3 Physiology of Transcranial Direct and Alternating Current Stimulation

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3.1 Introduction

Brain stimulation techniques have generated renewed interest in recent decades as promising tools to explore human cerebral functions and to treat neurological and psychiatric diseases [1]. Apart from invasive stimulation paradigms such as deep brain and vagal nerve stimulation, non-invasive tools like transcranial magnetic or electrical stimulation (tES), including transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) are attractive for use in humans, because they permit painless modulation of cortical activity and excitability through the intact skull [2]. This chapter gives an overview of the physiological effects of tES. Their application and impact on brain functions and cognitive processes are also discussed.

3.2 tDCS

Tonic application of direct currents to the brain, although a relatively old method in strict terms, has regained increasing interest as a potentially valuable tool for the induction and modulation of central nervous system neuroplasticity. About 55 years ago, it was demonstrated that in anaesthetised rats, direct currents, delivered by intracerebral or epidural electrodes, induce stimulation polarity-dependent activity and excitability alterations of the sensorimotor cortex, which can be stable for hours after the end of stimulation [3]. A few years later, it was verified that also transcranial application of direct currents can induce an intracerebral current flow sufficiently large to achieve physiological and functional effects [4, 5]. The number of studies in humans in these early days was however limited. In one of the few neurophysiological studies, it was found that this kind of stimulation alters EEG patterns and evoked potentials at the cortical level in humans [6]. With regard to cognitive and behavioural effects, early clinical studies describe a mixed impact on depression and other psychiatric diseases [7–9] and improved performance in a choice reaction time task in healthy subjects [10]. In the fol-

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lowing years, electrical stimulation of the human brain via transcranial application of direct currents as a tool to influence brain function was nearly forgotten, most probably due to mixed results of initial studies and limited options to explore physiological effects in humans. Nevertheless, in the last decades, it has been re-evaluated following the development of methods that allow probing its neurophysiological effects (e.g. transcranial magnetic stimulation – TMS, functional magnetic resonance imaging – fMRI and positron emission tomography – PET). tDCS developed into a technique that reliably induces and modulates neuroplasticity in the human cerebral cortex non-invasively and painlessly in order to elicit prolonged – but yet reversible – shifts of cortical excitability [2, 11–13]. This section offers an overview of tDCS protocols and their physiological effects.

3.2.1 tDCS Protocols and Effects

For tDCS, the direct current is usually applied via conductive rubber or metal electrodes embedded in a sponge soaked with saline, or covered with cream or gel or by gel-filled cap electrodes [14]. The electrodes are connected to a stimulator delivering constant current which is essential for stable current strength to ensure reliable tDCS effects. Usually applied stimulation parameters range from 1 to 2 mA current intensity, from 3.5 to 100 cm^2 electrode size and up to 20 min stimulation duration in most studies, although longer stimulation duration and higher stimulation intensity have been probed. These parameters are considered safe, as shown by behavioural measures, electroencephalography (EEG), serum neurone-specific enolase concentration, diffusion-weighted and contrast-enhanced MRI measures and missing severe side effects in healthy and diseased humans, as well as in animal experiments [2, 12, 13, 15–19]. Electrode positions above cranial foraminae and fissures should be evaluated with caution or avoided because these could increase effective current density relevantly and thus have damaging effects. Although tDCS is usually well tolerated, at the beginning of stimulation most subjects will perceive a slight itching sensation, which normally fades with time [20, 21]. To avoid retinal phosphenes due to the tenfold higher sensitivity of the retina compared to the brain to electrical stimulation [22], as well as stimulation make-and-break effects, ramping up and down of current intensity for 8–30 s at both, the start and end of stimulation is suggested [23]. Blinding can furthermore be improved by application of topical anaesthesia to reduce somatosensory perception [24], especially with higher stimulation intensities, and application of ketoprofen to reduce erythema under the electrodes [25]. For an extensive methodological overview, please refer to Woods et al. [14].

Physiological tDCS effects, including efficacy, direction and focality of neuronal excitability changes, are determined by *stimulation polarity, current density, stimulation duration, electrode size, configuration and position*. These parameters are discussed in the following sections.

