The Effects of Medication Use in Transcranial Direct Current Stimulation: A Brief Review

Molly E. McLaren^a, Nicole R. Nissim^{a,b} and Adam J. Woods^{a,b}

^a Center for Cognitive Aging and Memory, Department of Clinical and Health Psychology,
University of Florida, PO Box 100165, Gainesville FL, 32610, USA

^b Department of Neuroscience, University of Florida, PO Box 100244, Gainesville, FL, 32610,
USA

Email: memclaren@phhp.ufl.edu, nnissim18@ufl.edu, ajwoods@phhp.ufl.edu

Corresponding Author: Adam J. Woods, Ph.D., Center for Cognitive Aging and Memory,
Department of Clinical and Health Psychology, University of Florida, P.O. Box 100165,
Gainesville, FL, 32610-0165, USA. Phone: 352-294-5842. Email: ajwoods@phhp.ufl.edu

Abstract

Background: There has been increased interest in the potential use of transcranial direct current stimulation (tDCS) as treatment for multiple conditions including depression, pain, and cognitive impairment. However, few studies account for the possible influence of comorbid medications when conducting tDCS research.

Objective/ Hypothesis: This literature review was conducted to examine what is currently known about the impact of medications on tDCS, provide recommendations for future research practices, and highlight areas where more research is needed.

Methods: Key terms were searched in PubMed and Web of Science to identify studies that examine the impact of medication on tDCS effects in adults. Relevant papers' reference lists were also reviewed for thoroughness. Studies examined the effects of medication on 1mA tDCS stimulation delivered to M1 (motor) and orbit/supraorbital (SO) area. All studies measured the effects of tDCS via MEP TMS paradigm.

Results: Results of the literature review suggest multiple classes of medications, including sodium and calcium channel blockers, and medications that influence various neurotransmitter systems (GABA, dopamine, serotonin, etc.) may all impact tDCS after effects.

Conclusions: Research to date suggests multiple classes of medications may impact tDCS effects. These results highlight the importance of documenting medication use in research subjects and carefully considering what types of medications should be allowed into tDCS trials. Many questions still remain regarding the exact mechanisms of action for tDCS and how various parameters (medication dosages, tDCS stimulation intensity, etc.) may further impact the effects of medications on tDCS.

Keywords: transcranial direct current stimulation, tDCS, comorbid medication interactions, outcomes, study design

Introduction

Transcranial Direct Current Stimulation (tDCS), a type of non-invasive electrical brain stimulation, has gained renewed interest in recent years in the treatment of multiple conditions including depression, chronic pain, and cognitive impairment [1-5]. It has also been proposed as a potential cognitive enhancer in healthy aging [6]. TDCS involves passing a weak electric current (typically 1-2mA stimulation) through two or more electrodes placed on the scalp [7, 8]. Current penetrates skin, skull, meninges, and cerebrospinal fluid to stimulate underlying cortical and subcortical tissue, altering membrane permeability to ions and larger molecules [9]. Under a 1mA stimulation paradigm, tDCS tends to produce excitability enhancement in the area located under and around the placement of the anode (i.e. “under the anode”) and excitability reduction in neurons located under and around the placement of the cathode (i.e. “under the cathode”) with after effects of stimulation reported from minutes to hours post tDCS [9]. The duration of after effects varies based on duration of stimulation and stimulation intensity [10, 11].

The exact mechanisms of action for tDCS are unclear, and may vary depending on the location of stimulation [12]. Immediate, or acute, effects of stimulation under the anode appear to rely on sodium and calcium concentrations, and long-term potentiation- or depression-like plasticity generated by tDCS may depend on NMDA receptor-dependent glutamatergic neurons [12, 13]. It is hypothesized under the anode, 1mA of tDCS stimulation increases permeability to positively charged ions, such as sodium, resulting in an influx of these ions into the cell [13]. The influx of ions causes a partial depolarization of the neuron, which increases the probability of an action potential when adjacent neurons stimulate the cell. Depolarization as a result of tDCS also allows for magnesium, which typically blocks NMDA receptors to dislodge, allowing for increased influx of calcium into the cell following an action potential. This increase of

calcium stimulates an intracellular chemical cascade, which results in upregulation of receptors, and long term potentiation.

Mechanisms of action resulting in hyperpolarization under the cathode following tDCS stimulation appears less clear. It has been proposed the neuronal orientation in relation to the electrodes may dictate whether cells become hyperpolarized or depolarized as a result of tDCS stimulation [9, 14]. However, the relationship between polarity and stimulation appears to be at least somewhat dependent on stimulation intensity, as 2mA of stimulation has been shown in at least one study to produce depolarization under both the anode and the cathode electrodes [10].

Gamma-aminobutyric acid (GABA) and glutamate both appear to play an important role in the mechanism of action in tDCS and other neurotransmitters such as serotonin, dopamine, norepinephrine, and acetylcholine may modulate the impact of tDCS in the brain [15-19].

