HHS Public Access

Author manuscript

Pers Med Psychiatry. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

Pers Med Psychiatry. 2019 ; 17-18: 17–22. doi:10.1016/j.pmip.2019.03.001.

A review of transcranial direct current stimulation (tDCS) for the individualized treatment of depressive symptoms

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Abstract

Transcranial direct current stimulation (tDCS) is a low intensity neuromodulation technique shown to elicit therapeutic effects in a number of neuropsychological conditions. Independent randomized sham-controlled trials and meta- and mega-analyses demonstrate that tDCS targeted to the left dorsolateral prefrontal cortex can produce a clinically meaningful response in patients with major depressive disorder (MDD), but effects are small to moderate in size. However, the heterogeneous presentation, and the neurobiology underlying particular features of depression suggest clinical outcomes might benefit from empirically informed patient selection. In this review, we summarize the status of tDCS research in MDD with focus on the clinical, biological, and intrinsic and extrinsic factors shown to enhance or predict antidepressant response. We also discuss research strategies for optimizing tDCS to improve patient-specific clinical outcomes. TDCS appears suited for both bipolar and unipolar depression, but is less effective in treatment resistant depression. TDCS may also better target core aspects of depressed mood over vegetative symptoms, while pretreatment patient characteristics might inform subsequent response. Peripheral blood markers of gene and immune system function have not yet proven useful as predictors or correlates of tDCS response. Though further research is needed, several lines of evidence suggest that tDCS administered in combination with pharmacological and cognitive behavioral interventions can improve outcomes. Tailoring stimulation to the functional and structural anatomy and/or connectivity of individual patients can maximize physiological response in targeted networks, which in turn could translate to therapeutic benefits.

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Declarations of interest: none

Keywords

Transcranial electrical stimulation (TES); major depression; antidepressant treatment; neuromodulation; direct current

1. Introduction

Depression presents a major burden to global health, affecting more than 300 million people [1]. The impact of depression is compounded by the limited success of first-line antidepressant therapies where only a third of patients with major depressive disorder (MDD) are expected to remit after initial treatment [2]. Research that could promote the translation of more effective, accessible and individually-tailored antidepressant therapies into clinical practice is thus of major importance for reducing the economic and personal toll of this common and debilitating disorder. Transcranial direct current stimulation (tDCS) is a neuromodulation technique that uses low amplitude direct current (usually ≤2 mA) to enhance or suppress cortical excitability [3]. TDCS has shown therapeutic potential in a range of neuropsychiatric disorders, including MDD [4].

Conventional administration of tDCS involves a 2-electrode montage applied to the scalp to deliver constant current. In animal studies [5] with replication in humans [6], the positively charged electrode (i.e. anode) has been shown to increase cortical excitability locally, while an inhibitory effect is observed with the negatively charged electrode (cathode). Excitatory and inhibitory effects occur by shifting membrane potentials towards depolarization and hyperpolarization, respectively, and the biophysical effects of tDCS are shown to endure after stimulation. A preponderance of existing data supports that tDCS neuromodulation has probable antidepressant effects [7 8]. Though still experimental, due to its simple setup, portability, safety and low cost, tDCS could thus present a valuable noninvasive and relatively accessible treatment option for MDD. However, the antidepressant mechanisms of tDCS, identifying which individuals are most likely to benefit from treatment, and the dosing parameters optimal for achieving individualized therapeutic response, remain critical barriers to translation. In this review, we appraise recent evidence regarding the efficacy and selection of tDCS for treating individuals with major depression. We also discuss gaps in knowledge regarding the potential systems-level antidepressant mechanisms of tDCS, and research strategies to optimize and tailor tDCS to enhance its therapeutic effects.

2. The efficacy of tDCS for the treatment of depression

A growing amount of data from open-label, or randomized clinical trials (RCTs) suggests that tDCS can elicit antidepressant effects in patients with MDD [8-11]. The majority of prior depression trials have targeted the dorsolateral prefrontal cortex (DLPFC) for modulation by tDCS due to 1) its role in the top-down regulation of mood and of subcortical regions involved in emotional responses, 2) observed hypo- metabolism or activation and lateralized effects in depression imaging studies [12 13], and 3) its proximity to the scalp for external stimulation. To enhance activity (or reduce hypoactivity), the excitatory electrode (anode) has been used to target the left DLPFC (F3, international 10–20 EEG system) in the majority of studies, while the return electrode (cathode) has been placed over the right

