REVIEW

Tuning noninvasive brain stimulation with MRI to cope with intersubject variability

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Purpose of review
The review aims at highlighting the additional benefit that can be gained from combining noninvasive brain stimulation as well as repetitive sensory stimulation protocols with MRI techniques to account for the intersubject variability observed in those treatments. Potentially, this should help to identify predictive patterns in the individual receptiveness to the treatment.

Recent findings
Knowledge about the underlying physiological principles of excitability changes as induced by noninvasive brain stimulation or repetitive sensory stimulation is accumulating, revealing strong associations with plasticity processes at the synaptic level. In this context, MRI techniques, such as magnetic resonance spectroscopy and functional MRI, emerged as valuable tools for the qualitative assessment of baseline states and induced changes. Those physiological readouts can help explain the interindividual heterogeneity found in behavioural and/or clinical responses to the specific stimulation protocols. This knowledge will eventually translate, first, into the preliminary classification of study participants into treatment groups according to their neurophysiological baseline state and expected responses to a particular stimulation. Subsequently, this should also aid the optimization of stimulation protocols according to the classification outcome, resulting in retuned protocols for particular groups of study participants.

Summary
The consistent MRI-based monitoring of stimulation effects in the neural network promises a considerable gain for the customization of intervention protocols with improved therapeutic potential and rehabilitative predictions.

Keywords
intersubject variability, long-term potentiation, MRI, repetitive sensory stimulation, transcranial direct current stimulation

INTRODUCTION

Since time immemorial, humans have sought to boost their cognitive abilities. For many years, nootropic chemical substances were the means of choice, but over the past few decades, noninvasive brain stimulation (NIBS) techniques, including transcranial direct current stimulation (tDCS), stirred the scientific community. Positive impacts on vocabulary learning [1], multitasking performance [2], and visual search efficiency [3▪▪] number among the favourable effects attributed to NIBS. But also, more critical voices were raised [4], adducing ethical concerns [5] and the possibility of cognitive trade-offs [6]. Accumulating observations highlight the large heterogeneity of the responses across study participants [7], with some of them even addressing the possibility of a mere placebo effect [8]. In a constantly growing body of work, apart from promising neural enhancement in healthy individuals, tDCS is applied as a treatment for behavioural and neurological disorders nonetheless [9,10,11▪].

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Curr Opin Neurol 2016, 29:000–000
DOI:10.1097/WCO.0000000000000353

KEY POINTS

- Effects, which are induced by brain and sensory stimulation, coincide only partially with plasticity processes observed at the synaptic level.
- Magnetic resonance-based techniques can improve the understanding of metabolic and connectivity changes in the brain network elicited by NIBS or rSS.
- The characterization and quantification of the physiological changes induced by noninvasive brain stimulation can help account for the observed large intersubject variability in treatment effects and furthermore to predict the individual responsiveness to the treatment.

NEUROPHYSIOLOGICAL CHARACTERISTICS OF NONINVASIVE BRAIN STIMULATION AND REPETITIVE SENSORY STIMULATION EFFECTS

Insofar, there is a general consensus that as a neuromodulatory technique tDCS produces polarity-dependent changes in cortical excitability. Rather than eliciting action potentials, tDCS introduces a tonic depolarization or hyperpolarization to the membrane resting potential of the neurons in the targeted brain area. Similarly, repetitive sensory stimulation (rSS) protocols that stimulate peripheral sensory systems have been considered to produce network correlates of synaptic plasticity in a frequency-dependent manner, with higher frequencies of stimulus presentation producing long-term potentiation (LTP)-like effects, whereas lower frequencies induce long-term depression (LTD)-like effects [12–14]. Both processes, LTP and LTD, are currently considered as key synaptic underpinnings of learning and memory.

