Targeting brain networks with multichannel transcranial current stimulation (tCS)

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Abstract

The brain is a complex, plastic, electrical network whose dysfunctions result in neurological disorders. Multichannel transcranial electrical stimulation (tCS) is a non-invasive neuromodulatory technique with the potential for network-oriented therapy. Challenges to realizing this vision include the proper identification of involved networks in a patient-specific context, a deeper understanding of the effects of stimulation on interconnected neuronal populations - both immediate and plastic - and, based on these, developing strategies to personalize brain stimulation interventions. For this reason, personalized *hybrid* biophysical and physiological models of brain networks are poised to play a key role in the evolution of network-oriented transcranial stimulation. We review some of the recent work in this emerging area of research and provide an outlook for future modeling and experimental work, as well as for developing its clinical applications in fields such as epilepsy.

Highlights

- The human brain is a complex network, where dysfunction can ultimately be interpreted as network dysfunction
- Multichannel tCS offers a versatile, powerful non-invasive approach for network-oriented therapy
- Hybrid biophysical and physiological models of complex brain networks are crucial to realizing the potential of tCS
- Challenges include identifying relevant networks and modeling the effects of stimulation to define therapeutic strategies
- We discuss the application of multichannel network tCS in epilepsy, stroke and Parkinson's disease

1. INTRODUCTION

The brain is a complex, plastic, electrical network operating at multiple scales - neural processing is essentially mediated by functional and structural networks. Over the past decades, neuroscience has made significant advances in our understanding of brain function. There is a growing body of evidence suggesting that large-scale networks underlie both integration and differentiation processes which are fundamental for information processing in the brain. For instance, putatively simple cognitive tasks such as object recognition have been

shown to involve networks that include the bilateral occipital, the left temporal and the left/right frontal regions [1]. Neuropsychiatric disorders ultimately result from network dysfunctions which may arise from the abnormality in one or more isolated brain regions but produce alterations in larger brain networks (see [2-4] and references therein).

In such a context, networks become the natural target of neuromodulatory interventions. Advances in neuroimaging modalities such as positron emission tomography (PET), magneto- and electroencephalography (EEG/MEG), functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) provide valuable tools for the identification of networks. For instance, the 'resting state' paradigm is increasingly used to assess intrinsic brain activity and brain connectivity using modalities such as fMRI, EEG or MEG [5]. Activity recorded during spontaneous rest using fMRI can be decomposed into separate but integrated resting-state networks (RSNs) [6,7] also known as "modules" [8] or "architectures" [9], with specific RSNs reflecting the activity within sensory (e.g., visual, motor, auditory) and associative brain regions related to high-order cognitive processes such as abstract reasoning, attention, language, and memory. This organization, as captured via functional connectivity (FC) analysis of fMRI data collected during resting-state (rs-fcMRI), is correlated with individual variability in several cognitive functions and personality traits [10-13], with recent studies suggesting the possibility of capturing individual brain uniqueness by means of finely tailored FC analysis [14]. A similar approach can be used for the spatiotemporal decomposition of electrophysiological signals at higher temporal resolution (~1ms) into so-called microstates [15,16]. These have been linked to a variety of cognitive functions and pathologies [16-19]. While such approaches provide stimulation targets at relatively high spatial resolution, currently used noninvasive brain stimulation techniques - such as Transcranial Magnetic Stimulation (TMS) - cannot easily be employed to simultaneously engage multiple network nodes or sub-networks. TMS network manipulation based on the induction of spike-timing-dependent plasticity (STDP) has been recently proposed [20,21], but requires relatively expensive hardware and can only be performed in laboratory settings. Novel, safe, portable solutions for network-engagement are needed.

Transcranial electrical current stimulation (*tCS*, sometimes also called *tES*), which includes both direct and alternating current variants known as tDCS and tACS, is a non-invasive sub-threshold neuromodulatory technique pioneered by Nitsche and Paulus [22]. Low intensity, controlled currents (typically ~1 mA but <4 mA) are applied through scalp electrodes in repeated 20-40-minute sessions. This subtle but persistent modulation of neuronal activity is believed to lead to plastic effects deriving from Hebbian mechanisms (see [23-25] and references therein). That is, tCS induces concurrent and plastic effects from persistent (in time), mesoscale (in space), weak electric fields acting on brain networks. Its clinical applications include neuropathic chronic pain, major depression, stroke rehabilitation, addictive disorders and epilepsy [26]. tCS is recognized for its applicability and safety [27].

The recent evolution of tCS has delivered multichannel systems using small electrodes much like EEG. This advance comes with opportunities and challenges.