Electrode Position/Configuration/ Current Direction

Stimulation polarity determines the direction of cortical excitability changes elicited by tDCS at the macroscopic level within specific limits of stimulation intensity and duration. In most studies, both in humans and animals, anodal DC stimulation enhances cortical excitability and activity, whereas cathodal stimulation results in reversed effects [11, 12, 26]. However, deviating results have also been reported for subgroups of neurons [26, 27], hippocampal slice preparations [28] and specific return electrode positions [29]. One explanation for these heterogeneous effects is the fact that not so much the polarity of the electrode over the stimulated area per se is the decisive factor for the net effects of tDCS on excitability, but rather the direction of current flow relative to neuronal orientation: the respective current has to flow along the longitudinal axis of a given neuron to induce relevant effects on membrane polarity [30]. Polarisation of the soma and axon might determine the direction of the effects more than dendritic polarisation, because of higher receptor and ion channel density at the soma and axon level. Consequently, the position of the return electrode is critical for achieving the intended

excitability shifts, because together with the stimulation electrode it determines the electric field orientation in relation to neuronal orientation. In accordance, the position of the return electrode had been shown to determine the direction of the effects and efficacy of tDCS to induce cortical excitability alterations for motor and visual cortex stimulation [11, 29, 31, 32], and identical electrode arrangements result in opposite effects on cortical excitability in case of antagonistically oriented neurons [28]. Moreover, for motor cortex stimulation, it was demonstrated that positioning of the return electrode at the shoulder or arm results in diminished efficacy, as compared to the "classical" bipolar electrode configuration with the return electrode positioned over the contralateral orbit [33]. On the other hand, too low inter-electrode distance results in massive shunting of current flow between electrodes via the skin. Thus, also distance between electrodes is relevant for the efficacy of tDCS.

The "classical" tDCS protocols to induce neuroplastic excitability alterations involve stimulation with two relatively large electrodes (usual size between 25 and 35 cm^2) positioned on the head. These electrodes induce relatively non-focal effects of the underlying cortex, but also at remote areas, as shown experimentally for stimulation of the primary motor cortex [34, 35], and via modelling approaches [36]. Low focality is not necessarily a problem for each application of tDCS. In clinical syndromes, modulation of pathologically altered excitability of larger regions might be preferable, and in some cases, where the intended effects are thought to originate from an interaction of task- and stimulation-generated activity alterations, functional focality might result from this interaction. However, focality is crucial for basic studies aiming to explore the contribution of a specific area to brain function. Thus, new tDCS protocols suited to increase focality of stimulation have been developed. At least two factors contribute to the low focality of tDCS, the size of the relatively large electrode positioned over the target area and the physiological effects of the return electrode, if positioned at the scalp. Focality of tDCS over the target area can be enhanced by reducing electrode size and keeping current density constant. By this modification of the stimulation protocol, it has been shown for the motor cortex that a more selective alteration of excitability of specific hand muscle representations is accomplished [35]. Following the same rationale, increasing the size of the return electrode at constant current strength of 1 mA from 35 to 100 cm^2 makes this electrode functionally inefficient with respect to the area under that electrode, most probably due to reduced current density, and thus results in an at least functionally monopolar stimulation [35]. Alternatively, the return electrode can be positioned at another location than the scalp, for example, the neck, shoulder, arm or knee [7, 29, 37]. However, this remote position of the return electrode might diminish the efficacy of stimulation [33], and it is unclear if other sets of neurons would be affected by these approaches due to different electrical field orientation.

Based on modelling of electrical field strength, alternative electrode configurations have been developed to optimise stimulation focality and tDCS with one central electrode over the target region, and four electrodes arranged in its vicinity (4 × 1, or HD-tDCS) is one of these approaches. Here relatively small electrodes are used, and a central stimulation electrode is surrounded by four return electrodes placed nearby the central electrode [36]. Since the distance between the respective electrodes is relatively short, and thus shunting is enhanced relative to the more conventional electrode arrangements, current density has to be relatively high to obtain similar effects as with the large electrodes. Taking this into account, the cortical excitability alterations induced by this protocol seem to be similar to those elicited by conventional tDCS [38]. However, information about the physiological focality of these excitability alterations is not available so far. The functional efficacy of this electrode configuration has been demonstrated in some pilot studies, including pain perception [39]. Another optimising future strategy might be multi-electrode approaches. These can be based on functional networks [40], or arranged to tackle a specific target region based on modelling approaches [41, 42].