Varying ion or neurotransmitter concentrations via medications may impact the complex mechanisms that result in immediate excitability enhancement or excitability reduction due to tDCS and the long term potentiation or depression induced by tDCS stimulation [13]. However, few intervention studies to date discuss the potential confounds of participant medication use on the effectiveness of tDCS. This poses a problem in the interpretability of tDCS stimulation studies currently reported in the literature, and, if medication interactions are not systematically addressed, could pose significant difficulties in understanding the efficacy of tDCS as the field moves forward.

To highlight the impact of medication use in tDCS this review briefly examines what is currently known about the potential influence medication use has on tDCS efficacy and highlights the importance of controlling for medication use in subjects undergoing tDCS. It also provides recommendations for the field regarding documentation of participants' medication

usage and future directions in the study of how tDCS in combination with medications may affect neuronal firing rates.

Materials and methods

Articles in this review were found via PubMed and Web of Science search engines. Initial keyword searches included “transcranial direct current stimulation” and “medication”, as well as “transcranial direct current stimulation” and “drug effects”. These initial searches resulted in 208 results from PubMed and 364 results from Web of Science. Additionally, more specific searches for classes of drugs and specific patient populations were also conducted including “transcranial direct current stimulation” and “NMDA”, “transcranial direct current stimulation” and “nicotine”, and “tDCS” and “medication” and “schizophrenia.” Titles and relevant abstracts were reviewed to create an initial list of relevant publications. References lists from reviewed papers, as well lists of papers which cited the original papers identified were also reviewed for thoroughness. Studies utilizing a non-MEP TMS paradigm, or back-to-back tDCS administration (anode followed by cathode with no assessment in between) were excluded from the review. A total of 23 peer-reviewed articles were found to examine the impact of different medications on tDCS effects, and were included in this review.

All studies reviewed in this paper stimulated using electrodes placed over M1 (motor) and contralateral orbital/ supraorbital region (SO, also consistent with Fp1 or Fp2 in International 10-20 EEG nomenclature) with 1mA of tDCS. The majority of studies reviewed described measuring motor evoked potentials (MEPs) via a Magstim 200 magnetic stimulator (Magstim, Whiteland, Dyfed, UK) with a figure-of-eight coil held tangentially (45 degree angle) to the skull above the abductor digiti minimi (ADM). One study did not explicitly describe their methodology (e.g. did not specify stimulator used, angle of positioning, etc.) while another used

an alternative method [e.g. utilized different stimulatory system; 20, 21]. TMS intensity was adjusted to provoke a 1mV MEP at baseline in most studies, although one study did not specify this [20]. Signals were amplified and filtered with a time constant of 10ms and a low-pass filter of 2.5kHz in 14 of the 23 total studies, and digitization and analogue-to-digit-rate of 5kHz was used in 16 out of 23 studies. Some minor variations in regards to amplification and filtering technique were present across studies, as was documentation of digitizing and analogue protocols[17, 19-26]. In this review of results, acute effects refer to excitability changes during tDCS, while after effects refer to excitability changes following stimulation.

Results

Influence of ion channel blockers on tDCS effects

Medications affecting either sodium or calcium channels have been shown to impact the efficacy of tDCS. Blocking sodium channels via 600mg of carbamazepine prevents both acute and after effects of tDCS under the anode [n=8-12 subjects; 13, 27]. Blocking calcium channels via 10mg of flunarizine diminishes the acute excitability enhancement effects seen under the anode following tDCS, and blocks any after effects under the anode following stimulation [n=11-14 subjects; 13]. This suggests 10mg of flunarizine has a larger impact on the after effects of tDCS stimulation than the acute effects [13]. Of note, neither sodium nor calcium channel blockers appear to impact either the acute or after effects of excitability reduction observed under the cathode in tDCS [13]. Other ion channels that may be affected by medication use, such as potassium and chloride have not been systematically studied in tDCS.

Impact of NMDA on long-term effects of tDCS

Long-term potentiation-like effects of tDCS have been proposed to work via NMDA-receptors excitation [13]. While acute effects of tDCS have not been shown to be impacted by

administration of a NMDA antagonist, after effects of tDCS under both the anode and cathode have been shown to be abolished by the administration of a NMDA antagonist [dextromethorphan, 150mg; n=6-13 subjects; 13, 27-29]. The impact of dextromethorphan on excitability enhancement following tDCS under the anode appears to be dose-dependent, with low dosages (50mg) having no impact on tDCS efficacy under the anode, but medium (100mg) and high dosages (150mg) of dextromethorphan resulting in no excitability enhancement effects following tDCS stimulation [n=13 subjects; 28]. Administration of a partial-NMDA agonist, d-Cycloserine (100mg) has been shown to prolong the after effects of tDCS under the anode [n=12 subjects; 30]. D-Cycloserine has also been shown to increase the intensity of excitability reduction seen under the cathode 10 minutes post tDCS stimulation, although it does not appear to prolong the excitability reduction effects [30]. These results suggest administration of medications that impact NMDA receptor activity may have significant effects on the after effects of tDCS.

