tDCS-Pharmacotherapy Interactions

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38.1 Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique which induces cortical excitability alterations via application of continuous, weak direct current through the scalp, leading to bidirectional plasticity induction according to the stimulation protocols [1, 2]. Neuroplasticity induced by tDCS also shares common features with synaptic plasticity in animal studies. The process involves glutamatergic mechanisms and can be modulated by different transmitters, including dopamine, acetylcholine, serotonin, and noradrenaline, which are also associated with a broad range of psychiatric diseases. In recent years, tDCS has been increasingly implemented as an adjuvant to conventional clinical therapy with promising results. As the majority of psychiatric disorders is connected to dysfunctions of specific neuromodulator systems, respective pharmacotherapy is a primary option for treatment. It is therefore crucial to consider the possible interacting factors between tDCS and medications, in order to maximize treatment efficacy. Here we briefly review the neurochemistry of tDCS effects and discuss the knowledge obtained so far from pharmacological experiments with healthy participants, as well as clinical trials and pilot studies, with the aim to inform future combined pharmaco-stimulation approaches in basic research, and clinical application.

38.2 tDCS Physiology: Ion Channel- and Neurotransmitter-Dependent Mechanisms

tDCS induces neuroplasticity via a primary effect on neuronal membrane polarization, which involves modulation of neuronal ion channel activities. Prolonged stimulation over some minutes results in excitatory plasticity, similar to long-term potentiation (LTP), following anodal tDCS, while cathodal stimulation induces excitability inhibition comparable to long-term depression (LTD). Pharmacological studies revealed an abolishment of the acute effects of anodal tDCS via calcium and sodium channel block, but not NMDA receptor antagonists, and GABA receptor activity enhancement [3], which

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is in accordance with an involvement of ion channels, but not synaptic mechanisms, in these immediate polarization-dependent tDCS effects. Furthermore, the neuroplastic after-effects of anodal tDCS-induced LTP-like plasticity were blocked by the respective calcium and sodium channel blockers carbamazepine and flunarizine, which stresses the relevance of the initial polarization effects for the induction of plasticity by tDCS [3]. Neuroplasticity elicited by tDCS is also dependent on NMDA receptors, and thus glutamatergic mechanisms, as the blockade of these receptors results in diminution of cortical plasticity [3, 4], while enhancing NMDA activity via the partial agonist d-cycloserine prolonged and consolidated LTP-like plasticity following anodal tDCS [5]. The mechanism underlying glutamatergic plasticity is associated with the dynamics of calcium concentration [6]. Animal research revealed an alteration of the neuronal calcium profile after direct current stimulation [7, 8]. Accordingly, anodal tDCS-induced excitatory plasticity in humans was abolished by calcium channel block, and the nonlinearity of tDCS effects has been shown to be associated with calcium dynamics [3, 9]. In addition to the involvement of NMDA receptors, tDCS effects are also associated with regulation of AMPA receptor activities [10].

The neuroplasticity-inducing effect of tDCS is also related to GABA activity, which is one of the key regulators of the cortical excitation/inhibition balance. In the primary motor cortex, anodal, and cathodal tDCS reduces local GABA, as revealed by magnetic resonance spectroscopy (MRS) [11], and also by the enhancement of I-wave facilitation following anodal, and cathodal tDCS, as this specific TMS measure is determined by the GABAergic system [12]. Reduction of GABA might thus have a gating effect on tDCS-induced glutamatergic plasticity. It also explains the relatively minor effect of benzodiazepines on tDCS-induced plasticity, as these work only on active GABA receptors. For prefrontal stimulation, MRS results however revealed no change of the GABA level at the left dorsolateral PFC (dlPFC) after anodal tDCS, with the return electrode attached to contralateral right dlPFC [13]. This might mean that the modulatory effect of tDCS on GABAergic activity is different across cortical areas. It should however be noted that stimulation parameters were not identical between studies, and more studies are required for more conclusive comparisons. The recent development of noninvasive brain research techniques such as the combination of transcranial magnetic stimulation and electroencephalography (TMS-EEG) allows direct excitability measures also in associative cortical modalities [14]. Specific components of TMS-evoked potentials (TEP) have been shown to be related to the dynamics of neurotransmission, including the GABAergic system [15], and might help to further clarify mechanisms.

As the involvement of glutamate/GABA neurotransmitter systems in psychiatric disorders came increasingly into attention recently, both have been targeted for the purpose of more efficient treatment. For instance, pathological connectivity alterations in glutamatergic and GABAergic systems have been proposed to partially explain the pathophysiology of depression, and corresponding medication such as ketamine or GABA-targeting compounds have shown therapeutic potential in clinical trials [16, 17]. Given the increasing implementation of tDCS in psychiatry, it is crucial to obtain a better understanding about the modulation of tDCS effects by these neurotransmitters also in clinical populations, which might require an adjustment of treatment in case of combined application.

38.3 Modulation of tDCS Effects by Neuromodulators

In contrast to the abovementioned neurotransmitters, which are involving fast-acting signals across the synaptic cleft to induce excitatory and inhibitory postsynaptic potentials, neuromodulators are associated with diffuse, volume-transmitted mechanisms, which have no large effects on their own, but modulate neuronal activities at a slower time course. In this section, the impact of neuromodulatory systems which are critically involved in the majority of neuropsychiatric diseases, including dopamine, acetylcholine, serotonin,

and noradrenaline, on tDCS-induced plasticity will be covered.