2. MULTICHANNEL STIMULATION AND ITS OPTIMIZATION

In the past years, methods have been proposed to optimize multichannel tCS (see, e.g. [28]) proved that this problem is mathematically well-posed and showed that optimized electric fields display significantly higher focality and, in general, a better alignment with the target vector than those produced by standard bipolar electrode montages [29]. Based on work from Miranda et al. [30] and Fox et al. [31], Ruffini et al. [32] proposed a method for optimization of multichannel tCS (*Stimweaver*). Its main features are a focus on cortical excitability, the use of an interaction mechanism inferred from prior *in-vivo* and *in-vitro* work (called the *lambda-E model*, [23]) that places emphasis on the component of the electric field orthogonal to the cortical surface, MRI driven finite element modeling of the electric fields produced by multichannel tCS, and a rapid optimization method exploring number, current intensity and spatial location of electrodes. The method requires as key inputs a specification of the target electric field on the cortex, a weight map to prioritize target regions for the optimizer and other parameters such as the maximal number of electrodes and currents allowed. Defining these maps is, of course, key and requires a deep understanding of cortical function – including its network aspects.

This method has been employed by several research groups. For example, Fisher et al. [33] explored whether the effects of tCS on a region can be enhanced by targeting its associated network. In particular, a network associated with a local target on the left motor cortex (M1) was defined using rs-fcMRI. In a cross-over study, fifteen healthy subjects were stimulated in several conditions, including one with a bipolar montage targeting the seed (M1), another with an eight-electrode montage targeting its associated resting state network, and a sham condition. Cortical excitability of the left M1 was probed using TMS/MEPs, as in the pioneering work by Nitsche and Paulus [22]. The authors observed that network-targeted tDCS led to a significant increase in left M1 excitability over time compared to traditional tDCS.

Dagan et al. [34] recently studied the use of multichannel tDCS in Parkinson's disease (PD) with freezing of gait (FOG), one of its most disturbing and least understood symptoms. Several hypotheses suggest that FOG is not only a motor problem but also partly the result of deficits in executive function mediated by the dorsolateral prefrontal cortex (DLPFC)(see [34] and references therein). Indeed, targeting the DLPFC with tDCS appears to positively affect cognition, gait, and postural control in other populations. Because PD manifests strongly as a motor disturbance phenomenon, including FOG, most studies in PD have also focused on M1, reporting motor function and gait improvements with bipolar tDCS compared to sham stimulation (see references in [34]). Dagan et al. [34] employed multichannel tCS optimized for maximizing facilitation of both primary the motor cortex (M1) and the left dorsolateral prefrontal cortex (DLPFC), and compared this to stimulation of M1 only and a Sham condition. Multitarget stimulation of both areas provided a significant improvement over the other conditions.

In another recent example, research in disorders of consciousness has employed multichannel network stimulation [35] sought to engage the external (frontoparietal) consciousness network in severely brain-injured patients using a target map derived from rs-fMRI. Finally, in yet another example with healthy subjects, attempts have been made to optimize multichannel solutions

engaging cortical networks relevant for cognitive training, e.g., targeting flexibility or working memory-related nodes while participants were undergoing executive function training [36].

