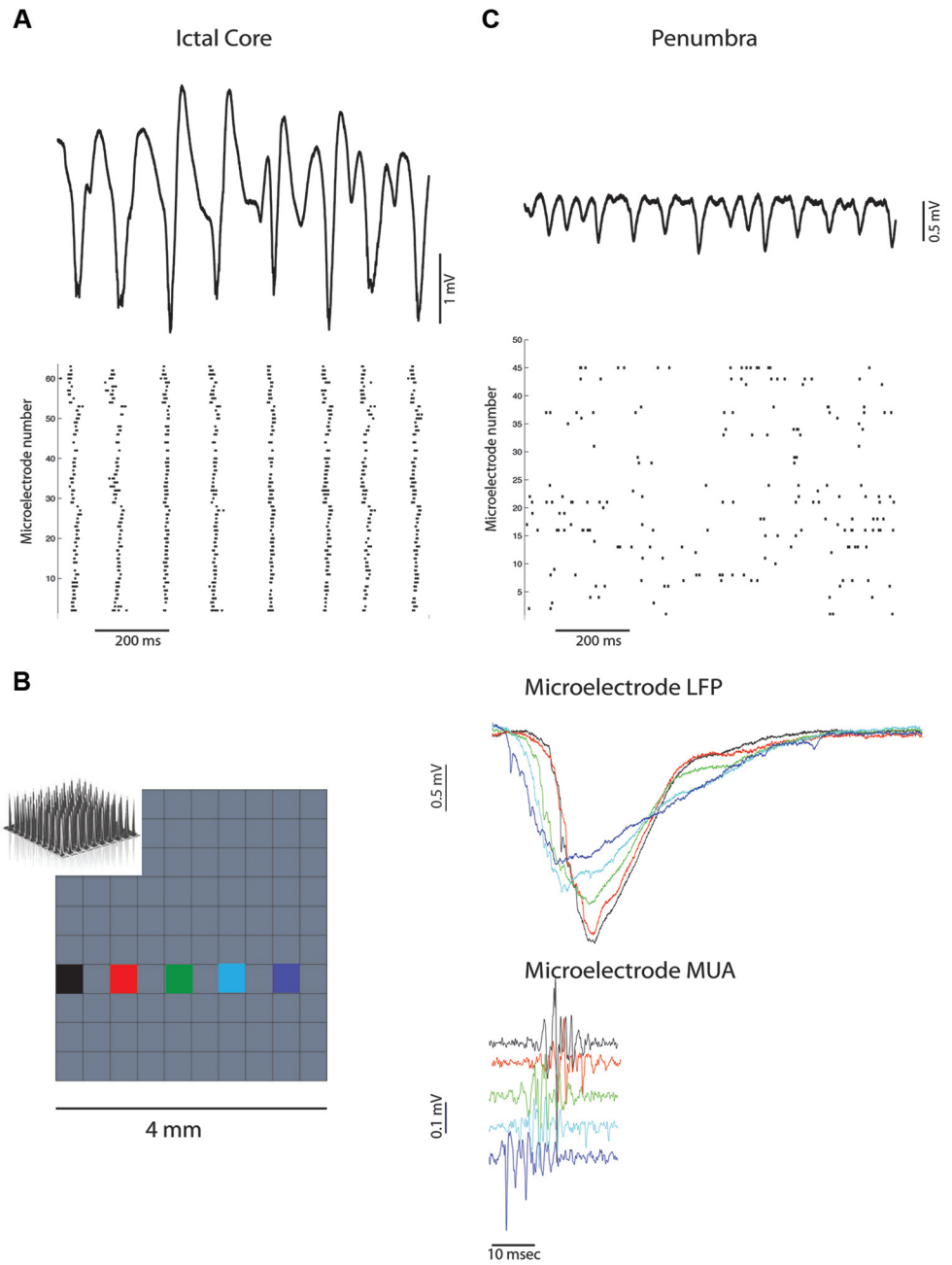

FIGURE 1 | Ictal discharges are associated with neural synchronization in the ictal core but not the penumbra. **(A)** Broadband recording of ictal discharges from one of the microelectrodes in the array implanted in the ictal core (above). Corresponding raster plot of multi-unit action potentials recorded from all the active electrodes (below) illustrating synchronization at the scale of 10 ms. **(B)** Propagation of an ictal discharge (right) recorded by the multi-electrode array (left). Corresponding multi-unit activity reflects propagation and the lack of synchronization at the scale of 1 ms. **(C)** Broadband recording of ictal discharges from one of the microelectrodes in the array implanted in the penumbra (above). Corresponding raster plot of multi-unit action potentials illustrate heterogeneity and lack of global synchrony.

that population level spike coherence to exogenous non-uniform oscillating fields occurs at strengths ranging from 1–4 mV/mm.