Current Intensity/Density

In most of the studies, in which conventional tDCS with relatively large electrodes (see above) is applied, current intensity is set at 1–2 mA, which results in about 0.03–0.06 mA/cm^2 current density at the level of the skin. Resulting electrical fields and current densities at the level of the brain depend on the tissue properties between the electrode and the brain and might differ accordingly, as suggested by the results of modelling studies [43]. These stimulation intensities are sufficient to induce relevant excitability shifts in the human primary motor cortex (M1) and alter physiological, perceptual and cognitive processes in prefrontal, parietal, temporal and occipital cortices [2, 11, 13, 44, 45]. Increasing current density within certain limits might increase efficacy of stimulation due to a larger membrane polarisation shift [11]. It might also affect additional neuronal populations because of a greater efficacy of the electrical field in deeper cortical layers and different sensitivities of specific neuronal populations to DC stimulation [26]. Moreover, because of physiologically-based non-linearity of tDCS effects (see also below), more intensive stimulation can convert the directionality of effects [46, 47], and different participant populations might display altered sensitivity to tDCS [48].

Stimulation Duration/Interval

Stimulation duration determines the occurrence and duration of after-effects of DC stimulation in animals and humans. In humans, a typical protocol to induce acute effects of tDCS on cortical excitability without generating after-effects is applied with a stimulation duration of 4 s [11]. This stimulation protocol induces the respective excitability alterations only during stimulation. tDCS for more than 3 min seems necessary to induce cortical excitability and activity alterations, which outlast stimulation [11]. Hereby, at least within certain limits, extended stimulation protocols induce prolongation of the resulting after-effects. tDCS from 3 to 7 min results in polarity-specific excitability alterations for some minutes after the end of stimulation, whereas anodal tDCS for 13 min and cathodal tDCS for 9 min results in after-effects lasting for about 1 h in the human motor cortex [12, 16]. This specific duration dependency of effects does gradually differ for other cortical regions, including the visual cortex [32]. Moreover, this relation between stimulation duration, and duration of after-effects, is not linear under all conditions: recently it was shown that anodal tDCS for 26 min results in excitability-diminishing and not -enhancing after-effects, most probably caused by intraneuronal calcium overflow [49]. Thus, for the induction of after-effects lasting relevantly longer than 1 h after tDCS, which are desirable especially to achieve therapeutic effects in clinical studies, simply prolonging stimulation duration might not be the optimal strategy. One alternative might be the repetition of stimulation sessions. Indeed, repeating cathodal or anodal tDCS within a time window of 30 min increases and prolongs the after-effects of both anodal and cathodal tDCS relevantly, for anodal tDCS, for more than 24 h after stimulation [49, 50]. On the other hand, tDCS intervals of 3 and 24 h diminished the after-effects of the second protocol in both studies conducted in healthy participants. Thus, specific timing is important for prolongation of tDCS effects on cortical excitability. Moreover, the results of these studies suggest that consecutive tDCS protocols might interact even when the overt impact on cortical excitability has vanished. Therefore, a sufficient interval between experimental sessions is recommended, when it is not intended to induce cumulative after-effects.

Taken together, for tDCS various protocols are available, which differ with respect to stimulation polarity, current density, stimulation duration, as well as electrode size and placement. Dependent on these parameters, stimulation protocols can be customised at least to a certain extent to achieve the desired direction, strength, focality and duration of effects on cortical activity and excitability. However, systematic studies about optimised physiological and functional effects are rare so far. For functional effects, the development of optimised protocols might

have to take into account not only the impact of tDCS on cortical processes, but also the interaction between stimulation and task-related cortical activity alterations, which might not be trivial in each case. Another future challenge is the development of individually adapted stimulation protocols, which take inter-individual differences of anatomy and physiology into account. It should also be noted that, given the large number of tDCS studies investigating the effects of different parameters, a one-to-one transferability of effects obtained by stimulation of one target region to another cannot be taken for granted due to state dependency, anatomical differences and other factors [16, 51–53]. Therefore, titration of stimulation parameters is recommended if no reference is available for a particular tDCS protocol [13, 52, 53].