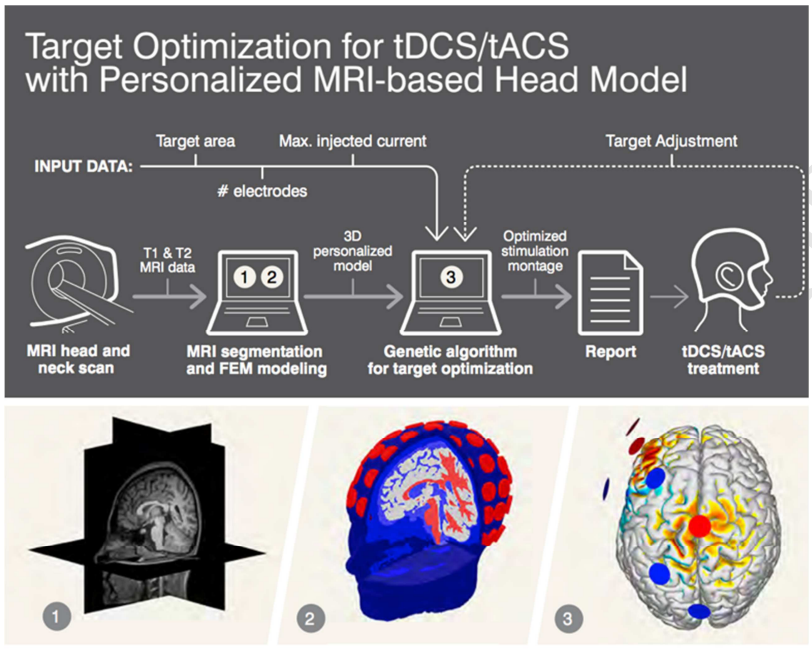

Figure 1. Workflow for the creation of a biophysical model and for model-driven tCS optimization. Anatomical MRI data (1) is used to create a finite element biophysical model (FEM), and electrodes are placed using the 10-10 EEG system (2) (see Miranda et al. 2018 [37] for a review). A target specification is provided, together with the desired number of electrodes and maximal currents. The *Stimweaver* algorithm provides the solution (3, i.e., electrode positions and currents). The approach is applicable to tDCS, tACS and other tCS modalities [32].

3. tCS AND BRAIN NETWORKS: FROM BIOPHYSICS TO PHYSIOLOGY

If the critical features of pathological networks can be effectively captured in computational models, they can be used for diagnosis and delivery of personalized therapeutic weak electric fields (Figure 1). Multiple studies in theoretical and computational neuroscience have developed whole-brain network models [38-41] to explore the relationship between brain function and its underlying connectivity. This increased interest in finding the origin of the structure-function relationship has led to a newly developing field known as *network neuroscience* (Bassett and Sporns, 2017) [42] that relies on graph theory to study the brain across its multiple scales and complexities. Following earlier work by Merlet et al. [39], Sanchez-Todo et al. [43] develop a method that allows for the use of a subject's EEG and MRI for the creation of a personalized whole brain model. The model is optimized to reproduce a subject's EEG and allows for virtual brain stimulation, and hence optimization. Earlier, Bansal et al. [44], Spiegler et al. [45], and Muldoon et al. [46] proposed a similar approach. Although "hybrid" models can produce physiologically-plausible EEG and simulate the generation of realistic tCS electric fields (see Miranda et al. [37] in this issue, and references therein), representing faithfully the effects of neuromodulation on brain plasticity remains an unresolved, important challenge. We now know from experimental work that tCS can directly impact

neuronal excitability and synaptic plasticity [47,48]. Marquez-Ruiz et al. [49], e.g., showed that blocking adenosine A1 receptors prevents the long-term depression evoked in the somatosensory cortex after cathodal tDCS in the rabbit. Based on molecular and functional investigations (immunoblotting, immunofluorescence, and electrophysiological recordings), Paciello et al. [50] provide novel evidence that anodal tDCS affects structural plasticity of the rat auditory cortex in a paradigm of noise-induced hearing loss. Wischnewski et al. [51] also reported that 20 Hz tACS can alter NMDA Receptor-Mediated plasticity in the human motor cortex. A number of studies indicate that tCS can alter the release of neurotransmitters, typically dopamine [52], glutamate and GABA [53]. Ultimately, electric field mediated effects translate into short- or long-term changes in the network connectivity - and therapeutic effects. As the precise mechanisms involved in tCS-induced plasticity changes still remain elusive, multiscale computational models offer a unique framework to untangle them, allowing, for instance, to distinguish effects occurring at presynaptic (membrane polarization of axon terminals, neurotransmitter release) or postsynaptic (GABA or glutamate receptors) level.