38.4 Dopamine

As one of the most important neuromodulators in the category of monoamines, dopamine is a key player in many cognitive functions, including reward, decision making, or working memory. The disturbance of respective operations leads to behavioral dysfunctions, which are linked to many neuropsychiatric diseases. Physiological and cognitive studies in both animal models and humans have demonstrated complex modulatory effects of dopamine on brain physiology, which underlie respective psychological processes. At the molecular level, dopamine mediates brain physiology via clusters of receptors on neuronal membranes, classified as D1- and D2-like receptors, which can be distinguished by pharmacological agonists and antagonists. It is proposed that dopamine exerts its function as a result of the dynamic balance between D1 and D2 activation, revealed as differential modulatory effects of the two receptor subtypes on cortical activity and neuroplasticity [18], which are thought to account for nonlinear effects of dopamine on physiological, psychological, and motor functions [19].

38.4.1 Dopaminergic Effects on Neurophysiology and Cognition in Humans

Evidence from animal studies indicates that dopamine modulates neuroplasticity via its impact on the specific interaction between NMDA and GABA receptors, based on distinct D1 and D2 receptor contributions on the activity of these receptors [18, 20]. A biphasic effect of dopamine on synaptic plasticity has been shown in numerous studies [21, 22], which is assumed to be caused by its impact on NMDA and GABA receptors. DA potentiates NMDA currents or membrane depolarization via D1 receptor activation [23, 24], although an inverted U-shaped dose-dependency has also been described [18]. On the other hand, D2 receptors have a suppressing effect on NMDA receptors, and neuronal calcium influx [25]. Dopamine has also the capacity to evoke a biphasic modulation of GABA-mediated currents: D2-like receptors reduce, while D1-like receptors increase GABAergic activity [26–28]. The dopaminergic effects on NMDA and GABA responses are furthermore neuronal activity-dependent. In case of low network activity, it is assumed that the D1 receptor exerts synaptic plasticity-reducing effects, as the increase of low-level NMDA activation is outweighed by concurrent, large-range GABA currents enhanced by D1 receptor activity [27]. On the other hand, higher network activity results in persistent stronger NMDA receptor activation [29], which is further strengthened by D1 receptors [21, 27]. The opposite effect is observed with D2 activation, where glutamatergic plasticity is reduced via reduction of activation of NMDA receptors, but enhanced by D2-decreased GABA responses when higher network activity is present. Dopamine is thus assumed to have a complex modulatory effect on synaptic plasticity, based on its effects on glutamatergic and GABAergic transmission.

For the human brain, the impact of dopamine on brain physiology was studied most extensively for the motor cortex as a model system. The contribution of dopamine to motor cortical plasticity in humans is complex, and seems to depend on a couple of factors, such as receptor subtype activation, amount of activation (i.e., dosage of respective dopaminergic substances), as well as history and state of activation of the target structures. Dopamine has been shown to be essential for neuroplasticity induction by tDCS. The D2 antagonist sulpiride abolished tDCS-induced cortical plasticity [30]. Results of further studies suggest—similarly to those of related animal models (see above)—that dopamine enhances the signal-to-noise ratio in the human brain, and that this effect depends on the amount of receptor activation, and receptor subtypes. Whereas dopamine abolishes diffuse LTP-like plasticity, as induced by tDCS, or converts it into LTD-like plasticity, it preserves or enhances focal plastic-

ity, as generated by paired associative stimulation (PAS), if dopaminergic activity is moderately enhanced [31–33]. D1- and D2-like receptors contribute in discernible ways to this global dopamine effect. While D2 receptors have a similar impact on plasticity as dopamine itself, D1-like receptor activation fosters facilitatory plasticity independently from its focality [34, 35]. In addition, results from these studies also revealed a dose-dependency of dopaminergic modulation on neuroplasticity, where medium dosage resulted in most prominent effects, whereas low and high dosages reduced tDCS-induced plasticity. In case of low-dose dopaminergic enhancement, the respective plasticity-abolishing effect might be due to the activation of presynaptic, inhibitory autoreceptors [32, 33, 36].

38.4.2 Clinical Aspects

Dysfunctions of the dopaminergic system have been related to many psychiatric disorders including schizophrenia, where treatment with dopamine antagonists improves symptoms. tDCS has been probed for the treatment of schizophrenia symptoms, and improved negative symptoms, attention, and reduced auditory hallucinations [37–41]. Given the impact of DA-affecting substances on tDCS-induced plasticity, it would be important to learn about respective interactions also with respect to clinical studies. In one study, the efficacy of tDCS to reduce auditory hallucinations was compared in patients treated with neuroleptics with high and low D2 receptor affinity [40]. The result revealed less therapeutic efficacy when tDCS was combined with high-affinity antipsychotics, which is in accordance with the plasticity-abolishing effect of D2 receptor block described before [30].

Repetitive disorders, such as the Tourette syndrome, are also associated with imbalanced dopamine activity [42]. Beyond the modulation of tDCS effects by dopaminergic and antidopaminergic agents, the stimulation itself might affect dopaminergic activity, and thereby elicit clinical effects. Application of tDCS in an animal model of Tourette syndrome has been shown to alleviate pathological repetitive behavior via reducing dopaminergic hyperresponsivity in a sensorimotor cortico-striatal circuitry which has been targeted for therapy with deep brain stimulation [43]. Similarly, tDCS has also been shown in human studies to modulate dopaminergic activity in subcortical striatal regions, indicating the opportunity to apply tDCS for dopaminergic enhancement in clinical syndromes caused by dopamine deficiency [44, 45].