3.2.2 tDCS Physiology

A multitude of studies has been conducted to explore the physiological effects of tDCS in the last years. The primary motor hand area (M1) has been widely used as a model system in these studies in order to explore the modulation of cortical excitability by tDCS, mostly for practical reasons, because it is situated at the convexity of the precentral gyrus with a minimal distance to the scalp surface, and therefore can easily be reached by TMS, which is usually applied to monitor cortical excitability, including specific stimulation protocols to monitor different types of intracortical neurons as well as cortical output neurons [54]. Therefore, most of the existing knowledge about basic physiology of tDCS originates from studies in the human motor cortex. However, physiological effects of tDCS on other cortical areas have also been explored, and beyond TMS, evoked potential measures, EEG, and functional imaging have contributed to our understanding of the physiological background of tDCS. Whereas regional effects of tDCS were in the focus of investigations during the first years, the impact of tDCS on cortical network activity became a new topic of research recently.

Regional Effects of tDCS

Acute Alteration of Cortical Excitability

The primary mechanism of DC stimulation on the cerebral cortex is a subthreshold modulation of neuronal resting membrane potentials. Current has to enter and leave a given neuron to exert any physiological effects due to physical reasons, thus in any case, DC stimulation – independent from the polarity of the electrode over a target area – will have de- and hyperpolarising effects on a given neuron. For the direction of the effects on cortical excitability and activity, it is relevant to acknowledge that the soma and initial axon segment of a neuron are more sensitive for the alteration of membrane potentials via weak electrical fields. Thus, the physiological effects of DC stimulation might primarily depend on alteration of these membrane segments [55]. In animal experiments, anodal stimulation (i.e. stimulation with the anode positioned over the respective target region) results in an enhancement of cortical excitability, and activity, while cathodal stimulation has antagonistic effects [26, 27]. However, this polarity-dependent effect has to be qualified. As mentioned above, orientation of electrical field relative to neuronal orientation determines the direction of the effects. Accordingly, antagonistic effects of DC stimulation were described not only for subgroups of neurons, but also for specific preparations, such as hippocampal slice experiments [27, 28]. In humans, similar stimulation polarity-dependent effects have been shown for short stimulation durations of few seconds, which do not induce after-effects. Anodal tDCS enhances cortical excitability, while cathodal stimulation diminishes it in the human motor cortex, as demonstrated by TMS at the macroscale level. These effects are largely restricted to global parameters of corticospinal excitability, which are determined by ion channel conductivity, such as single-pulse MEP amplitudes induced by medium TMS intensity and recruitment curves. They do not involve major alterations of intracortical facilitation and inhibition, as monitored by TMS double-pulse stimulation protocols [11, 56]. Accordingly, blocking voltage-gated sodium

and calcium channels abolishes the excitability enhancement accomplished by anodal tDCS, but blocking glutamatergic NMDA receptors or enhancement of GABAergic inhibition does not affect the acute effects of tDCS [57, 58]. Thus, taken together, the primary effects of tDCS seem to involve polarity-specific membrane potential alterations, but no synaptic effects. It is important to realise that these effects are observable at the macroscale level. TMS affects large groups of neurons, and thus it cannot be excluded, but due to the physiological effects of stimulation described above, it is probable that specific groups of neurons react differently to tDCS.

Sustained Change of Cortical Excitability and Activity

In experiments in anaesthetised rats, Bindman and colleagues described prolonged enhancements of cortical activity and excitability lasting for hours after anodal stimulation, while cathodal DC stimulation had antagonistic effects, if stimulation was conducted for 5 min or longer [3]. Identically directed after-effects of tDCS are accomplished when stimulation duration exceeds 3 min in humans. tDCS over the motor cortex for up to 7 min results in after-effects of about 5–10 min duration, while longer stimulation durations for up to 13 min induce excitability alterations stable for about 60–90 min [11, 12, 16] (Fig. 3.1). However, the duration of the after-effects might differ between cortical regions, with somewhat shorter lasting effects induced by tDCS over the visual cortex with identical stimulation durations [32, 59].