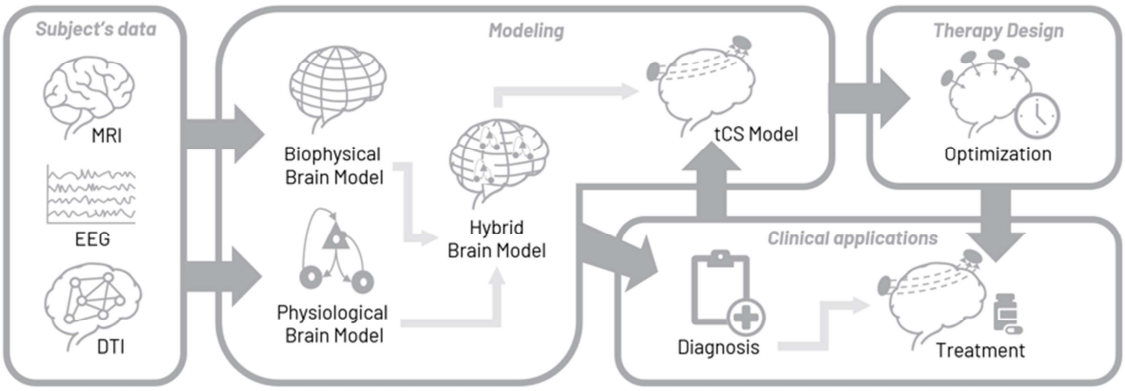

Figure 2. Workflow for the creation of hybrid models model-driven tCS optimization. DTI and anatomical MRI data are combined to create a finite element biophysical model (FEM), which is then personalized using EEG and other data to reflect *both* biophysical and physiologic characteristics – from excitation/inhibition balance to plastic potential (long-term effects physiological model). The personalized hybrid brain model can be used to generate EEG and to simulate the effects of brain stimulation. As a result, personalized diagnosis and treatment can be applied, such as optimized stimulation protocols.

4. FUTURE APPLICATIONS

Epilepsy

Epilepsy is a devastating, chronic disease that severely affects the quality of life of 65 million people worldwide (WHO, Fact Sheet on Epilepsy, 2012), 35% of whom do not respond to drugs. Almost a third of patients (29%) are untreatable: in 19 million patients, drugs fail, and surgery is not an option or has failed too. Treatment-resistant epilepsies represent not only a considerable challenge for the health care system but also a tremendous burden at the individual, family, and community levels [54]. They are characterized by an epileptogenic network (EN) interconnecting distant brain areas located in one of the two hemispheres. There is a large body of evidence

suggesting that patient-specific ENs [55] are responsible for the generation and spread of seizures through synchronization processes that interconnect neuronal assemblies with altered excitability [56]. Of note, some studies have tried to predict surgical outcome by removing EN edges of the patient specific connectivity data in computational models of the subject's brain [57-61]. In this context, tCS can represent a valuable alternative to surgery [62], provided that fundamental issues are addressed. First, epileptogenic networks are patient-specific. Therefore, interventions must be "tailored" to each patient based on the accurate definition of target brain areas and networks. Second, stimulation protocols must achieve a therapeutic effect through a "network-aware" management of hyperexcitability - a hallmark of epileptogenic systems. Third, therapeutic effects must be optimized in order to prevent the occurrence of seizures. A protective and durable effect will certainly require a better understanding of the mechanisms of action of weak electric fields on brain networks from short (minutes to hours) to long (days, weeks) time scales.

Reaching subcortical targets via networks

Fox et al. [63] identified diseases treated with both non-invasive and deep brain stimulation (DBS), listed the target sites thought to be most effective in each disease and tested the hypothesis that these sites are nodes within a brain network as defined by rs-fcMRI. They found that sites in which DBS was effective were functionally connected to sites where noninvasive brain stimulation had been found to be effective in diseases including depression, PD, obsessive-compulsive disorder, essential tremor, addiction, pain, minimally conscious state, and Alzheimer's disease. This suggests that rs-fcMRI may be useful for translating therapy across stimulation modalities, optimizing treatment, and for the identification of new stimulation targets. It also supports a more general network approach toward understanding and treating neuropsychiatric disease, highlighting the therapeutic potential of targeted brain network modulation. Examples of potential cortical and subcortical targets relevant for neuropsychiatric conditions, as well as their rs-fcMRI map and corresponding multichannel optimization, are shown in Figure 3 (see also Ruffini et al. [32] for further discussion on the use of these maps for multichannel tCS optimization).