It has been demonstrated that tDCS *in vivo* modulates short as well as long-term types of synaptic plasticity [15,16▪▪], paired-pulse facilitation (PPF), and LTP in particular. Despite the conflictive results regarding the exact effects of tDCS on PPF, which might be attributed to the different recording sites and distinct neurotransmitter release probabilities in these brain regions, the impact of the stimulation on the presynaptic sites is noteworthy. Moreover, an additional effect of tDCS on the postsynaptic sites was implicated in a study by Rohan and colleagues [16▪▪], wherein, subsequent to tDCS, the induction of LTP in acutely prepared brain slices was facilitated. This was reflected in a larger slope and amplitude of field potentials after tDCS as compared with the sham condition. This effect on synaptic plasticity, which was dose dependent and lasted for 24 h, is the most prominent link between tDCS and LTP. This labelling already implicates a connection to plasticity processes on the cellular level. However, the inflationary use of these terms is not always justified, given that the exact nature of the likeness is not documented in all studies. Accordingly, the existing criteria for the definition of LTP at the synapse, more specifically persistence, input specificity, associativity, and cooperativity, could be employed as a starting point to justify the choice of terminology on the network level while also entailing separate analyses of network stimulation effects. Finding a bridge between local plasticity processes observed at the cellular level and the global network behaviour might provide researchers with crucial hints as to the underlying neurophysiological factors for the observed high interindividual variability [17–19], which impedes the efficacy and reliability of common tDCS paradigms [20,21▪▪].

To what extent are NIBS and rSS effects mediated by synaptic plasticity processes? To answer this question will require additional experimental work on animal models combining simultaneous measurements of neuronal circuits at meso and macroscopic levels. Some clues, however, can be found by following classic neurophysiological definitions of synaptic plasticity.

Among the array of characteristics attributed to LTP, the persistence of the induced changes is probably the most sought after in a clinical context. In clinical settings, this has been most commonly monitored with regard to amplitude changes of motor-evoked potentials (MEPs) [22,23], often derived from transcranial magnetic stimulation, prior to, during and at several time points after the stimulation period, thus tracking when the stimulation-induced effects would return to their baseline levels. Single tDCS sessions, lasting for 10–20 min, produced increased MEP amplitudes up to 90 min after terminating the stimulation [20]. Furthermore, tDCS-induced effects from repeated application over the course of 5 consecutive days were still detected at follow-up examinations 4 weeks after the stimulation [24].

Although on the synaptic level, input specificity, cooperativity, and associativity are additional aspects that characterize LTP processes, to date, no techniques exist to reliably acknowledge their presence on the systems level in humans, mainly owing to the larger stimulated areas during NIBS and rSS as compared with the more focal points in classic invasive LTP and LTD-inducing stimulation protocols. Alternatively, functional network connectivity could be assumed to be an approximation to the combined definitions of input specificity and associativity to the extent that excitability changes are

not restricted to the area directly beneath the electrodes but spread across different brain regions. Nor does this spreading proceed in an unspecific manner but it occurs along functional pathways instead, consequently rudimentarily modelling the synaptic concepts on a larger scale.

Although electroencephalographic recordings have been employed for reconstructing changes in functional connectivity patterns by means of neural synchronization in different frequency bands [25,26], functional MRI (fMRI) has emerged as the foremost technique in studies of this kind.

Studies like the one conducted by Meinzer and colleagues [27], who could associate a reduced activity in the ventral inferior frontal gyrus with an improved behavioural performance in picture naming during task-related fMRI, illustrate the power of combining brain stimulation and neuroimaging techniques. Such studies are comparatively scarce, with the vast majority of research carried out using resting state fMRI and focussing on established functional networks [28–30]. But even when tDCS is applied in the resting state, it has been suggested that it primes networks for their differential recruitment in future tasks [31].

To what extent and in which direction excitability changes appear in specified networks depends on the electrode montage, unilaterally or bilaterally [32], the polarity, cathodal or anodal [33], and the stimulated cortical area. Furthermore, despite the adherence to the same parameters, different outcomes have been reported. For instance, Polanía and colleagues [33] reported a boost in local functional connectivity triggered by cathodal tDCS, whereas anodal tDCS affected functional connectivity at longer distances, whereas Amadi and colleagues [34] only found an increase in interhemispheric functional connectivity induced by cathodal tDCS, whereas neither sham nor anodal stimulation took any effect. Notwithstanding the diverging results, there is a common agreement as to the overall modulatory power of tDCS on the network connectivity of distinct, long-range functional networks with matching results derived from blood oxygen level-dependent signal and arterial spin labelling [35].