Impact of GABA on tDCS

In placebo-controlled experiments (n=12 subjects per group) administration of a GABA agonist (lorazepam, 2mg) did not impact acute tDCS effects [31]. In contrast, lorazepam (2mg) has been shown to initially delay but then prolong the excitability enhancing after effects seen under the anode following both short (5 minutes) and long (11 minutes) stimulation sessions of tDCS [n=9-10 subjects per group; 31]. In contrast, lorazepam did not appear to impact the excitability reducing after effects of tDCS under the cathode [31].

Neuromodulatory Neurotransmitters effects on tDCS

Dopamine

Administration of L-DOPA, a dopamine precursor, has an inverted-U dose response effect on tDCS, with low (25mg) and high (200mg) dosages of L-DOPA eliminating the after effects of tDCS under both the anode and cathode [n=12 subjects; 22]. A medium dosage of L-DOPA (100mg), however, has been shown to switch the excitability enhancing after effects under the anode into excitability reduction, and prolong the excitability reducing after effects of tDCS under both the anode and cathode in sample sizes of 12 to 18 subjects [20, 22].

The impact of dopamine medications appears to not only be dose-dependent but also receptor specific. In a small sample of 4 medicated subjects versus 12 controls, Nitsche found blocking D2 receptors via 400mg of sulpiride reduced both the typical excitability enhancement after effects under the anode and the excitability reduction after effects under the cathode for up to 60 minutes post stimulation [32]. Administration of a D2 agonist, bromocriptine, at low and high dosages (2.5mg or 20mg) has been shown to eliminate the after effects of tDCS under both the anode and cathode [n=12 subjects; 23]. Medium dosages (10mg) have been shown to reverse the excitability enhancing after effects of tDCS under the anode resulting in a trend toward excitability reduction, while prolonging the excitability reducing after effects under the cathode [23]. In contrast, administration of a D2/D3 agonist, ropinirole, has been shown to eliminate or reverse the after effects of tDCS under the anode at low dosages (0.125mg or 0.25mg, respectively), while having no effect at medium dosage under the anode [0.5mg; n=12 subjects; 33]. At high dosages, ropinirole has been shown to decreased the magnitude of stimulation after effects under the anode [1.0mg; 33]. Under the cathode, ropinirole eliminates the after effects of tDCS at low dosages (0.125mg, 0.25mg), elongates and enhances the after effects of tDCS after medium dosages (0.5mg), and reverses the after effects of tDCS from excitability reduction to excitability enhancement at high dosages [1.0mg; 33]. Different still are the after effects of

D1/D2 agonists, with one study finding the administration of pergolide (0.025mg) in 12 subjects did not impact excitability enhancing after effects under the anode following tDCS administration, but that the drug prolonged the excitability reducing after effect observed under the cathode [32].

Several studies have further examined the effects on tDCS of administration of multiple drugs affecting dopamine concentrations. In a study of 4 medicated subjects versus 12 placebo controls the administration of pergolide (0.025mg) after blocking D2 receptors via 400mg of sulpiride, thereby theoretically increasing D1 receptor activity alone, did not restore either the excitability enhancing or reducing after effects of tDCS [32]. Similarly, low and high dosages of L-DOPA (25mg and 200mg) given in conjunction with 400mg of sulpiride to block D2 receptors, thereby theoretically increasing D1 receptor activity, resulted in elimination of excitability enhancing after effects of tDCS under the anode, and a trend towards reversal of excitability reduction to enhancement under the cathode [n=12 subjects; 17]. At medium dosage of L-DOPA (100mg) while blocking D2 receptors, however, excitability enhancing after effects of tDCS under the anode were restored, save for the first 5 minutes post stimulation [n=12 subjects; 17, 34]. The effects under the cathode are less clear, with one study reported elimination of the excitability reducing after effects under the cathode, while another study reported shortened after effects following tDCS [17, 34]. Taken together, these results suggest D1 receptors may play a modulatory role in the after effects under both anode and cathode electrodes during tDCS, but their ability to do so appears to be dose dependent. These results as a whole suggest altering dopamine concentrations has a significant, dose and receptor-dependent impact on tDCS stimulation after effects.

Norepinephrine and Epinephrine

A single administration of a selective norepinephrine reuptake inhibitor (reboxetine, 8mg) to 16 subjects has been shown to reverse the after effects of tDCS under the cathode-from excitability reduction to enhancement and increase the level of excitability enhancement under the anode from 10-25 minutes post stimulation [19]. Chronic administration of reboxetine has a similar pattern of results, with increased excitability enhancement under the anode, and reversal from excitability reduction to enhancement under the cathode [19]. Additionally, with chronic administration of reboxetine, tDCS after effects under the anode were prolonged until the next evening following stimulation [19]. Administration of a beta-adrenergic antagonists (propranolol) has been shown to shorten the after effects of tDCS [n=12 subjects; 35]. Together, these results suggest manipulation of the adrenergic system may impact the effects of tDCS.

Amphetamine

Amphetamine has been shown to prolong the excitability enhancing after effects seen under the anode and slightly reduce the excitability reduction typically seen under the cathode following 1mA tDCS stimulation [n=6-9 subjects; 35]. This effect appears to be NMDA dependent, as administration of dextromethorphan in conjunction with amphetamine eliminates the excitability enhancing after effects seen under the anode following tDCS [n=5 subjects; 35].