At the cortico-spinal level, tDCS elicits similar after-effects as those accomplished during short stimulation. The slope of the recruitment curve is

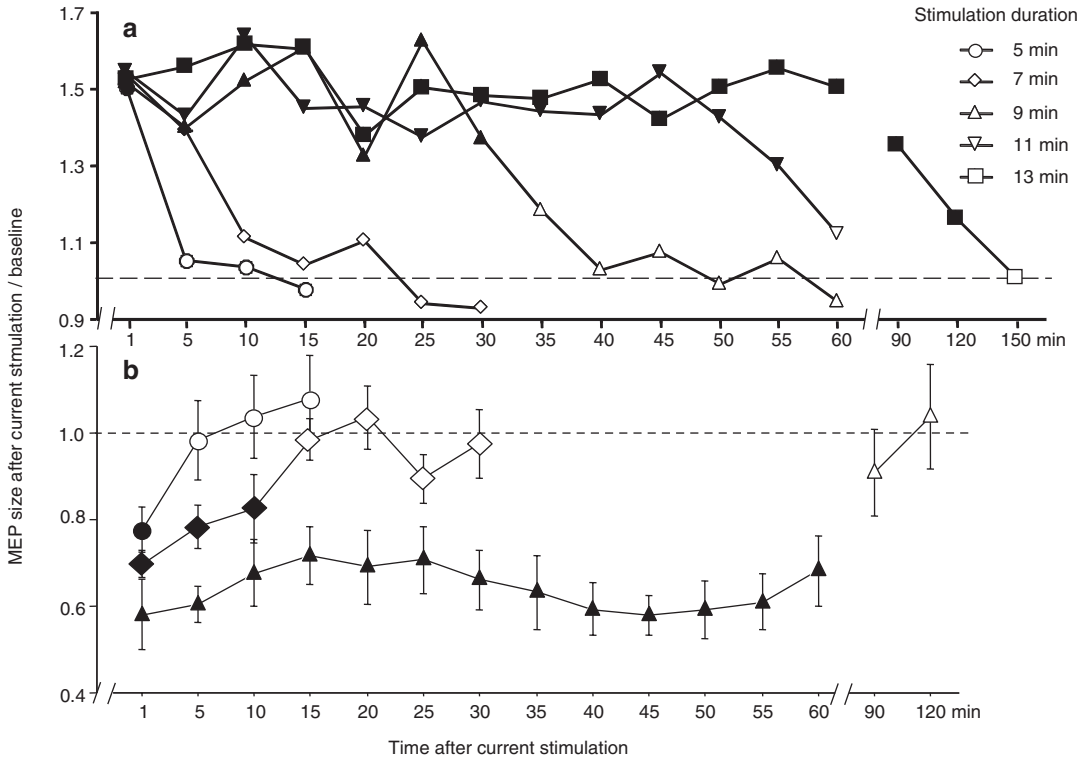

Fig. 3.1 After-effects of transcranial direct current stimulation (tDCS) on motor cortical excitability. tDCS of the human motor cortex modulates TMS-elicited MEP amplitudes after stimulation for up to an hour, depending on stimulation duration. Anodal stimulation (**a**) enhances, while cathodal (**b**) diminishes cortical excitability. Note that 5–7 min stimulation results in short-lasting after-effects, while prolonged tDCS increases the duration of the after-effects over-proportionally. (Nitsche et al. [12, 16], with permission of *Neurology* and *Clin Neurophysiol*)