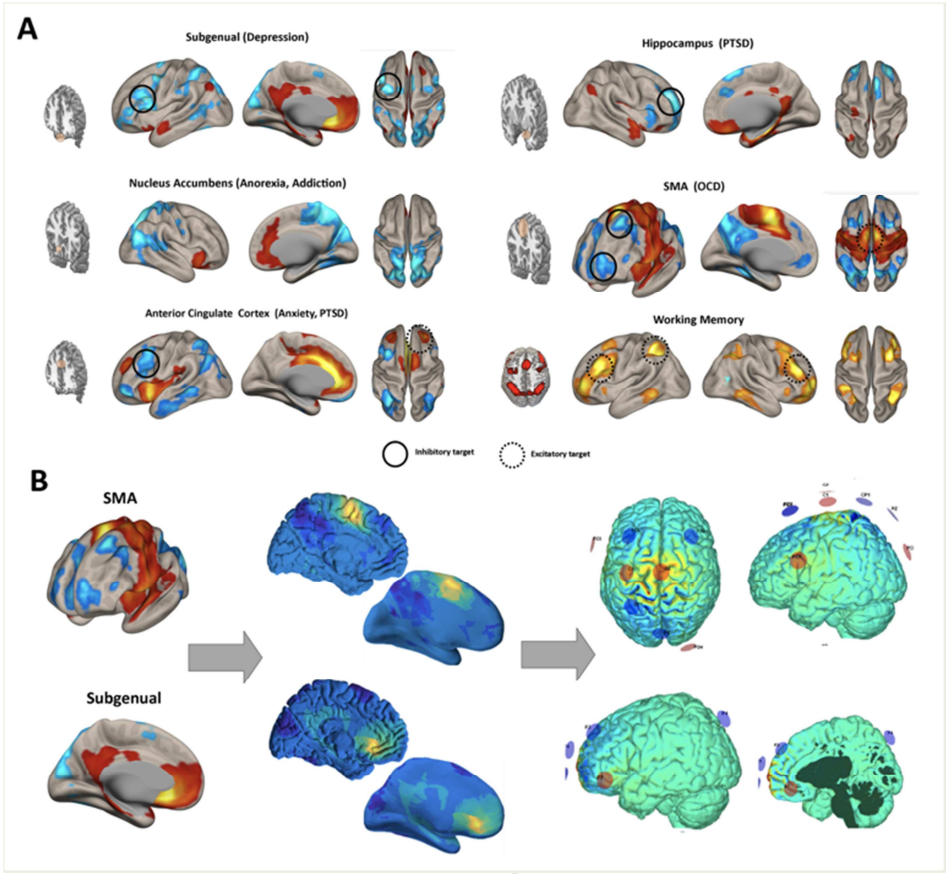

Figure 3. Connectivity-based network targeting. (A) Cortical representation of rs-fMRI connectivity patterns of selected brain regions of clinical relevance in various neuropsychiatric conditions. The target regions are used as seeds, and their pattern of positively and negatively correlated regions in the brain are computed. Multichannel tCS can be optimized to enhance positive ("excitatory") or negative ("inhibitory") cortical nodes, inducing changes in their connectivity with the seed region and possibly modulating its spontaneous activity. (B) Examples of multichannel tCS solutions derived from *Stimweaver* [32] for targeting the supplementary motor area in patients with obsessive-compulsive disorder (OCD) and subgenual cortex in patients with depression.

Stroke

In another example, Otal et al. [64] proposed to identify networks affected by a stroke at the individual level: location, extent, and pattern of functional network connectivity disruption should be considered when determining the optimal tDCS intervention. Alstott et al. [65] did a related *in silico* study where network edges were removed to investigate the effect of such perturbations on simulated brain activity. See an extended review of Aerts et al. [66] regarding computational lesion and empirical studies investigating brain network alterations in cancer, stroke and traumatic injury patients. In the case of stroke, each lesion type displays a particular functional and structural connectivity signature that determines the tDCS intervention goals. Lesion topography is usually subcortical, with intracortical connectivity disruptions contributing strongly

to behavioral deficits [67]. In general, we may consider three main approaches: a) targeting a single region or node, b) targeting the single region indirectly via a network as described above, or c) select a network or sub-network (i.e., multi-nodal) as the target. The latter may be especially relevant given the correlation of connectivity disruption and symptoms. Depending on the approach chosen, different optimization strategies can be envisioned. Tools based on tractography can be used to assess damaged networks and devise therapeutic strategies [68].

5. CONCLUSIONS

Multichannel tCS provides a promising tool for targeting networks but is not yet used as a standard treatment in any disease. This is related to several challenges and methodological limitations: an overwhelming number of stimulation parameter combinations, empirical parameter setting, an absence of a rational definition of targets and protocols, the qualitative nature of results, unknown mechanisms of action, and an insufficient account for patient-specific factors. A bottom-up, science-based mechanistic understanding of both the effects of tCS and the desired cortical network changes is lacking. Research should aim to overcome this by providing a better understanding mechanism of interaction - including both immediate and longer-term plastic effects of electric fields in networks across scales. We also need to refine our methods to better identify networks to be targeted and design the strategies for intervention in each disease and patient. Finally, experiments should be carried out to investigate how network interactions can best be leveraged by tCS, measuring the functional and structural alterations induced by tCS using tools such as fMRI or DTI. Modeling in sufficient detail the combined biophysics and physiology of tCS will be paramount for the design and interpretation of studies and for their ultimate clinical translation.

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DECLARATION OF INTEREST

Giulio Ruffini is a shareholder and works for Neuroelectrics, a company designing medical devices for brain stimulation. Roser Sanchez-Todo is a researcher at Neuroelectrics.

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