If weak electric fields contribute to neuronal synchronization, it would be expected that neuronal synchrony would be observed during the large electric fields generated by ictal discharges in humans. Despite the importance of neural synchrony in seizures, there is a dearth of multi-electrode recordings demonstrating such synchrony over extended cortical territories. Recent recordings of partial seizures from the human cortex with the Utah microelectrode array (House et al., 2006) provide indirect

evidence both for and against a role for field effects in ictal neural synchronization (Truccolo et al., 2011; Schevon et al., 2012).

Schevon et al., recorded single unit activity during partial seizures with the microelectrode array implanted within the seizure onset zone. In three patients, each of the electrodes detected synchronous unit activity phase locked to the trough of the ictal discharge. However, in two other patients the microelectrode array recorded heterogeneous unit activity (Schevon et al., 2012).

Figure 1A demonstrates marked neural synchrony at the temporal scale of ∼10 ms during ictal discharges when the microelectrode array was implanted in the ictal core. To calculate the electric field strength generated by these ictal discharges requires multi-contact depth electrode recordings. However, a rough estimate can be made using prior depth electrode recordings of ictal discharges induced by penicillin application in rabbit cortex (Pockberger et al., 1984). Based on these recordings, the measured ictal discharge amplitude of 1–2 mV in layer 4/5 corresponds with an electric field with a strength of approximately 2–6 mV/mm. Based on *in vitro* (Anastassiou et al., 2011), and *in vivo* (Ozen et al., 2010), evidence this field strength is sufficient to induce population level spike field coherence when the alternating field is applied for an extended duration. Thus, the small variability in the timing of action potentials during ictal discharges suggests that neocortical pyramidal neurons may interact directly via electrical interactions.

Alternatively, neural synchrony during ictal discharges in humans may be solely due to the strong uniform synaptic depolarization and field effects may not play a role. To prove that field effects contribute to neuronal synchronization requires paired intracellular and extracellular recordings from pyramidal neurons during the ictal discharge (Weiss and Faber, 2010). However, paired recordings during ictal discharges recorded from cat neocortex *in vivo* did demonstrate considerable ephaptic depolarization (Grenier et al., 2003a,b).

Thus, neuronal synchrony during ictal discharges may be enhanced in the ictal core by field effect interactions that synergistically pace and entrain the rhythmic paroxysmal depolarizing shifts generated by glutamatergic synaptic transmission (Traub et al., 1985; Parra and Bikson, 2004). Synchronization at the temporal scale of ∼1 ms does not appear to be achieved over extended territories as ictal discharges propagate across the cortex at speeds of ∼500 mm/s (Trevelyan et al., 2007; Schevon et al., 2010, 2012), and action potential firing is affected by the lag times (**Figure 1B**). This does not rule out the possibility of field effects playing a role in synchronization however, since neocortical slow waves which also propagate rapidly across the cortex (Massimini et al., 2004), can produce fields that enhance and entrain network activity locally (Fröhlich and McCormick, 2010).

Figure 1C demonstrates the heterogeneous asynchronous firing during the ictal discharges recorded by the microelectrode array in another patient (Schevon et al., 2012). Similar observations of heterogenous asynchronous firing during human seizures have been previously reported (Truccolo et al., 2011). The microelectrode array was implanted in the ictal penumbra in this case. It is apparent that the ictal discharges are smaller amplitude than that recorded from the ictal core in **Figure 1A** and produce an estimated electric field across the cortical layers of approximately 1–2.1 mV/mm (Pockberger et al., 1984). This field strength should be sufficient to influence spike timing (Francis et al., 2003; Radman et al., 2007a; Anastassiou et al., 2011; Weiss and Faber, 2010), but not necessarily result in strong population level spike field coherence (Ozen et al., 2010; Anastassiou et al., 2011).