Serotonin

Selective serotonin reuptake inhibitors (SSRIs) have been shown to impact the after effects of tDCS. Administration of a single dose of citalopram (20mg) has been shown to increase and prolong the excitability enhancing after effects of tDCS under the anode [n=12 subjects; 18]. Under the cathode, a single dose of citalopram (20mg) reversed the typical excitability reduction to excitability enhancement and prolonged after effects [18]. Chronic administration of citalopram (35 days) resulted in a similar pattern, with amplified and prolonged

excitability enhancing after effects seen under the anode, and a reversal from excitability reduction to enhancement under the cathode following tDCS [n=12 subjects; 24]. The impact of citalopram on tDCS appears to be NMDA-receptor dependent, as administration of dextromethorphan in combination with citalopram has been shown to eliminate any after effects of tDCS administration [24].

Acetylcholine (ACh)

Rivastigmine (3mg), a cholinesterase inhibitor, has been shown to initially block the after effects of tDCS under the anode, and initially delay but then prolong the excitability reducing after effects under the cathode [n=12 subjects; 36].

Nicotine

Nicotine has been shown to impact the efficacy of tDCS in both smokers and non-smokers. In non-smokers nicotine administration (10mg/ml nicotine spray) has been shown to eliminate the excitability enhancing after effects under the anode following tDCS, and diminish and delay the excitability reducing after effects under the cathode [n=21 to 48 subjects; 28, 37]. Administration of a nicotine patch 6 hours prior to tDCS stimulation resulted in abolishment of the excitability enhancing after effects under the anode and inhibitory after effects under the cathode following tDCS administration [n=48 subjects; 25]. This effect appears to be dose dependent [n=24 subjects; 26]. Administration of a nicotine receptor agonist, varenicline, at low dosages (0.1mg) did not impact tDCS after effects, while at medium dosages (0.3mg) it abolished all after effects of tDCS [26]. At high dosages (1.0mg) varenicline preserved the excitability reducing after effects seen under the cathode following tDCS administration and delayed the excitability enhancing effects seen under the anode by 25 minutes [26].

In non-smokers, the administration of dextromethorphan (100mg) allowed for the restoration of tDCS after effects under the anode following nicotine patch administration, suggesting nicotine in non-smoker results in an over-abundance of calcium in the cell which can be counteracted by the blockage of NMDA-receptors [28]. Of note, low (50mg) and high (150mg) dosages of dextromethorphan did not restore tDCS after effects under the anode following nicotine administration in non-smokers [28].

In smokers, withdrawal from nicotine (10 hours without smoking) has been shown to eliminate excitability enhancing after effects of tDCS under the anode, but did not impact the excitability reduction seen under the cathode [n=24 subjects; 38]. Similarly, short term (30 minutes or more) withdrawal from nicotine has not been shown to impact excitability reduction seen under the cathode in schizophrenic patients who smoke [n= 17 subjects; 21]. It is important, however, to recognize patients in this study were currently medicated (daily use of chlorpromazine) [21]. Administration of a nicotine patch to smokers undergoing withdrawal restored the excitability enhancement seen under the anode following tDCS stimulation, but eliminated the excitability reducing after effects of tDCS under the cathode [38].

INSERT TABLE 1

Discussion

Evidence to date suggests a wide variety of medications can influence the efficacy of tDCS. Patients with cardiac disease or risk factors including high blood pressure, cardiac arrhythmias, or peripheral vascular disease may be prescribed sodium or calcium channel blockers or beta-adrenergic antagonists that influence tDCS efficacy [13, 39-41]. Neuropathic pain and migraines may also be treated with drugs that impact sodium or calcium channels which could, in turn, impact the effects of tDCS [13, 42, 43]. Sleep disorders and anxiety may be

treated via benzodiazepines that alter GABA concentrations and may therefore impact the efficacy of tDCS [31, 44, 45]. Similarly, Parkinson's disease patients prescribed dopamine agonists, or individuals with dementia who are prescribed an anti-cholinesterase inhibitor may experience medication interactions with tDCS [22, 36, 46, 47]. Additionally individuals prescribed antipsychotics for schizophrenia or bipolar disorder may have a drug interaction with tDCS administration as a result of alterations to dopamine [33, 48]. Whether tDCS in combination with medication may be less or more efficacious in treating various conditions is still unclear. Significantly more research is needed to understand the complicated interaction between pharmacological intervention and tDCS [49].

The wide impact of drug interactions in tDCS suggest even populations typically regarded as "healthy" may experience unexpected medication interaction with tDCS. It is estimated that approximately 10% of adults take antidepressant medications (e.g., SSRIs), which may impact tDCS effects [18, 50]. In addition recreational drugs use, such as ketamine, phencyclidine, stimulant medications, and nicotine may all affect the mechanisms of action in tDCS [13, 31, 35, 38].