38.5 Acetylcholine

Acetylcholine (ACh) is involved in the arousal/attentional system as well as in many other cognitive functions, such as working and long-term memory. Apart from its wide distribution in both subcortical and cortical regions, cholinergic signaling also acts in a temporal- and spatial-specific manner [46, 47]. Dysfunction of cholinergic, particularly nicotinic receptor transmission, can lead to cognitive impairment or dementia, in which abnormal regulation of synaptic plasticity is thought to be involved at the neurophysiological level [48, 49]. Moreover, cholinergic function varies in healthy humans according to brain states, and nicotine consumption, which can explain partially its observed complex and heterogeneous effects on cognition.

38.5.1 Cholinergic Modulation of Cortical Excitability, Plasticity, and Cognition

Cholinergic activation alters cortical excitability, and thereby regulates neuroplasticity [50–52]. These effects are directly induced via cholinergic transmission, but also based on its impact on other neurotransmitters, such as glutamatergic, GABA-ergic and dopaminergic systems [53, 54]. In animal experiments, it has been shown that neuronal excitability can be enhanced by the activation of nicotinic ACh receptors (nAChRs) via the increase of glutamate release, or by muscarinic ACh receptors (mAChRs), which reduce presynaptic GABAergic inhibition on pyramidal

neurons [55, 56]. On the other hand, nAChRs also facilitate GABAergic inhibition, possibly via downregulation of Ca^{2+} signaling [57, 58]. This inhibitory effect of nicotine is reflected in human cortical excitability, as it significantly enhances GABA-associated cortical inhibition in nonsmokers [59]. An important role of nAChRs in synaptic plasticity has been also revealed (for review, see [52]). The activation of nAChRs enhances LTP induction with or without NMDA receptor involvement [49, 60, 61], but it has also been demonstrated to diminish LTP [62]. This heterogeneous effect, which underscores the neuromodulatory role of this system, might be explained by different factors, including specifics of the stimulation protocol, and brain states. With respect to the impact of cholinergic modulation on tDCS-induced plasticity, global cholinergic activation by application of rivastigmine, an acetylcholinesterase inhibitor, diminished LTP-like plasticity induced by anodal tDCS and slightly prolonged LTD-like plasticity following cathodal tDCS [63]. A similar pattern of results was also demonstrated for nAChR activation when applying nicotine or the α4β2-receptor partial agonist varenicline [64, 65]. The mechanisms underlying the LTP-like plasticity-diminishing effects of nicotinic receptor activation might involve calcium dynamics, since reduction of nicotine-induced calcium overflow by an NMDA antagonist as well as calcium channel blocker restituted neuroplasticity [9, 66]. Beyond these effects of nicotinic activation on nonsmoking healthy humans, in smokers LTP-like plasticity was not induced by anodal tDCS under nicotine withdrawal, most likely to nicotinic receptor desensitization induced by chronic nicotine application [67]. Administration of nicotine or varenicline however reestablished compromised plasticity in these participants [67, 68].

38.5.2 Implications for Basic and Clinical Research

For studies in healthy humans, the results imply that inclusion of smokers should be avoided in basic studies which do not aim to explore the effects of nicotine, because of the relevant effect of smoking, and especially nicotine withdrawal, on the physiological effects of tDCS. For clinical studies with tDCS application, the situation might be more complex, as excluding smokers would mean to reject a relevant portion of the patients. Here it would be crucial to implement nicotine consumption, that is, smoking, during experimental sessions, as well as the timing since last consumption, at least as confounding factors for control. Indeed, it has been shown that smoking has a relevant impact of tDCS effects in clinical populations. tDCS-induced motor cortical plasticity was reduced in schizophrenia patients who are nonsmoking or smokers under nicotine withdrawal, while in smoking patients the tDCS effect was restored by nicotine application [69, 70]. Smoking state also had a relevant impact on the therapeutic effect of tDCS. In one study where multiple-session tDCS was applied in schizophrenia patients to reduce auditory hallucinations, the results demonstrated a lack of response in smokers when compared to nonsmoking patients, possibly due to partial self-regulated abstinence in smokers before treatment sessions [71]. In contrast, under proper control of nicotine consumption during the experimental course, tDCS did improve cognitive performance in chronic smoking schizophrenics without withdrawal [72]. These results underline the importance of nicotine levels for tDCS efficacy, particularly for long-term smoking patients in clinical studies.

Based on the cholinergic hypothesis, pro-cholinergic drugs are applied to improve pathological cognitive decline in patients with mild cognitive impairment and dementia [73–75]. As cumulative evidence also suggests beneficial effects of tDCS for cognitive functions, it has been applied recently to augment the efficacy of respective pharmacological treatment in patients with cognitive deficits. Combination of the acetylcholinesterase inhibitor donepezil with 6-months tDCS treatment significantly improved global cognitive performance in patients with Alzheimer's disease, as compared to pharmacotherapy alone [76]. This approach provides initial evidence for a potential synergistic effect of both

interventions to prevent or diminish cognitive decline in dementia. At the first look, this effect is surprising, given that in healthy humans, cholinergic activation diminishes plasticity. The likely explanation is however that respective patients have a hypofunctional cholinergic system, similar to smokers under nicotine withdrawal, which is counteracted upon by pharmacological activation of the system, and thus reestablishes plasticity induction by tDCS.