DLPFC or a neutral region [8-11]. Though results from individual studies are less consistent, likely influenced by the inclusion of small and heterogeneous samples, antidepressant effects have been reported in the majority of investigations. The estimation of effect sizes has been made possible via meta- and/or mega analyses [8 11], which differ in that former aggregates previously reported results while the latter includes reexamination of raw data. Specifically, the most recently published meta-analyses including 7 RCTs and n=259 patients [11], reported effects for active versus sham tDCS considered small-to-medium (pooled odds ratio (OR) for response characterized as ≥50% improvement in depressive symptoms: 1.63, 95% CI 1.26–2.12; and for remission of symptoms: 2.5, 95% CI 1.26–2.49) and low publication bias. Antidepressant effects were also significant and viewed as clinically meaningful when examining clinical outcomes as a continuous variable (Hedges' g = 0.37; 95% CI 0.04–0.7). A subsequently published mega-analysis [8] re-analyzing raw data from n=289 participants from 6 RCTs found more robust clinical effects (OR for response: 2.44, 95% CI 1.38–4.32, and remission: 2.38, 95% CI 1.22–4.64, and depression improvement β = 0.347, 95% CI 0.12–0.57). Further, when examining the number necessary to treat (NNT) (i.e., the number of patients necessary to treat to prevent one undesirable outcome) compared to other depression treatment studies, response and remission were found as likely for tDCS as for commonly prescribed antidepressants and neuromodulation with repetitive transcranial magnetic stimulation (rTMS).

In a recently completed non-inferiority study, and the largest single trial to date including n=245 patients divided into three treatment arms (tDCS plus oral placebo, sham tDCS plus escitalopram, or sham tDCS plus oral placebo), both tDCS and drug therapy were found to be significantly more effective than placebo. However, in this trial (the ELECT-tDCS study), the non-inferiority margin for tDCS was not met, such that even though treatment efficacy was not shown to differ significantly across treatment modalities, pharmacotherapy was judged superior [14]. Further, another relatively large and recently completed multisite tDCS RCT including N=130 patients showed that clinical improvement, though significant, was similar in patients receiving both active and sham tDCS [15]. Although placebo effects may account for these unexpected findings, results have also brought to question whether the transient stimulation designed to mimic scalp sensations during sham also elicits biophysical effects. Taken together, the available evidence supports that left DLPFC tDCS can ameliorate depression symptoms, although there is not currently clear evidence to support that tDCS has a clinical advantage over standard treatments. However, as discussed below, it is possible that tDCS might be more effective for particular forms of depressive illness and that further optimization of treatment parameters tailored to individual patients may substantially improve efficacy.

3. Clinical factors associated with tDCS response in depression

Depression is a heterogeneous disorder, where a DSM diagnosis allows for 200+ possible symptom combinations. Different constellations of symptoms and their severity, the presence of comorbid disorders, demographics, and psychiatric and treatment histories are amongst some of the factors that could impact individual antidepressant response [16-18]. Patient selection may thus similarly affect tDCS antidepressant outcomes. To date, independent studies have shown that tDCS is clinically beneficial in mild-to-moderate,

severe as well as refractory depression [8 11]. However, combined analyses of individual patient data [8], found inverse relationships between response or remission rates and the level of treatment resistance. Therefore, as for other antidepressant treatments including including ECT and rTMS [19-21], individuals who have failed previous antidepressant trails also appear less likely to respond to tDCS. Notably, although some individual studies have examined more specific features of illness with regard to tDCS outcomes (e.g., number and duration of past depressive episodes, age of onset, duration of illness), small samples have limited interpretation of these potential moderators. The effects of tDCS for patients with different diagnostic classifiers or psychiatric comorbidies are also less studied. However, tDCS has been shown to reduce depressive symptoms in individuals with both unipolar and bipolar depression [22]. Further, in megaanalyses, bipolar depression was also shown to be a predictor of tDCS clinical improvement. Other predictors of response included severe depression, being female and melancholic depression [8].