Recommendations and Future Directions

Given the wide variety of medications that have been shown to impact tDCS stimulation, there is a high likelihood for studies that do not screen for medication usage will inadvertently enroll participants who are taking medications that may impact the mechanisms of action of tDCS. It is therefore imperative for researchers to thoroughly review medication list and recreational drug use with potential participants before enrolling them in a tDCS research study. When studying healthy populations, individuals taking medications that have been shown to impact tDCS should be excluded from studies when possible. For example, mechanistic studies

of tDCS effects are well advised to exclude participants taking medications shown previously to interact with tDCS effects. However, this may significantly undermine feasibility of data collection. Thus, a hybrid approach could also be used such that certain medications shown to block tDCS effects are used as exclusion criteria (e.g., sodium channel blockers, calcium channel blockers, and NMDA receptor antagonist), while other medications shown to modulate tDCS effects are tracked and used as covariates in statistical analyses.

It is unclear at this time what the potential impact of medication use is on specific patient populations undergoing tDCS treatment. Physiological differences between patient and healthy populations may result in altered responses to tDCS. Medications may similarly differentially affect patient groups compared to healthy individuals which may further alter the effects of medication on tDCS results in specific populations. While significant work has been done examining the impact of tDCS on patient populations, there is a dearth of research examining the potential impact of various medication dosages, types, and combinations of medications on tDCS efficacy in patients. Until more research has been completed to address this gap in the literature it is important when studying medical or psychiatric populations, to document , medication use, including time course of medication usage, and used as covariates in analyses. Whenever possible, variation in medication type or dosage should be limited, and studies should clearly document the specific medications used in their samples. In the absence of medication data and tracking, it becomes quite difficult to interpret study findings, especially from small sample sizes – a common issue in tDCS research. It remains possible that previously reported tDCS effects might in fact be larger than currently reported were variability from medication interaction addressed. Careful consideration for medication interaction in future studies will help to address

this possibility. Regardless, reducing variability of effects of tDCS to maximize interpretability of outcomes is an important and necessary goal in the field of tDCS.

While research to date provides strong evidence the mechanisms behind tDCS can be heavily affected by medication, large gaps in the literature remain. The majority of studies reviewed in this paper utilized <20 subjects, and were conducted by the same research group. The data from these studies therefore should be interpreted as pilot, proof-of-concept results. Larger studies from multiple groups of investigators, utilizing more participants is needed to be able confirm patterns of interaction effects between tDCS and various medications. The mechanism of action of tDCS have been proposed to vary based on location of stimulation [12]. It is therefore unclear if different medications will have the same pattern of effects on tDCS in non-motor cortex areas. Additionally, all studies investigating drug effects on tDCS excitability to date utilize a 1mA stimulation paradigms. The effects of tDCS have been shown to vary at different stimulation intensities, and it is therefore unclear whether the pattern of medication and tDCS interactions would be maintained following 2mA stimulation [10]. Length of time or repetitive tDCS administration may also alter drug interaction effects, but this has yet to be systematically explored in the literature. Drug potency and duration of medication use may also impact the interaction between medications and tDCS. As the majority of studies reviewed only utilized a single administration of medication, it is still unclear what prolonged medication uses effects on tDCS are, and if specific drug types may have different one-time versus prolonged use effects of tDCS. Finally, very few studies have examined the potential impact of polypharmacy on tDCS efficacy, something that may be very common in psychiatric and medical populations.

Conclusions

While much is still unknown regarding the effects of medication and tDCS, results to date highlight the importance of monitoring and controlling for this potential confound in tDCS research moving forward. As tDCS continues to be studied as a potential intervention for both medical and psychiatric conditions, it is important to monitor and report participant medication and recreational drug usage to insure interpretability of study results.

Acknowledgements

Funding: Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under University of Florida Clinical and Translational Science Awards TL1TR001428 and UL1TR001427. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Molly McLaren is supported by a grant from the National Institute on Aging (T32 AG020499). Adam Woods is supported by grants from the National Institute on Aging (NIA R01AG054077 and NIA K01AG050707). Additional Support for this research is from the Cognitive Aging and Memory Clinical Translational Research Program and the McKnight Brain Research Foundation.

Conflicts of Interest: none

References:

- [1] Antal A, Terney D, Kühnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. *J Pain Symptoms Manage* 2010;39:890-903.
- [2] Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A. Treatment of depression with transcranial direct current stimulation (tDCS): a review. *Exp Neurol* 2009;219:14-9.
- [3] Ferrucci R, Mameli F, Guidi I, Mrakic-Spota S, Vergari M, Marceglia S, et al. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. *Neurology* 2008;71:493-8.
- [4] Szymkowicz SM, McLaren ME, Suryadevara U, Woods AJ. Transcranial direct current stimulation use in the treatment of neuropsychiatric disorders: a brief review. *Psychiatr Ann* 2016;46:642-6.
- [5] Ahn H, Woods AJ, Kunik ME, Bhattacharjee A, Chen Z, Choi E, et al. Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: an experimenter-and participant-blinded, randomized, sham-controlled pilot clinical study. *Brain Stimul* 2017;10:902-9.
- [6] Hsu W-Y, Ku Y, Zanto TP, Gazzaley A. Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis. *Neurobiol Aging* 2015;36:2348-59.
- [7] Woods A, Antal A, Bikson M, Boggio PS, Brunoni A, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clin Neurophysiol* 2016;127:1031-48.
- [8] Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimul* 2016;9:641-61.
- [9] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000;527:633-9.
- [10] Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J Physiol* 2013;591:1987-2000.
- [11] Ho K-A, Taylor JL, Chew T, Gálvez V, Alonzo A, Bai S, et al. The effect of transcranial direct current stimulation (tDCS) electrode size and current intensity on motor cortical excitability: evidence from single and repeated sessions. *Brain Stimul* 2016;9:1-7.
- [12] Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neuroscientist* 2011;17:37-53.
- [13] Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J Physiol* 2003;553:293-301.
- [14] Kabakov AY, Muller PA, Pascual-Leone A, Jensen FE, Rotenberg A. Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. *J Neurophysiol* 2012;107:1881-9.
- [15] Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *J Neurosci* 2009;29:5202-6.
- [16] Agarwal SM, Bose A, Shivakumar V, Narayanaswamy JC, Chhabra H, Kalmady SV, et al. Impact of antipsychotic medication on transcranial direct current stimulation (tDCS) effects in schizophrenia patients. *Psychiatry Res* 2016;235:97-103.
- [17] Fresnoza S, Paulus W, Nitsche MA, Kuo M-F. Nonlinear dose-dependent impact of D1 receptor activation on motor cortex plasticity in humans. *J Neurosci* 2014;34:2744-53.

- [18] Nitsche MA, Kuo M, Karrasch R, Wächter B, Liebetanz D, Paulus W. Serotonin affects transcranial direct current–induced neuroplasticity in humans. *Biol Psychiatry* 2009;66:503-8.
- [19] Kuo H, Paulus W, Batsikadze G, Jamil A, Kuo M, Nitsche MA. Acute and chronic effects of noradrenergic enhancement on transcranial direct current stimulation - induced neuroplasticity in humans. *J Physiol* 2016;595:1305-14.
- [20] Kuo M-F, Paulus W, Nitsche MA. Boosting focally-induced brain plasticity by dopamine. *Cereb Cortex* 2008;18:648-51.
- [21] Strube W, Bunse T, Nitsche MA, Wobrock T, Aborowa R, Misewitsch K, et al. Smoking Restores Impaired LTD-Like Plasticity in Schizophrenia: a Transcranial Direct Current Stimulation Study. *Neuropsychopharmacology* 2015;40:822-30.
- [22] Monte-Silva K, Liebetanz D, Grundey J, Paulus W, Nitsche MA. Dosage - dependent non - linear effect of l - dopa on human motor cortex plasticity. *J Physiol* 2010;588:3415-24.
- [23] Fresnoza S, Stiksrud E, Klinker F, Liebetanz D, Paulus W, Kuo M-F, et al. Dosage-dependent effect of dopamine D2 receptor activation on motor cortex plasticity in humans. *J Neurosci* 2014;34:10701-9.
- [24] Kuo H, Paulus W, Batsikadze G, Jamil A, Kuo M, Nitsche MA. Chronic enhancement of serotonin facilitates excitatory transcranial direct current stimulation-induced neuroplasticity. *Neuropsychopharmacology* 2016;41:1223-30.
- [25] Thirugnanasambandam N, Grundey J, Adam K, Drees A, Skwirba AC, Lang N, et al. Nicotinic impact on focal and non-focal neuroplasticity induced by non-invasive brain stimulation in non-smoking humans. *Neuropsychopharmacology* 2011;36:879-86.
- [26] Batsikadze G, Paulus W, Grundey J, Kuo M-F, Nitsche MA. Effect of the nicotinic $\alpha 4\beta 2$ -receptor partial agonist varenicline on non-invasive brain stimulation-induced neuroplasticity in the human motor cortex. *Cereb Cortex* 2015;25:3249-59.
- [27] Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC - stimulation - induced after - effects of human motor cortex excitability. *Brain* 2002;125:2238-47.
- [28] Lugon MDMV, Batsikadze G, Fresnoza S, Grundey J, Kuo M-F, Paulus W, et al. Mechanisms of nicotinic modulation of glutamatergic neuroplasticity in humans. *Cereb Cortex* 2017;27:544-53.
- [29] Monte-Silva K, Kuo M-F, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimul* 2013;6:424-32.
- [30] Nitsche MA, Jaussi W, Liebetanz D, Lang N, Tergau F, Paulus W. Consolidation of human motor cortical neuroplasticity by d-cycloserine. *Neuropsychopharmacology* 2004;29:1573-8.
- [31] Nitsche MA, Liebetanz D, Schlitterlau A, Henschke U, Fricke K, Frommann K, et al. GABAergic modulation of DC stimulation - induced motor cortex excitability shifts in humans. *Eur J Neurosci* 2004;19:2720-6.
- [32] Nitsche MA, Lampe C, Antal A, Liebetanz D, Lang N, Tergau F, et al. Dopaminergic modulation of long - lasting direct current - induced cortical excitability changes in the human motor cortex. *Eur J Neurosci* 2006;23:1651-7.
- [33] Monte-Silva K, Kuo M-F, Thirugnanasambandam N, Liebetanz D, Paulus W, Nitsche MA. Dose-dependent inverted U-shaped effect of dopamine (D2-Like) receptor activation on focal and nonfocal plasticity in humans. *J Neurosci* 2009;29:6124-31.
- [34] Nitsche MA, Kuo M, Grosch J, Bergner C, Monte-Silva K, Paulus W. D1-receptor impact on neuroplasticity in humans. *J Neurosci* 2009;29:2648-53.
- [35] Nitsche MA, Grundey J, Liebetanz D, Lang N, Tergau F, Paulus W. Catecholaminergic consolidation of motor cortical neuroplasticity in humans. *Cereb Cortex* 2004;14:1240-5.