38.6 Serotonin and Noradrenaline

38.6.1 Neuromodulatory Effect of Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) has been classified as a neurotransmitter or -modulator [77]. The serotonergic system is involved in cognition, mood, behavior, motor processes [78] and also linked to executive functions [79]. Increased serotonin levels improve learning, memory, and motor functions in healthy and post-stroke patients [80, 81]. Dysfunction of this system contributes to the pathophysiology of psychiatric diseases, such as depression [82]. Studies in humans and animals have provided evidence for a relevant role of 5-HT in neuroplasticity [83, 84]. Animal studies have revealed that 5-HT interferes with LTP and LTD, and these effects are related to drug dosage, receptor subtypes, and duration of 5-HT receptor activation [85, 86]. Activation of 5-HT2 receptors results in calcium release from intracellular storages, while 5-HT3 activation increases conductance of calcium influx, and both effects contribute to LTP induction [87]. It was also shown that LTD in hippocampal slices was converted to LTP vis 5-HT4 enhancement, suggesting an excitatory modulation of serotonin on neuroplasticity [86]. In humans, it was shown that the enhancement of serotonin levels by a selective serotonin reuptake inhibitor (SSRI) modulates neuroplasticity in different modalities. In the visual area, long-term SSRI administration augmented visual plasticity in healthy participants [88]. A related LTP-like plasticity-enhancing effect was also observed in the motor cortex, where application of citalopram resulted in enhanced LTP-like plasticity induced by tDCS or PAS, and reduction or even conversion of LTD-like into LTP-like plasticity [89–91]. Moreover, similar, but stronger effects have been shown under chronic application of the same SSRI, which might be associated with long-term therapeutic effects of respective pharmacological treatment in clinical settings [90]. A recently published study also showed beneficial influences of SSRI on cognitive functions in both healthy young and aging humans, and revealed a more prominent effect when medication was combined with anodal tDCS over the right temporoparietal region [92]. These results indicate a potential of combined treatment with SSRI and tDCS in associated basic and clinical domains, which might be due to synergistic effects on LTP-like plasticity.

38.6.2 Neuromodulatory Effect of Noradrenaline

Similar to serotonin, cortical excitability and plasticity, both LTP and LTD, are modulated by noradrenergic activation via its impact on various intracellular processes. Animal studies have shown that neuronal excitability is enhanced by the activation of β-adrenoreceptors via suppressing GABAergic inhibition and facilitating the activation of NMDA receptors [93]. On the other hand, α-adrenoreceptors decrease neural excitability by facilitating GABAergic inhibition, possibly via downregulation of calcium signaling [94]. Similar results have been found in human studies. Here, noradrenergic enhancement increases cortical excitability via enhancement of NMDA receptor-dependent facilitation and reduction of GABAergic inhibition, in principle accordance with a primarily ß-adrenergic enhancing effect [95]. Regarding synaptic plasticity, animal studies have shown that activation of β-adrenoreceptors strengthens LTP, while α-adrenoreceptors promote LTD [96, 97]. In a human study, enhancement of monoamine availability fostered noninvasive brain stimulation-induced LTP-like plasticity, whereas

stimulation-induced plasticity was reduced by a ß-adrenergic antagonist [98]. Acute and chronic administration of the selective noradrenaline reuptake inhibitor (NRI) reboxetine increased and prolonged stimulation-induced LTP-like plasticity, whereas it converted LTD-like plasticity into LTP-like plasticity [99, 100]. Similar to adrenergic effects on excitability, this pattern of results is in accordance with a primary impact of ß-adrenoceptors on plasticity in humans [98].

38.6.3 Clinical Aspects

Pathophysiological disturbances or lesions of the prefrontal cortex are closely related to numerous neuropsychiatric disorders. Major depression is associated with a task-associated dysbalance of bilateral prefrontal cortex activation, where lower activity was shown in the left dorsolateral prefrontal cortex [101]. Moreover, reduced LTP is also suggested as a pathological agent in depression, and might involve large parts of the brain, since a reduction of visual cortical plasticity was observed in depression [88]. These findings might explain the therapeutic benefit of serotonin for depression, as 5-HT exerts excitatory effects on LTP-like neuroplasticity as shown in healthy participants [89–91]. Furthermore, the observed facilitation of LTP-like plasticity resulting from the combination of drugs and stimulation establishes a rationale for combined application in depression. Indeed, it has been demonstrated that sertraline combined with tDCS over the dorsolateral PFC had a superior impact on major depression when compared with placebo and the respective single interventions [81]. Interestingly, patients who received only tDCS treatment also showed significantly better improvement than placebo. This approach to augment clinical treatment effects is currently further explored in ongoing clinical trials [102]. Following a similar rationale, as discussed in the previous section, noradrenergic medication has also been implemented in treating depression, as well as other psychiatric diseases such as attention-deficit/hyperactivity disorders or panic disorder, although consensus over its efficiency remains to be established (see [103] for an overview). Combining NRIs with tDCS might be a way to enhance treatment outcomes, following the rationale outlined above, which however needs validation in clinical trials.