At least two studies have explored relationships between tDCS response and clinical dimensions of depression in independent depression samples using factors derived from the Hamilton (HDRS) or Montgomery–Åsberg depression (MADRS) rating scales. One study using data from a previously published RCT (n=64) [23] used a three factor model of MADRS items, including (i) dysphoria (reported sadness, pessimistic thoughts, and suicidal thoughts), (ii) retardation (apparent sadness, concentration difficulties, lassitude, and inability to feel) and (iii) vegetative symptoms (inner tension, reduced sleep and reduced appetite) to examine differential effects of tDCS on these features [24]. Results showed significant improvements in all three MADRS factors following a 3-week course of tDCS. However, only the dysphoria and retardation factors differentiated the active and sham groups; similar findings were observed after a follow-up open-label phase of tDCS treatment. Focusing instead on addressing how pretreatment features of depressive illness might relate to subsequent tDCS response, another study used a published HDRS six factor structure, including (i) anxiety/ somatization, (ii) body weight, (iii) cognitive disturbances, (iv) circadian fluctuations, (v) retardation, and (vi) sleep disturbances, to examine predictors of tDCS response [25]. Including n=171 participants with unipolar and bipolar depression from 3 independent open-label trails, results from this study showed significant relationships between baseline cognitive disturbances, retardation and anxiety/somatization factors with tDCS response and no moderating effects of age, sex or type of depression diagnosis. Though requiring replication, these results provide initial evidence to support that tDCS may preferentially target core features of depressive illness over vegatative sympotoms, and that patients with particular clinical profiles might benefit more from treatment. Notwithstanding, to better understand how features of depression in individual patients might impact tDCS outcomes, much larger and well-characterized samples are clearly needed. Data-driven approaches might be particularly informative for identifying clinical predictors and correlates of response to allow for more tailored treatment strategies.

4. Biological factors associated with tDCS response in depression

Using blood-oxygen-level dependent (BOLD) and arterial spin labeling (ASL) perfusion imaging in animals, anodal tDCS is shown to lead to increased activation [26] and CBF [27] in specific brain areas, supporting that physiological effects could lead to downstream

neuroplastic processes. BOLD fMRI has been applied in human tDCS studies and the results showed that tDCS elicits long-lasting, polarity dependent changes in BOLD signal and network connectivity [28-31]. Similarly, ASL perfusion MRI has also shown polarity dependent changes in regional cerebral blood [31 32].

Neurotrophic factors, the proteins (including brain derived neurotrophic factor (BDNF)) supporting neuroplasticity, are shown as altered in MDD, and are related to antidepressant effects [33 34]. In line with the neurotrophic hypothesis of depression [33], animal tDCS induces long-lasting synaptic potentiation and BDNF-dependent synaptic plasticity [35], suggesting a possible mechanism of clinical response. To establish whether changes in BDNF and other neurotrophic factors might associate with tDCS or sertraline treatment in patients with MDD, plasma-levels of BDNF and neurotrophins 3 (NT-3) and 4 (NT-4), nerve growth factor (NGF) and glial cell line derived neurotrophic factor (GDNF) were measured patients with MDD (n=73) before and after randomization to active/sham tDCS or sertraline/placebo as part of the SELECT-tDCS RCT [36 37]. No changes in BDNF or other neurotrophic factors were shown to predict or relate to treatment response for either treatment modality [36 37]. However, a separate RCT investigating the non-inferiority of tDCS to escitalopram (ELECT-TDCS study, n=236, [14]), found that baseline NGF plasma levels predicted depression improvement for tDCS versus escitalopram.

Disruptions in immune system function are repeatedly implicated in pathophysiology of MDD [38], interact with neurotrophic factors [39], and are shown to be affected by neuromodulation therapies [40]. However, in the ELECT and SELECT tDCS studies [14 41], cytokines were not shown associate with clinical response though they decreased over time across treatment groups (the ELECT trial measured interleukins (IL) IL-1 ß, IL-6, IL-8, IL-10, IL-12p70, IL-18, IL-33, tumor necrosis factor-alpha (TNF-alpha), and its soluble receptors sTNFr1 and sTNFr2, and the SELECT trail measured IL-2, IL-4, IL-6, IL-10, IL-17a, TNF-alpha, IFN-γ). Though early changes in neurotrophic processes and immune response (i.e. changes occurring shortly after the initiation of treatment) might also predict or signal subsequent changes in clinical outcome, trajectories of change in these biomarkers have not been investigated in relation to tDCS treatment in MDD. With the exception of NGF, viable leads are mostly lacking at this time. However, peripheral blood biomarkers of neuroplasticity and inflammation might still prove relevant for determining predictors and correlates of tDCS response with further research in larger samples.