- [36] Kuo M, Grosch J, Fregni F, Paulus W, Nitsche MA. Focusing effect of acetylcholine on neuroplasticity in the human motor cortex. *J Neurosci* 2007;27:14442-7.
- [37] Grundey J, Thirugnanasambandam N, Kaminsky K, Drees A, Skwirba A, Lang N, et al. Rapid effect of nicotine intake on neuroplasticity in non-smoking humans. *Front Pharmacol* 2012;3.
- [38] Grundey J, Thirugnanasambandam N, Kaminsky K, Drees A, Skwirba AC, Lang N, et al. Neuroplasticity in cigarette smokers is altered under withdrawal and partially restituted by nicotine exposition. *J Neurosci* 2012;32:4156-62.
- [39] Antman EM, Stone PH, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. part I: basic and clinical electrophysiologic effects. *Ann Intern Med* 1980;93:875-85.
- [40] Elliott WJ, Ram CVS. Calcium channel blockers. *J Clin Hypertens (Greenwich)* 2011;13:687-9.
- [41] Zacest R, Gilmore E, Koch-Weser J. Treatment of essential hypertension with combined vasodilation and beta-adrenergic blockade. *N Engl J Med* 1972;286:617-22.
- [42] Kalso E. Sodium channel blockers in neuropathic pain. *Curr Pharm Des* 2005;11:3005-11.
- [43] Cohen GL. Migraine prophylactic drugs work via ion channels. *Med Hypotheses* 2005;65:114-22.
- [44] Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ* 2000;162:225-33.
- [45] Swartz M, Landerman R, George LK, Melville ML, Blazer D, Smith K. Benzodiazepine anti-anxiety agents: prevalence and correlates of use in a southern community. *Am J Public Health* 1991;81:592-6.
- [46] Jenner P. The rationale for the use of dopamine agonists in Parkinson's disease. *Neurology* 1995;45:S6-S12.
- [47] Birks JS. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Syst Rev* 2006.
- [48] Kapur S, Agid O, Mizrahi R, Li M. How antipsychotics work—from receptors to reality. *NeuroRX* 2006;3:10-21.
- [49] Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimul* 2012;5:175-95.
- [50] Mojtabai R, Olfson M. National trends in long-term use of antidepressant medications: results from the US national health and nutrition examination survey. *J Clin Psychiatry* 2014;75:169-77.

Neurotransmitter System	Paper	Drug	Dose	Main Effects Under the Anode & Cathode
Glutamate	Liebetanz et al., 2002 [16] Lugon et al., 2017 [17] Monte-Silva et al., 2013 [18] Nitsche et al., 2003 [9] Nitsche et al., 2004 [19]	Dextromethorphan (NMDA antagonist)	50mg (low) 100mg (med) 150mg (high)	<u>Anode:</u> Dose dependent effects. No impact on excitability enhancement with low doses. Eliminated excitability enhancing after-effects with medium and high doses. <u>Cathode:</u> Eliminated after-effects at high dosages.
		d-Cycloserine (partial-NMDA agonist)	100mg	<u>Anode:</u> Prolonged excitability enhancing after-effects. <u>Cathode:</u> Increased intensity of excitability reduction 10-minutes post-stimulation.
GABA	Nitsche et al., 2004 [20]	Lorazepam (GABA _A receptor agonist)	2mg	<u>Anode:</u> Initially delayed then prolonged excitability enhancing after-effects, following both short (5 mins) and long (11 mins) stimulation. <u>Cathode:</u> No impact the excitability reduction response.
Dopamine	Monte-Silva et al., 2010 [21] Kuo et al., 2008 [22]	L-DOPA (Dopamine precursor)	25mg (low) 100mg (med) 200mg (high)	<u>Anode:</u> Inverted U-dose response effect. Eliminated excitability enhancing after-effects at low and high doses. Reversed effects from excitability enhancement to excitability reduction at medium doses. <u>Cathode:</u> Inverted U-dose response effect. Eliminated excitability reducing after-effects at low and high doses. Prolonged excitability reducing after-effects at medium dose.
	Fresnoza et al, 2014 [24]	Bromocriptine (D2 agonist)	2.5mg (low) 10mg (med) 20mg (high)	<u>Anode:</u> Eliminated excitability enhancing after-effects at low and high dosages. Reversed excitability enhancement to trend toward excitability reduction at medium dosages. <u>Cathode:</u> Eliminated excitability reducing after-effects at low and high dosages. Prolonged excitability reducing after-effects at medium dosages.
	Nitsche et al., 2006 [23]	Sulpiride (selective D2/D3 antagonist)	400mg	<u>Anode:</u> Reduced excitability enhancing after-effects. <u>Cathode:</u> Reduced excitability reducing after-effects.
	Monte-Silva et al., 2009 [25]	Ropinirole (D2/D3 agonist)	0.125mg or 0.25mg (low) 0.5mg (med) 1.0mg (high)	<u>Anode:</u> Eliminated or reversed excitability enhancing after-effects at low doses. No effect at medium dosages. Decreased magnitude of excitability enhancement at high dosages. <u>Cathode:</u> Eliminated excitability reducing after-effects at low doses. Enhanced and elongated after-effects at medium doses. Reversed excitability reduction into excitability enhancement at high doses.
	Nitsche et al., 2006 [23]	Pergolide (D1/D2 agonist)	0.025mg	<u>Anode:</u> No impact on excitation after-effects. <u>Cathode:</u> Prolonged excitability reducing after-effect.
	Nitsche et al., 2006 [23]	Multiple: Pergolide taken after Sulpiride (D2 blocker)	0.025mg (Pergolide) & 400mg (Sulpiride)	<u>Anode:</u> Eliminated excitability enhancing after-effects. <u>Cathode:</u> Eliminated excitability reducing after-effects.
	Fresnoza et al., 2014 [13] Nitsche et al., 2009b [26]	Multiple: L-DOPA with Sulpiride	25mg L-DOPA (low), 100mg L-DOPA (med) 200mg L-DOPA (high) & 400mg Sulpiride	<u>Anode:</u> Excitability enhancing after-effect eliminated at low and high doses. Excitability enhancing effects restored at medium dosages of L-DOPA. <u>Cathode:</u> Trend towards excitability enhancement with low and high dosages. Unclear results at medium dosages of L-DOPA.
Norepinephrine/ Epinephrine	Kuo et al., 2016 [15]	Reboxetine (Selective NE reuptake inhibitor)	8mg	<u>Anode:</u> Increased and prolonged excitability enhancement with chronic administration <u>Cathode:</u> Reversed excitability reducing into excitability enhancing after-effects