38.7 Conclusion

As a noninvasive brain stimulation tool which modulates cortical excitability and induces plasticity, tDCS has been implemented in psychiatry to normalize pathological excitability and plasticity alterations. Technically it is often combined with conventional pharmacological therapy, because patients are under routine medication, or in a targeted way to further enhance therapeutic efficacy. Hence it is crucial to better understand the synergies, as well as interaction of tDCS and pharmacotherapy. Evidence from both basic and clinical studies has provided important information about the co-application of tDCS and medication, as discussed above. The outcomes of combined interventions are heterogeneous, and manifested as diminished, enhanced, or stratified tDCS effects, which is explained by the neurophysiological mechanisms of stimulation effects, and their association with the sites of action of respective medications. Neuroplasticity induced by tDCS is determined by NMDA receptors and modulated by several neuromodulators such as dopamine, acetylcholine, serotonin, and noradrenaline. The effects of neuromodulators on tDCS-induced plasticity can be further classified into two principle patterns of action: for dopamine and acetylcholine, the activation of both neurochemical systems strengthened LTD-like plasticity induced by tDCS, and reduced LTP-like plasticity, or even converted it into inhibition, while serotonin and noradrenaline exerted an overall facilitatory effect, resulting in LTP-like plasticity enhancement, and a conversion of LTD-like plasticity into LTP-like plasticity. These effects are also determined by the applied dosage and the balance between receptor subtypes, for which the mechanisms have not been fully identified, particularly in humans. It should also be noted that most of the findings from human

studies so far are based on the motor cortex as model system. A one-to-one translation to the prefrontal cortex, which is involved in the majority of psychiatric disorders, as well as translation from healthy humans to patients requires caution and further exploration for support and guidance of clinical applications.

In general, the design of patient studies should take into consideration the concurrent treatment with different types of medication, as well as consumption of recreational substances such as nicotine, which affect the outcome of tDCS. This is relevant to elucidate synergistic, and antagonistic effects of combined stimulation, and pharmacological interventions, which is crucial to tailor therapeutic approaches for improvement of treatment success. Specifically, tDCS has revealed potential as an adjunctive therapy in psychiatry, and results from clinical experiments combining stimulation and pharmacology are encouraging. Such combination might be extended in future to a synergistic, multimodal treatment module, especially when tDCS protocols could be adapted to normalize pathological plasticity. It is expected that accumulating results from future studies will bring more insight into therapeutic mechanisms and thereby benefit the field (Fig. 38.1).

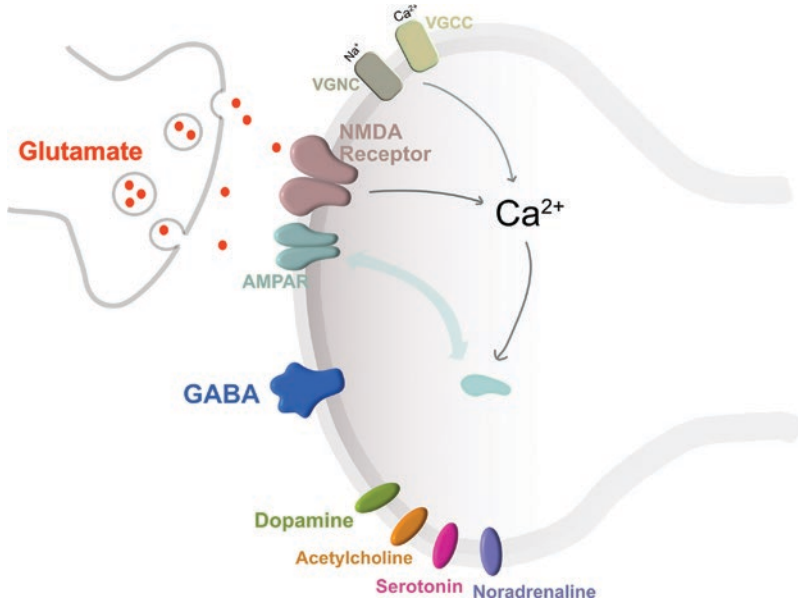

Fig. 38.1 Neurophysiology and modulation of tDCS-induced neuroplasticity
Shown are the main plasticity mechanisms of glutamatergic synapses, and the modulation of ion channels as well as neuromodulators relevant for tDCS-induced plasticity. NMDA receptors are activated via glutamate release in combination with tDCS-induced neuronal membrane depolarization, which results in neuronal calcium influx through the subsynaptic membrane. In addition to NMDA receptors, the activity of voltage-gated calcium channels (VGCCs) contributes to respective intracellular calcium alterations via polarization effects of tDCS. The enhanced intracellular calcium concentration activates enzyme cascades and consequently AMPA receptor trafficking, which further determines the probability of supra-threshold postsynaptic activation upon a given presynaptic activity level. Hereby, the amount of calcium concentration determines if AMPA receptors are inserted into or removed from the subsynaptic membrane. As such, the modification of AMPA receptor density is the main basis of LTP and LTD. Various neurotransmitters such as GABA, dopamine, acetylcholine, serotonin, adrenaline, and noradrenaline influence these mechanisms of action in a complex, sometimes nonlinear way via their specific receptors, and impact on glutamatergic receptors and ion channels.