5. Dosing parameters and tDCS response in depression

The tDCS “dose” required to induce optimal neurobiological effects may depend on electrode montage, size, or other parameters (current intensity, polarity, duration), as well as the context of stimulation. Different RCTs of tDCS in MDD have manipulated dose by varying current intensity (0.5 to 2.5 mA), duration (20-30 minutes) and the number (usually 5-15) and frequency of tDCS sessions (once or twice daily, or on alternate days). In a prior meta-analysis of studies using different parameters, tDCS charge per electrode surface area (C/cm^2), and total summed charge were not shown to significantly influence clinical outcomes, though a trend suggested higher current charges may elicit larger antidepressant effects [11 23]. However, in megaanalysis of individual patient data, both greater tDCS

charge and longer session duration were found to statistically improve antidepressant response, suggesting future trials might be optimized accordingly.

Though almost all modern RCTs of MDD have targeted the left DLPFC for excitatory stimulation, cathode position, which also affects the path of electric current through the brain, has varied across studies. However, clinical outcomes do not appear to differ for montages using the right DLPFC (F4, 10-20 EEG location) or the right supraorbital area for cathode placement, which have been used in the majority of MDD studies. While F3 anodal tDCS may better engage dorsal forebrain-limbic systems involved in mood regulation, bitemporal tDCS may more effectively engage ventro-limbic circuits [42 43] involved in emotion reactivity. Notably, computational modelling has shown that anodal F3 stimulation with extra-cephalic right upper arm cathode placement is more effective for inducing changes in current flow in deeper ventro-limbic structures [42 43], though no RCTs have compared this montage to other montages typically used in MDD. Since dysregulated activity in dorsal prefrontal-limbic circuits and in subcortical hippocampal-amygdala-striatal-thalamic circuits are linked with depression pathophysiology and repeatedly observed in structural and functional imaging studies of depression [44 45], it appears likely that modulation of both systems by tDCS may work to elicit a therapeutic response. Further, patient-specific clinical characteristics and/or symptom profiles may ultimately dictate if a given tDCS montage may be more effective for a particular patient. Finally, studies using stimulation targets informed by individual functional and structural anatomy, and that address links between regional current density in relation to changes in clinical response might be of important value for better optimizing and tailoring tDCS treatment in MDD.

6. Intrinsic and extrinsic moderators of tDCS response in depression

Since low intensity stimulation shifts the balance of neural excitation and inhibition [46], other brain network dynamics can influence whether or not downstream changes in brain activity occur with tDCS [47]. Indeed, animal studies show that weak, but simultaneous polarization of a large number of neurons are amplified in an already active neural network [48]. TDCS neuromodulation is thus partially dependent on the concurrent activity of particular neural circuits, where changes are more likely to occur in activated over inactive networks [49]. These biophysical interactions also explain why tDCS effects on behavior are mostly observed when cognitive or behavioral probes are used together with stimulation [50 51]. However, in MDD, tDCS is suggested to affect pathological network activity selectively without a behavioral probe [49] and is usually applied without simultaneous manipulation of behavioral state. Nonetheless, the therapeutic effects of tDCS might still be strengthened by intrinsic or extrinsic potentiation of neural function. For example, pharmacological therapies perturb intrinsic state by modulating neurotransmission and antidepressant effects might be greater with combination drug therapy. Data from several individual trials as well as from mega-analysis support this hypothesis where the initiation or augmentation of antidepressant drug treatment *with* tDCS is shown to significantly improve clinical efficacy [41 52].

Cognitive behavioral interventions, which can elicit response rates similar to antidepressant medications [53], present a means for extrinsic modulation of depression-related brain circuits. For DLPFC tDCS, cognitive behavioral interventions are suggested to modulate