Owing to the historical studies of the N-methyl-D-aspartate receptor (NMDAR)-dependent LTP along the Schaffer collaterals in the hippocampus, the involvement of the aforementioned receptor is usually required when referring to LTP-like changes. It acts as a coincidence detector that recognizes the paired activity at pre and postsynaptic sites, which instigates lasting forms of synaptic plasticity by strengthening the synaptic contact. Several studies on rat hippocampi [16▪▪,36] as well as in human volunteers [37] have demonstrated that the enhanced excitability induced by direct current stimulation and tDCS, respectively can be blocked by the application of NMDAR antagonists. This demonstrated the similarity between cellular and network plasticity processes, pertaining to the early phase of LTP induction, which mainly relies on the regulation of glutamate receptor activity and their insertion into the postsynaptic membrane. Additionally, late effects, which rely on gene expression and protein synthesis, were attested after the stimulation period. Fritsch and colleagues [38] could only show a heightened brain-derived neurotrophic factor (BDNF) secretion and a simultaneously increased activation of tropomyosin receptor kinase B when direct current stimulation and low-frequency synaptic activation were combined; the epigenetic enhancement of *BDNF* gene expression could be related to an exclusive tDCS protocol in the animal model elsewhere [39▪]. In accordance with the observed absence of LTP effects after stimulation in *BDNF* knockout mice, the Val66Met polymorphism of the *BDNF* gene in humans has an impact on stimulation effects [40▪]. More specifically, Met carriers exhibited a greater corticospinal excitability and produced larger MEP responses to transcranial magnetic stimulation after stimulation as compared with Val/Val homozygotes.

Similarly, baseline γ-amino butyric acid (GABA) levels measured by magnetic resonance spectroscopy (MRS) can predict motor learning insofar as higher baseline concentrations are indicative of a lower stimulation gain [41]. Similar correlations emerged during rSS [42▪▪]. Therein, local GABA concentrations measured prior to the stimulation explained 60% of the variance in a tactile learning task even though no alterations in the corresponding neurotransmitter concentration substantiated after the treatment. Rather than quantifying neurotransmitter concentrations at individual synapses, MRS can be used to evaluate the levels of various inhibitory and excitatory neurometabolites in larger brain regions. Thus, it has been demonstrated that, contrary to either sham or cathodal tDCS, anodal stimulation reduces GABA concentrations locally in the left primary motor cortex M1 in healthy controls [41,43▪▪] as well as in the ipsilesional M1 in stroke patients [44]. These results coincide with the current notion that anodal tDCS leads to an increase of excitability, whereas a decrease in excitability is observed upon cathodal tDCS. Apart from the reduction of inhibitory neurotransmitters in the neural network, anodal tDCS also operates in the opposite direction, increasing excitatory neurotransmitter concentrations. This has been demonstrated for glutamatergic metabolites, glutamate

and glutamine, as well as for combined N-acetylaspartate and N-acetylaspartylglutamate [45,46▪▪]. Those changes were restricted to the areas beneath the anodal stimulation electrode, whereas no augmentation appeared in homologous regions in the contralateral hemisphere.

Evidence for the multiplicity of tDCS effects on different physiological levels, not all being tantamount to conventional synaptic LTP, can be gathered from schizophrenia patients. The latter exhibit demonstrably decreased NMDAR levels [47] and decreased GABA transmission [48▪], whereas tDCS still enhanced their working memory performance, presumably by restoring gamma oscillations [49▪].