Besides a weaker endogenous field, another potential explanation for the heterogeneous, asynchronous firing, in the face of the observed ictal discharges in **Figure 1C**, is that the neurons in the penumbra have a membrane potential farther from threshold than in the ictal core. Calcium imaging and patch clamp recording from cortical slices bathed in zero magnesium suggest that in the penumbra territory a combination of rhythmic inhibitory post-synaptic potentials (IPSPs) and excitatory post-synaptic potentials (EPSPs) contribute to the ictal discharges (Trevelyan et al., 2006; Trevelyan, 2009; Schevon et al., 2012). Assuming that this is the case in the human ictal penumbra (**Figure 1C**) the synergistic influence of field effects on neuronal synchronization may be negated. Additional experimental and modeling studies are required to support this hypothesis.

The recordings from the ictal core demonstrate profound neuronal synchrony during ictal discharges. While, paired intra- and extracellular recordings are required to confirm that field effects help to generate this synchronization, the electrical field strength is likely sufficient (Ozen et al., 2010; Anastassiou et al., 2011). In contrast, the recordings from the ictal penumbra highlight how endogenous or exogenous field effects may be affected by synaptic inhibition.

REFERENCES

Anastassiou, C. A., Perin, R., Markram, H., and Koch, C. (2011). Ephaptic coupling of cortical neurons. *Nat. Neurosci.* 14, 217–223. doi: 10.1038/nn.2727

Bikson, M., Fox, J. E., and Jefferys, J. G. R. (2003). Neuronal aggregate formation underlies spatiotemporal dynamics of nonsynaptic seizure initiation. *J. Neurophysiol.* 89, 2330–2333. doi: 10.1152/jn.00764.2002

Bikson, M., Inoue, M., Akiyama, H., Deans, J. K., Fox, J. E., Miyakawa, H., et al. (2004). Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *J. Physiol.* 557, 175–190. doi: 10.1113/jphysiol.2003.055772

Deans, J. K., Powell, A. D., and Jefferys, J. G. R. (2007). Sensitivity of coherent oscillations in rat hippocampus to AC electric fields. *J. Physiol.* 583, 555–565. doi: 10.1113/jphysiol.2007.137711

Dudek, F. E., Yasumura, T., and Rash, J. E. (1998). "Non-synaptic" mechanisms in seizures and epileptogenesis. *Cell Biol. Int.* 22, 793–805.

Faber, D. S., and Korn, H. (1989). Electrical field effects: their relevance in central neural networks. *Physiol. Rev.* 69, 821–863.

Francis, J. T., Gluckman, B. J., and Schiff, S. J. (2003). Sensitivity of neurons to weak electric fields. *J. Neurosci.* 23, 7255–7261.

Fröhlich, F., and McCormick, D. A. (2010). Endogenous electric fields may guide neocortical network activity. *Neuron* 67, 129–143. doi: 10.1016/j.neuron.2010.06.005

Goldensohn, E. S., and Purpura, D. P. (1963). Intracellular potentials of cortical neurons during focal epileptogenic discharges. *Science* 139, 840–842. doi: 10.1126/science.139.3557.840

Grenier, F., Timofeev, I., and Steriade, M. (2003a). Neocortical very fast oscillations (ripples, 80–200 Hz) during seizures: intracellular correlates. *J. Neurophysiol.* 89, 841–852. doi: 10.1152/jn.00420.2002

Grenier, F., Timofeev, I., Crochet, S., and Steriade, M. (2003b). Spontaneous field potentials influence the activity of neocortical neurons during paroxysmal activities in vivo. *Neuroscience* 119, 277–291. doi: 10.1016/s0306-4522(03)00101-5

House, P. A., MacDonald, J. D., Tresco, P. A., and Normann, R. A. (2006). Acute microelectrode array implantation into human neocortex: preliminary

technique and histological considerations. *Neurosurg. Focus* 20, 1–4. doi: 10.3171/foc.2006.20.5.5

Jefferys, J. G. (1995). Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. *Physiol. Rev.* 75, 689–723.

Jefferys, J. G., and Haas, H. L. (1982). Synchronized bursting of CA1 hippocampal pyramidal cells in the absence of synaptic transmission. *Nature* 300, 448–450. doi: 10.1038/300448a0

Jiruska, P., Csicsvari, J., Powell, A. D., Fox, J. E., Chang, W.-C., Vreugdenhil, M., et al. (2010). High-frequency network activity, global increase in neuronal activity and synchrony expansion precede epileptic seizures in vitro. *J. Neurosci.* 30, 5690–5701. doi: 10.1523/jneurosci.0535-10.2010

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., and Tononi, G. (2004). The sleep slow oscillation as a traveling wave. *J. Neurosci.* 24, 6862–6870. doi: 10.1523/jneurosci.1318-04.2004