top-down neural processing to regulate emotional states by engaging underactive prefrontal circuits to regulate overactive subcortical limbic circuits [54]. Notably, initial evidence supports that F3 anodal tDCS combined with cognitive behavioral therapy can produce both acute and lasting antidepressant effects [55]. Further, an open-label study combining tDCS with cognitive emotional training (CET), was shown to produce significant clinical improvements in medication-resistant major depression (41% achieved response criterion), as well as improvements in self ratings of psychological symptoms, ruminations and quality of life [56]. Though not a controlled trial, these findings thus suggest that tDCS used in combination with psychological interventions may improve efficacy, even in refractory depression. Prior studies have also attempted to prime DLPFC neural circuitry in MDD using neurocognitive training coupled with tDCS. In a prior RCT, patients receiving cognitive control/working memory training combined with active or sham tDCS (n=37) showed significant antidepressant effects, though between treatment groups differences were not observed [57]. However, older, higher-performing individuals showed particular benefits of combination therapy. A subsequent RCT using another variant of cognitive control training with concurrent tDCS showed antidepressant effects across all conditions at the end of the 5-session treatment series and sustained improvements in depressive symptoms in patients that received active cognitive training plus tDCS at 3-week follow-up [58]. Preliminary evidence thus suggests that pharmacotherapy and cognitive training used to augment tDCS may enhance or prolong antidepressant outcomes.

7. Individual optimization to improve tDCS treatment in depression

The extent to which tDCS can affect neural properties relies on the penetration of current and characteristics of the skull, CSF distribution and cortical morphology. Identical stimulation parameters may thus induce different physiological, behavioral, and therapeutic effects across individuals [9]. For example, even for a well-defined stimulation area, accuracy of electrode placement may vary based on individual anatomy. The diffusivity of current flow can also influence neural targeting, and is greater for larger scalp electrodes as used in most prior depression RCTs. Strategies to mitigate (or leverage) these factors could maximize tDCS therapeutic response in individual patients. Though it is not yet clear whether more focal or diffuse stimulation might improve clinical outcomes in MDD, electrode configurations are now available that allow for high-definition (HD) tDCS [59]. HD-tDCS consists of 4 small “return” disk electrodes arranged around a center electrode, which determines the direction of unifocal modulation without requiring a regionally separated anode and cathode [60]. On direct comparison, HD-tDCS produces changes in brain excitability that exceed the magnitude and duration of standard tDCS [61]. However, no published RCTs have yet compared the therapeutic efficacy of conventional versus HD-tDCS in MDD. Also, as relevant to the spatial focality of stimulation, prior tDCS trials of MDD have performed mostly the same left DLPFC electrode localization procedures without attempting to standardize electrode placement based on skull size and brain morphology, which can impact neural engagement [62]. For example, prior studies have shown that MRI-guided neuronavigation reduces inter-subject variability for DLPFC targeting for rTMS [63]. Further, targeting rTMS to DLPFC using structural anatomy [64] as well as functional coordinates extracted from meta-analysis of functional neuroimaging

studies resulted in greater anti-depressive effects in MDD patients compared to standard localization methods (i.e., 5 cm or 10-20 method) [65]. The use of MRI-guided neuronavigation to target the DLPFC may similarly reduce inter-individual variability to optimize tDCS.

Computational modeling of tDCS electric field current direction and intensity suggest the perturbation of distinct neural regions for different tDCS montages [66]. To understand the relationships between tDCS dose parameters and electric-field distributions based on individual anatomy (e.g., scalp and skull thickness, CSF and gray and white matter, topography of the cortex as well as white matter anisotropic conductivities), modeling of electric field distributions in individual patients using structural MRI can improve neural targeting. Recently, our group has developed MRI-based electric current mapping techniques to measure tDCS induced electric currents in the human brain *in vivo* by tracking corresponding changes in magnetic fields or phase maps [67-69]. Thus, unlike head models, or other imaging modalities that provide surrogate markers of tDCS stimulation, it is possible to visualize the magnetic field induced by tDCS current with high spatial resolution in individual subjects. In line with results from modeling experiments [70], *simultaneous* tDCS-MRI shows that tDCS induces cortical electrical field changes under the electrodes as well as in brain regions connected to the stimulation site [Figure 1.]. Realtime MRI mapping of tDCS neural engagement in individual subject can ensure modulation of targeted networks to maximize possible antidepressant effects.