References

1. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
2. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57:1899–901.
3. Nitsche MA, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003;553:293–301.
4. 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.
5. Nitsche MA, et al. Consolidation of human motor cortical neuroplasticity by D-cycloserine. Neuropsychopharmacology. 2004;29:1573–8.
6. Lisman J, Three E. Ca2+ levels affect plasticity differently: the LTP zone, the LTD zone and no man's land. J Physiol. 2001;532:285.
7. Monai H, et al. Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. Nat Commun. 2016;7:11100.
8. Islam N, Aftabuddin M, Moriwaki A, Hattori Y, Hori Y. Increase in the calcium level following anodal polarization in the rat brain. Brain Res. 1995;684:206–8.
9. Grundey J, et al. Nicotine modulates human brain plasticity via calcium-dependent mechanisms. J Physiol. 2018;596:5429.
10. Martins CW, de Melo Rodrigues LC, Nitsche MA, Nakamura-Palacios EM. AMPA receptors are involved in prefrontal direct current stimulation effects on long-term working memory and GAP-43 expression. Behav Brain Res. 2019;362:208–12.
11. Stagg CJ, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci. 2009;29:5202–6.
12. Nitsche MA, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol. 2005;568:291–303.
13. Hone-Blanchet A, Edden RA, Fecteau S. Online effects of transcranial direct current stimulation in real time on human prefrontal and striatal metabolites. Biol Psychiatry. 2016;80:432–8.
14. Chung SW, Rogasch NC, Hoy KE, Fitzgerald PB. Measuring brain stimulation induced changes in cortical properties using TMS-EEG. Brain Stimul. 2015;8:1010–20.
15. Du X, et al. TMS evoked N100 reflects local GABA and glutamate balance. Brain Stimul. 2018;11:1071–9.
16. Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. Neuron. 2019;102:75–90.
17. Wilkinson ST, Sanacora G. A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems. Drug Discov Today. 2019;24:606–15.
18. Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol. 2004;74:1–58.
19. Goto Y, Grace AA. The dopamine system and the pathophysiology of schizophrenia: a basic science perspective. Int Rev Neurobiol. 2007;78:41–68.
20. Tritsch NX, Sabatini BL. Dopaminergic modulation of synaptic transmission in cortex and striatum. Neuron. 2012;76:33–50.
21. Seamans JK, Durstewitz D, Christie BR, Stevens CF, Sejnowski TJ. Dopamine D1/D5 receptor modulation of excitatory synaptic inputs to layer V prefrontal cortex neurons. Proc Natl Acad Sci U S A. 2001;98:301–6.
22. Beurrier C, Malenka RC. Enhanced inhibition of synaptic transmission by dopamine in the nucleus accumbens during behavioral sensitization to cocaine. J Neurosci. 2002;22:5817–22.
23. Chen G, Greengard P, Yan Z. Potentiation of NMDA receptor currents by dopamine D1 receptors in prefrontal cortex. Proc Natl Acad Sci U S A. 2004;101:2596–600.
24. Jocoy EL, et al. Dissecting the contribution of individual receptor subunits to the enhancement of N-methyl-d-aspartate currents by dopamine D1 receptor activation in striatum. Front Syst Neurosci. 2011;5:28.
25. Higley MJ, Sabatini BL. Competitive regulation of synaptic Ca2+ influx by D2 dopamine and A2A adenosine receptors. Nat Neurosci. 2010;13:958–66.
26. Gribkoff VK, Ashe JH. Modulation by dopamine of population responses and cell membrane properties of hippocampal CA1 neurons in vitro. Brain Res. 1984;292:327–38.
27. Seamans JK, Gorelova N, Durstewitz D, Yang CR. Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. J Neurosci. 2001;21:3628–38.
28. Gorelova N, Seamans JK, Yang CR. Mechanisms of dopamine activation of fast-spiking interneurons that exert inhibition in rat prefrontal cortex. J Neurophysiol. 2002;88:3150–66.