	Nitsche et al., 2004 [27]	Propranolol (Unselective Beta-adrenergic antagonist)	80mg	<u>Anode:</u> Shortened duration of excitability enhancing after-effect. <u>Cathode:</u> Shortened duration of excitability reducing after-effects.
Amphetamine	Nitsche et al., 2004 [27]	Amphetaminil (Precursor of amphetamine)	20mg	<u>Anode:</u> Prolonged excitability enhancing after-effects. <u>Cathode:</u> Slightly diminished excitability reducing after-effects.
Serotonin (5-HT)	Kuo et al., 2016 [28] Nitsche et al., 2009 [14]	Citalopram (SSRI)	20mg	<u>Anode:</u> Increased and prolonged excitability enhancing after-effects. <u>Cathode:</u> Reversed excitability reduction response to excitability enhancement and prolonged after-effects.
Acetylcholine	Kuo et al., 2007 [29]	Rivastigmine (Cholinesterase inhibitor)	3mg	<u>Anode:</u> Initially blocked excitability enhancing after-effects. <u>Cathode:</u> Initially blocked then prolonged excitability reducing after-effects.
Nicotine	Grundey et al., 2012 [30] Lugon et al., 2017 [17]	Nicotine spray in non-smokers	10mg/ml	<u>Anode:</u> Eliminated excitability enhancing after-effects. <u>Cathode:</u> Diminished and delayed excitability reducing after-effects.
	Thirugnanasambanadam et al., 2011 [31]	Nicotine patch in non-smokers	--	<u>Anode:</u> Eliminated excitability enhancing after-effects. <u>Cathode:</u> Eliminated excitability reducing after-effects.
	Batsikadze et al., 2015 [32]	Varenicline (Nicotine receptor agonist) in non-smokers	0.1mg (low dose) 0.3mg (med dose) 1.0mg (high dose)	<u>Anode:</u> No impact at low dosages. Abolished after-effects at medium dosage. Delayed excitability enhancing after-effects at high dosages. <u>Cathode:</u> No impact at low and high dosages. Abolishes after-effects at medium dosages.
	Lugon et al., 2017 [17]	Nicotine Patch + Dextromethorphan in non-smokers	50mg (low) 100mg (med) 150mg (high)	<u>Anode:</u> Excitability enhancing after-effects eliminated with nicotine patch and low or high dosages of dextromethorphan. Excitability enhancing effects restored with medium dextromethorphan dosages.
Ion Channels	Liebetanz et al., 2002 [16]	Carbamazepine (Sodium channel blocker)	600mg	<u>Anode:</u> Prevented acute and after-effects. <u>Cathode:</u> No impact on excitability reduction response.
	Nitsche et al., 2003 [9]	Flunarizine (Calcium channel blocker)	10mg	<u>Anode:</u> Diminished acute excitability enhancement and blocked after-effects. <u>Cathode:</u> No impact on excitability reduction response.
	Nitsche et al., 2003 [9]			

Table 1: Overview of the impact of different medications on tDCS stimulation under the anode and cathode.