Ozen, S., Sirota, A., Belluscio, M. A., Anastassiou, C. A., Stark, E., Koch, C., et al. (2010). Transcranial electric stimulation entrains cortical neuronal populations in rats. *J. Neurosci.* 30, 11476–11485. doi: 10.1523/jneurosci.5252-09.2010

Parra, L. C., and Bikson, M. (2004). Model of the effect of extracellular fields on spike time coherence. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 6, 4584–4587. doi: 10.1109/IEMBS.2004.1404271

Pockberger, H., Rappelsberger, P., and Petsche, H. (1984). Penicillin-induced epileptic phenomena in the rabbit's neocortex I. The development of interictal spikes after epicortical application of penicillin. *Brain Res.* 309, 247–260. doi: 10.1016/0006-8993(84)90591-2

Radman, T., Datta, A., and Peterchev, A. V. (2007a). In vitro modulation of endogenous rhythms by AC electric fields: Syncing with clinical brain stimulation. *J. Physiol.* 584, 369–370. doi: 10.1113/jphysiol.2007.140947

Radman, T., Ramos, R. L., Brumberg, J. C., and Bikson, M. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimul.* 2, 215–228, e1–e3. doi: 10.1016/j.brs.2009.03.007

Radman, T., Su, Y., An, J. H., Parra, L. C., and Bikson, M. (2007b). Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. *J. Neurosci.* 27, 3030–3036. doi: 10.1523/jneurosci.0095-07.2007

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2010). Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J. Neurosci.* 30, 15067–15079. doi: 10.1523/jneurosci.2059-10.2010

Schevon, C. A., Goodman, R. R., Mckhann, Jr. G., and Emerson, R. G. (2010). Propagation of epileptiform activity on a submillimeter scale. *J. Clin. Neurophysiol.* 27, 406–411. doi: 10.1097/wnp.0b013e3181fdf8a1

Schevon, C. A., Weiss, S. A., Mckhann, Jr. G., Goodman, R. R., Yuste, R., Emerson, R. G., et al. (2012). Evidence of an inhibitory restraint of seizure activity in humans. *Nat. Commun.* 3:1060. doi: 10.1038/ncomms2056

Taylor, C. P., and Dudek, F. E. (1982). Synchronous neural afterdischarges in rat hippocampal slices without active chemical synapses. *Science* 218, 810–812. doi: 10.1126/science.7134978

Taylor, C. P., and Dudek, F. E. (1984). Synchronization without active chemical synapses during hippocampal afterdischarges. *J. Neurophysiol.* 52, 143–155.

Traub, R. D., Dudek, F. E., Snow, R. W., and Knowles, W. D. (1985). Computer simulations indicate that electrical field effects contribute to the shape of the epileptiform field potential. *Neuroscience* 15, 947–958. doi: 10.1016/0306-4522(85)90245-3

Traub, R. D., Miles, R., and Jefferys, J. G. (1993). Synaptic and intrinsic conductances shape picrotoxin-induced synchronized after-discharges in the guinea-pig hippocampal slice. *J. Physiol.* 461, 525–547. doi: 10.1016/0304-3940(93)90391-w

Trevelyan, A. J. (2009). The direct relationship between inhibitory currents and local field potentials. *J. Neurosci.* 29, 15299–15307. doi: 10.1523/jneurosci.2019-09.2009

Trevelyan, A. J., Baldeweg, T., van Drongelen, W., Yuste, R., and Whittington, M. (2007). The source of afterdischarge activity in neocortical tonic-clonic epilepsy. *J. Neurosci.* 27, 13513–13519. doi: 10.1523/jneurosci.3005-07.2007

Trevelyan, A. J., Sussillo, D., Watson, B. O., and Yuste, R. (2006). Modular propagation of epileptiform activity: evidence for an inhibitory veto in neocortex. *J. Neurosci.* 26, 12447–12455. doi: 10.1523/jneurosci.2787-06.2006

Truccolo, W., Donoghue, J. A., Hochberg, L. R., Eskandar, E. N., Madsen, J. R., Anderson, W. S., et al. (2011). Single-neuron dynamics in human focal epilepsy. *Nat. Neurosci.* 14, 635–641. doi: 10.1038/nn.2782

Weiss, S. A., and Faber, D. S. (2010). Field effects in the CNS play functional roles. *Front. Neural. Circuits* 4:15. doi: 10.3389/fncir.2010.00015

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