29. Lisman J, Grace AA, Duzel E. A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. Trends Neurosci. 2011;34:536–47.
30. Nitsche MA, 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.
31. Kuo MF, Paulus W, Nitsche MA. Boosting focally-induced brain plasticity by dopamine. Cereb Cortex. 2008;18:648–51.
32. 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.
33. Thirugnanasambandam N, Grundey J, Paulus W, Nitsche MA. Dose-dependent nonlinear effect of L-DOPA on paired associative stimulation-induced neuroplasticity in humans. J Neurosci. 2011;31:5294–9.
34. Fresnoza S, Paulus W, Nitsche MA, Kuo MF. Nonlinear dose-dependent impact of D1 receptor activation on motor cortex plasticity in humans. J Neurosci. 2014;34:2744–53.
35. Fresnoza S, et al. Dosage-dependent effect of dopamine D2 receptor activation on motor cortex plasticity in humans. J Neurosci. 2014;34:10701–9.
36. Galloway MP, Wolf ME, Roth RH. Regulation of dopamine synthesis in the medial prefrontal cortex is mediated by release modulating autoreceptors: studies in vivo. J Pharmacol Exp Ther. 1986;236:689–98.
37. Gögler N, et al. Parameter-based evaluation of attentional impairments in Schizophrenia and their modulation by prefrontal transcranial direct current stimulation. Front Psych. 2017;8:259.
38. Gomes JS, et al. Left dorsolateral prefrontal cortex anodal tDCS effects on negative symptoms in Schizophrenia. Brain Stimul. 2015;8:989–91.
39. Mondino M, Haesebaert F, Poulet E, Suaud-Chagny MF, Brunelin J. Fronto-temporal transcranial Direct Current Stimulation (tDCS) reduces source-monitoring deficits and auditory hallucinations in patients with schizophrenia. Schizophr Res. 2015;161:515–6.
40. Agarwal SM, et al. Impact of antipsychotic medication on transcranial direct current stimulation (tDCS) effects in schizophrenia patients. Psychiatry Res. 2016;235:97–103.
41. Valiengo LDCL, et al. Efficacy and safety of transcranial direct current stimulation for treating negative symptoms in Schizophrenia a randomized clinical trial. JAMA Psychiat. 2020;77:121–9.
42. Singer HS, Minzer K. Neurobiology of Tourette's syndrome: concepts of neuroanatomic localization and neurochemical abnormalities. Brain and Development. 2003;25(Suppl 1):S70–84.
43. Edemann-Callesen H, et al. Non-invasive modulation reduces repetitive behavior in a rat model through the sensorimotor cortico-striatal circuit. Transl Psychiatry. 2018;8:11.
44. Fonteneau C, et al. Frontal transcranial direct current stimulation induces dopamine release in the ventral striatum in human. Cereb Cortex. 2018;28:2636–46.
45. Meyer B, et al. Increased neural activity in meso-striatal regions after prefrontal transcranial direct current stimulation and l-DOPA administration. J Neurosci. 2019;39:5326–35.
46. Sarter M, Parikh V, Howe WM. nAChR agonist-induced cognition enhancement: integration of cognitive and neuronal mechanisms. Biochem Pharmacol. 2009;78:658–67.
47. Hasselmo ME, Sarter M. Modes and models of forebrain cholinergic neuromodulation of cognition. Neuropsychopharmacology. 2011;36:52–73.
48. Rasmusson DD. The role of acetylcholine in cortical synaptic plasticity. Behav Brain Res. 2000;115:205–18.
49. Gu Q. Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. Neuroscience. 2002;111:815–35.
50. Mansvelder HD, van Aerde KI, Couey JJ, Brussaard AB. Nicotinic modulation of neuronal networks: from receptors to cognition. Psychopharmacology. 2006;184:292–305.
51. Lucas-Meunier E, et al. Involvement of nicotinic and muscarinic receptors in the endogenous cholinergic modulation of the balance between excitation and inhibition in the young rat visual cortex. Cereb Cortex. 2009;19:2411–27.
52. McKay BE, Placzek AN, Dani JA. Regulation of synaptic transmission and plasticity by neuronal nicotinic acetylcholine receptors. Biochem Pharmacol. 2007;74:1120–33.
53. Pistillo F, Clementi F, Zoli M, Gotti C. Nicotinic, glutamatergic and dopaminergic synaptic transmission and plasticity in the mesocorticolimbic system: focus on nicotine effects. Prog Neurobiol. 2015;124:1–27.
54. Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. Psychopharmacology. 2006;184:523–39.
55. Lambe EK, Picciotto MR, Aghajanian GK. Nicotine induces glutamate release from thalamocortical terminals in prefrontal cortex. Neuropsychopharmacology. 2003;28:216–25.
56. Kruglikov I, Rudy B. Perisomatic GABA release and thalamocortical integration onto neocortical excitatory cells are regulated by neuromodulators. Neuron. 2008;58:911–24.
57. Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA. Hippocampal synaptic transmission enhanced by low concentrations of nicotine. Nature. 1996;383:713–6.
58. Léna C, Changeux JP. Role of Ca2+ ions in nicotinic facilitation of GABA release in mouse thalamus. J Neurosci. 1997;17:576–85.
59. Grundey J, et al. Cortical excitability in smoking and not smoking individuals with and without nicotine. Psychopharmacology. 2013;229:653–64.