MRI TECHNIQUES FOR THE SYSTEMATIC SURVEILLANCE OF NONINVASIVE BRAIN STIMULATION EFFECTS

A pioneer study combining simultaneously fMRI with intracranial electrophysiological recordings and deep brain stimulation in rats was conducted to investigate the influence of local synaptic plasticity on long-range functional connectivity in the brain [50–52]. In this work, induction of LTP by high-frequency stimulation of the perforant pathway connecting the medial entorhinal cortex with the dorsal hippocampus resulted in brain-wide reorganization of neuronal networks. More specifically, after LTP stimulation and during several hours afterward, the authors found enhanced functional coupling of the hippocampal formation with the prefrontal cortex and the mesolimbic dopaminergic system [50], all brain structures functionally engaged in memory encoding and consolidation processes. Apart from the systems-level implications of these results for memory formation, they already demonstrated the important influence of local synaptic plasticity on activity propagation in brain-wide networks. Furthermore, the potentiation of neuronal responses, indicated by the steepened slope of the population excitatory postsynaptic potentials and the increased amplitude of the population spikes, correlated with the amplitude of the blood oxygen level-dependent signal, thus validating the usefulness of MRI for assessing global plasticity changes [51]. In contrast to detecting the effects elicited by noninvasive stimulation protocols only by means of their final parameters and comparing those to the corresponding datasets gathered prior to NIBS or rSS, a coupled on-going monitoring of stimulation effects is probably the more advantageous alternative. A multiparametric analysis of stimulation candidates, including noninvasive imaging data, may help establish treatment groups, defined as a homogenous sample of study participants that could benefit from personalized stimulation protocols. MRI techniques in particular lend themselves to this task, offering a high spatial resolution of the effect origin as well as being able to trace its spreading along brain-wide functional networks. What is more, connections between separate MRI-assessed parameters were drawn by Stagg and colleagues [53], who revealed an inverse correlation between GABA levels and resting state motor network connectivity. In turn, the higher amount of accessible details through noninvasive neuroimaging would assist with developing a more graded distinction between individuals in comparison with solely differentiating between responders and nonresponders, of whom the latter turned out to be less rare than previously supposed [7].

When refraining from a posteriori sample enrichments by excluding individuals who did not exhibit a response in the expected direction, the intersubject variability at hand puts forth two consecutive considerations. First, basic research endeavours to pinpoint the neurophysiological underpinnings of NIBS and rSS, insights about which would help to identify possible disturbing factors in trying to homogenize group results. Second, this homogenization would lend immediate assistance to the effective application of such treatments in clinical cases. Naturally, not all covariates are as simple to supervise and to control for as the participants' attention to the task [54], their serotonin levels [55,56▪], or the presence of low doses of ethanol [57,58], which were all shown to affect the elicitation of plasticity processes. In fact, identified genotypic markers for the expected effect of stimulation protocols, like the Val66Met polymorphism [40▪], can only be registered and not regulated. Furthermore, different disease patterns, including major depression disorder [59], NMDAR encephalitis [23], and schizophrenia [60], are accompanied by a deficit of LTP-like plasticity. Nevertheless, knowledge concerning these influences can be used for the prediction of stimulation effects, which could still be considered a significant improvement to research proceeding along the lines of trial and error. At this point, the combination of NIBS and MRI techniques gains in importance, not only for the latter's usefulness in depicting a variety of different brain network properties, ranging from anatomical to neurochemical to functional, but also for the feasibility of continuously recording data *in vivo* during the ongoing stimulation period [61▪]. Even the baseline functional connectivity, provided by fMRI, was successfully consulted to predict the efficiency of tDCS-induced modulations in terms of network connectivity in healthy individuals [33] as well as relative to analgesic effects in fibromyalgia patients [8].

Correspondingly, MRS measurements of neurochemicals in general and glutamatergic metabolites in particular are of predictive value, as the higher baseline levels of the latter are correlated with greater reductions in clinical pain scores following tDCS in fibromyalgia patients [8].

CONCLUSION

This review outlines that the claim of a consistent congruence between long-term synaptic plasticity and NIBS-induced effects is largely unfounded and leads to a deceptive terminology. All the more, the need for clarifying the neurophysiological underpinnings of the observed stimulation effects persists. This is not solely motivated by basic research interests but instead, a profound understanding would contribute to the customization of various NIBS protocols, which is of two-fold importance. First, the prediction of treatment results would allow to select only those individuals who can be reasonably expected to profit from the stimulation. Even though no long-term adverse effects are known for tDCS nor for related stimulation protocols, this approach might help to control for unnecessary expenditure of time and funds. Second, a categorization of individuals prior to the stimulus application would render an intervention into the distinct baseline state possible, thereby increasing the chances of a favourable response to the stimulation. In future years, stimulation protocols attuned to distinct treatment groups will probably be in rising demand where the first step will be a general homogenization of employed study parameters across research groups.

Acknowledgements

None.

Financial support and sponsorship

S.C. is supported by grants from the Spanish MINECO BFU2015-64380-C2-1-R and from the EU Horizon 2020 Program 668863-SyBil-AA.

Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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