8. Conclusion

A growing body of evidence suggests that tDCS can elicit antidepressant effects. Though tDCS-related clinical response obtained using conventional F3 anodal tDCS has not been demonstrated as superior to standard first-line antidepressants in terms of overall efficacy, benefits include its minimal side effects and low risk for adverse events, low cost and accessibility. However, cumulating evidence suggests that tDCS can be further optimized to enhance its therapeutic effects. Optimization can occur by manipulating dose (including electrode size, configuration and charge), using combination pharmacological or cognitive therapies designed to sensitize brain circuits linked with disease pathophysiology, and refining spatial targeting (electrode placement) and stimulation based on individual structural and functional anatomy and connectivity. Understanding of how electric fields penetrate the brain to engage and modulate particular neural circuits will also advance efforts to tailor treatment, which can be achieved by computational modelling and novel in-vivo mapping of tDCS magnetic fields and current density. Though it is not yet clear whether particular patient characteristics can inform which individuals most likely to benefit from tDCS therapy, recent research suggests that tDCS elicits antidepressant effects in both unipolar and bipolar depression, but is less suited for treatment resistant patients. Research also suggests tDCS may better target dimensions of depressive illness, and that patients with particular pre-treatment symptom profiles will have a greater response. At present, measures of gene and immune system function have shown fewer links with tDCS-related clinical response, but few studies have addressed this question. Future research, including imaging guided tDCS, more comprehensive clinical and cognitive phenotyping and data-driven approaches to identify more salient predictors of response are still needed.

Acknowledgements:

Funding: This work was supported by the National Institutes of Health, including Grant Nos. MH110526 (to KLN and DJW), and K24 MH102743 (to KLN).

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Highlights:

- TDCS of the left dorsolateral prefrontal cortex can reduce depressive symptoms
- TDCS may be less suited for treatment-resistant depression
- Combining tDCS with pharmaco- or psychotherapies may enhance therapeutic outcomes
- Optimizing tDCS parameters to individual patients can improve physiological response

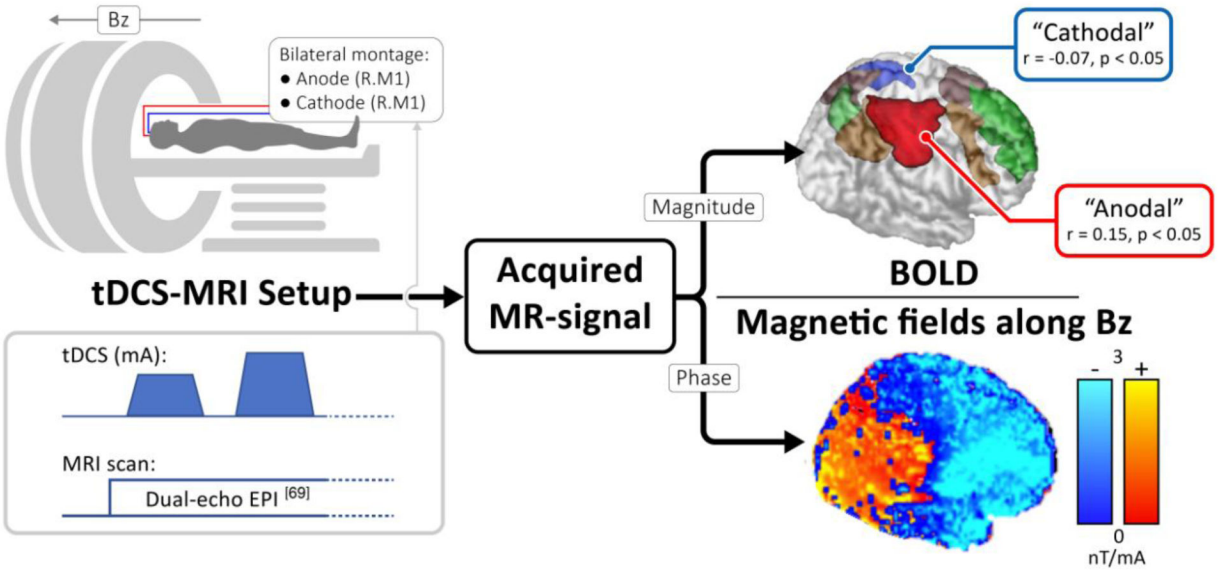

Figure 1. Simultaneous mapping of tDCS electric currents and functional changes in a sample subject.

Concurrent tDCS-MRI data can be acquired as shown, with the phase and magnitude of the MR signal encoding the current induced magnetic field (along Bz) and BOLD-contrast respectively. While the former is linearly proportional to tDCS electric currents along an orthogonal direction (Ampere's Law), the latter is an established marker for tracking brain activity. An ICA analysis on the BOLD-data identified brain networks including the default mode network (green) and the executive networks (brown). The analysis also identified two regions underneath the anode and cathode electrodes (labelled "anodal" and "cathodal"), which were found to correlate significantly with the applied tDCS current.