60. Placzek AN, Zhang TA, Dani JA. Nicotinic mechanisms influencing synaptic plasticity in the hippocampus. Acta Pharmacol Sin. 2009;30:752–60.
61. Matsuyama S, Matsumoto A, Enomoto T, Nishizaki T. Activation of nicotinic acetylcholine receptors induces long-term potentiation in vivo in the intact mouse dentate gyrus. Eur J Neurosci. 2000;12:3741–7.
62. Couey JJ, et al. Distributed network actions by nicotine increase the threshold for spike-timing-dependent plasticity in prefrontal cortex. Neuron. 2007;54:73–87.
63. Kuo MF, 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.
64. Thirugnanasambandam N, et al. Nicotinergic impact on focal and non-focal neuroplasticity induced by non-invasive brain stimulation in non-smoking humans. Neuropsychopharmacology. 2011;36:879–86.
65. Batsikadze G, Paulus W, Grundey J, Kuo MF, Nitsche MA. Effect of the nicotinic α4β2-receptor partial agonist Varenicline on non-invasive brain stimulation-induced neuroplasticity in the human motor cortex. Cereb Cortex. 2015;25:3249–59.
66. Lugon MD, et al. Mechanisms of nicotinic modulation of glutamatergic neuroplasticity in humans. Cereb Cortex. 2017;27:544–53.
67. Grundey J, et al. Neuroplasticity in cigarette smokers is altered under withdrawal and partially restituted by nicotine exposition. J Neurosci. 2012;32:4156–62.
68. Batsikadze G, et al. Compromised neuroplasticity in cigarette smokers under nicotine withdrawal is restituted by the nicotinic $\alpha_4\beta_2$-receptor partial agonist varenicline. Sci Rep. 2017;7:1387.
69. Hasan A, et al. Impaired long-term depression in schizophrenia: a cathodal tDCS pilot study. Brain Stimul. 2012;5:475–83.
70. Strube W, et al. Smoking restores impaired LTD-like plasticity in schizophrenia: a transcranial direct current stimulation study. Neuropsychopharmacology. 2015;40:822–30.
71. Brunelin J, Hasan A, Haesebaert F, Nitsche MA, Poulet E. Nicotine smoking prevents the effects of frontotemporal transcranial Direct Current Stimulation (tDCS) in hallucinating patients with schizophrenia. Brain Stimul. 2015;8:1225–7.
72. Smith RC, et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr Res. 2015;168:260–6.
73. Buckley JS, Salpeter SR. A risk-benefit assessment of dementia medications: systematic review of the evidence. Drugs Aging. 2015;32:453–67.
74. Newhouse P, et al. Nicotine treatment of mild cognitive impairment A 6-month double-blind pilot clinical trial. Neurology. 2012;78:91–101.
75. Mehta M, Adem A, Kahlon MS, Sabbagh MN. The nicotinic acetylcholine receptor: smoking and Alzheimer's disease revisited. Front Biosci (Elite Ed). 2012;4:169–180.
76. Im JJ, et al. Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease. Brain Stimul. 2019;12:1222–8.
77. Iversen L, Iversen S, Bloom FE, Roth RH. Introduction to neuropsychopharmacology. Oxford University Press; 2008.
78. Pereira M, Martynhak BJ, Andreatini R, Svenningsson P. 5-HT6 receptor agonism facilitates emotional learning. Front Pharmacol. 2015;6:200.
79. Enge S, Fleischhauer M, Lesch KP, Strobel A. On the role of serotonin and effort in voluntary attention: evidence of genetic variation in N1 modulation. Behav Brain Res. 2011;216:122–8.
80. Acler M, Robol E, Fiaschi A, Manganotti P. A double blind placebo RCT to investigate the effects of serotonergic modulation on brain excitability and motor recovery in stroke patients. J Neurol. 2009;256:1152–8.
81. Brunoni AR, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70:383–91.
82. Kraus C, Castrén E, Kasper S, Lanzenberger R. Serotonin and neuroplasticity - links between molecular, functional and structural pathophysiology in depression. Neurosci Biobehav Rev. 2017;77:317–26.
83. Ogren SO, et al. The role of 5-HT(1A) receptors in learning and memory. Behav Brain Res. 2008;195:54–77.
84. Bert B, Fink H, Rothe J, Walstab J, Bönisch H. Learning and memory in 5-HT(1A)-receptor mutant mice. Behav Brain Res. 2008;195:78–85.
85. Kojic L, Gu Q, Douglas RM, Cynader MS. Serotonin facilitates synaptic plasticity in kitten visual cortex: an in vitro study. Brain Res Dev Brain Res. 1997;101:299–304.
86. Kemp A, Manahan-Vaughan D. The 5-hydroxytryptamine4 receptor exhibits frequency-dependent properties in synaptic plasticity and behavioural metaplasticity in the hippocampal CA1 region in vivo. Cereb Cortex. 2005;15:1037–43.
87. Reiser G, Donié F, Binmöller FJ. Serotonin regulates cytosolic Ca2+ activity and membrane potential in a neuronal and in a glial cell line via 5-HT3 and 5-HT2 receptors by different mechanisms. J Cell Sci. 1989;93:545–55.
88. Normann C, Schmitz D, Fürmaier A, Döing C, Bach M. Long-term plasticity of visually evoked potentials in humans is altered in major depression. Biol Psychiatry. 2007;62:373–80.
89. Nitsche MA, et al. Serotonin affects transcranial direct current-induced neuroplasticity in humans. Biol Psychiatry. 2009;66:503–8.
90. Kuo HI, et al. Chronic enhancement of serotonin facilitates excitatory transcranial direct current stimulation-induced neuroplasticity. Neuropsychopharmacology. 2016;41:1223–30.

91. Batsikadze G, Paulus W, Kuo MF, Nitsche MA. Effect of serotonin on paired associative stimulation-induced plasticity in the human motor cortex. Neuropsychopharmacology. 2013;38:2260–7.
92. Prehn K, et al. Effects of anodal transcranial direct current stimulation and serotonergic enhancement on memory performance in young and older adults. Neuropsychopharmacology. 2017;42:551–61.
93. Lei S, Deng PY, Porter JE, Shin HS. Adrenergic facilitation of GABAergic transmission in rat entorhinal cortex. J Neurophysiol. 2007;98:2868–77.
94. Marzo A, Bai J, Otani S. Neuroplasticity regulation by noradrenaline in mammalian brain. Curr Neuropharmacol. 2009;7:286–95.
95. Wójtowicz AM, Fidzinski P, Heinemann U, Behr J. Beta-adrenergic receptor activation induces long-lasting potentiation in burst-spiking but not regular-spiking cells at CA1-subiculum synapses. Neuroscience. 2010;171:367–72.
96. McElligott ZA, Winder DG. Alpha1-adrenergic receptor-induced heterosynaptic long-term depression in the bed nucleus of the stria terminalis is disrupted in mouse models of affective disorders. Neuropsychopharmacology. 2008;33:2313–23.
97. Kemp A, Manahan-Vaughan D. Beta-adrenoreceptors comprise a critical element in learning-facilitated long-term plasticity. Cereb Cortex. 2008;18:1326–34.
98. Nitsche MA, et al. Catecholaminergic consolidation of motor cortical neuroplasticity in humans. Cereb Cortex. 2004;14:1240–5.
99. Kuo HI, et al. Acute and chronic noradrenergic effects on cortical excitability in healthy humans. Int J Neuropsychopharmacol. 2017;20:634–43.
100. Kuo HI, et al. Acute and chronic effects of noradrenergic enhancement on transcranial direct current stimulation-induced neuroplasticity in humans. J Physiol. 2017;595:1305–14.
101. Grimm S, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol Psychiatry. 2008;63:369–76.
102. Padberg F, et al. Prefrontal transcranial direct current stimulation (tDCS) as treatment for major depression: study design and methodology of a multicenter triple blind randomized placebo controlled trial (DepressionDC). Eur Arch Psychiatry Clin Neurosci. 2017;267:751–66.
103. Sepede G, Corbo M, Fiori F, Martinotti G. Reboxetine in clinical practice: a review. Clin Ter. 2012;163:e255–62.