reduced after cathodal tDCS, but enhanced after anodal stimulation [56]. For intracortical effects, anodal tDCS enhances intracortical facilitation and reduces intracortical inhibition, whereas cathodal tDCS induces antagonistic effects [56]. Most probably, these effects are accomplished by combined modulation of motor cortical afferents and motor cortex output neurons with conventional large electrodes, since selective premotor stimulation induces only the above-mentioned intracortical effects in M1, while focal stimulation over M1 with a small electrode only resulted in the above-mentioned cortico-spinal effects [60]. Because block of glutamatergic NMDA receptors abolishes the after-effects of tDCS, and the NMDA receptor agonist d-cycloserine prolonged the after-effects of anodal stimulation [57, 61]; it can be assumed that tDCS induces plasticity of the glutamatergic system, which is calcium-dependent. Calcium dependence of tDCS-induced plasticity has been demonstrated in another study [57]. These results are in accordance with animal experiments, in which it was shown that anodal tDCS enhances neuronal calcium content [62]. Beyond modulation of the glutamatergic system, it has recently been shown that both – anodal and cathodal tDCS– reduce free GABA in the cortical areas under the electrodes [63]. This result fits with an enhancing effect of both anodal and cathodal tDCS on TMS-induced I-wave facilitation, which is controlled by the GABAergic system [56]. GABA reduction has been shown to enhance glutamatergic plasticity in animal slice experiments and could have a facilitating effect on tDCS-induced plasticity in humans as well. It is worth to be mentioned that the induction of plasticity by tDCS seems to require spontaneous neuronal activity, as shown by Fritsch et al. [64]. This makes sense, because neuronal activity in the presence of subthreshold membrane depolarisation will enhance calcium influx relative to pure subthreshold depolarisation, or spontaneous activity alone, which in isolation might not suffice to open NMDA receptor channels.

Beyond the "classic" tDCS protocols, which induce after-effects of about 1 h duration, and thus early-phase plasticity, late-phase plasticity, which lasts for more than 24 h after intervention, can be induced by repeated tDCS within a critical time window of 30 min [49] similar to animal experiments [65]. Interestingly, continuous anodal tDCS with doubled stimulation protocol duration resulted in excitability-diminishing plasticity, and increasing the interval to 3 or 24 h duration diminished the efficacy of the stimulation protocol in the same study. The late-phase LTP-like effects of repeated anodal tDCS depend on the glutamatergic system. The excitability diminution induced by 26 min continuous stimulation might result from intracellular calcium overflow, since calcium channel block abolished this effect [49].

In summary, it can thus be concluded that the after-effects of tDCS depend on glutamatergic mechanisms, and that tDCS-induced reduction of GABA might serve as a "gating" mechanism.

Recently, stimulation intensity and duration have been extended beyond these classic protocols. Here it is shown that for anodal tDCS, prolongation of stimulation duration for up to 30 min, with a stimulation intensity of up to 3 mA, did result in fairly homogeneous excitability enhancement, with slightly better effects of stronger stimulation intensities [66, 67]. This effect was not only observable for TMS parameters, but also for MRI-derived measures of blood flow [68]. For cathodal tDCS, however, respective systematic titration of current intensity and stimulation duration resulted in an inverted U-shaped effect, with 1 and 3 mA resulting in an excitability diminution, while 2 mA current strength enhanced excitability [47]. This nonlinear effect might be caused by the known calcium dynamics of neuroplasticity [69], with low calcium influx inducing LTD, higher calcium influx inducing LTP and even higher calcium influx antagonised by opening of hyperpolarising potassium channels [70]. Alternative explanations, such as effects of tDCS on deeper cortical layers with larger stimulation intensity, can however not be ruled out at present.

Pharmacology of tDCS

Neuromodulators have a relevant impact on glutamatergic plasticity in animal models and humans

[71] (Fig. 3.2). In accordance, monoamines and acetylcholine have a prominent impact also on tDCS-induced plasticity. For dopamine, physiological receptor activity is critical for the induction of after-effects, because these are abolished by D2 receptor block [72]. Interestingly, increasing dopamine receptor activation by the non-selective precursor l-dopa has dosage-dependent non-linear effects on tDCS-generated plasticity. Whereas low- and high-dosage l-dopa abolish excitability-enhancing and -diminishing plasticity, medium dosage prolonged the excitability-diminishing after-effects of cathodal tDCS and converted anodal tDCS-induced facilitation into inhibition [73, 74]. Similar effects were accomplished with the D2 agonist bromocriptine [75]. In contrast, D1 receptor activation under D2 receptor block re-established tDCS-induced plasticity of both stimulation polarities dosage-dependently [76, 77]. Taken together, dopamine has prominent non-linear effects on tDCS-induced plasticity, which depend on dosage and receptor subtype activity. For the cholinergic system, enhancement of global cholinergic activation resulted in a similar effect as medium-dosage l-dopa on tDCS-generated plasticity, that is,

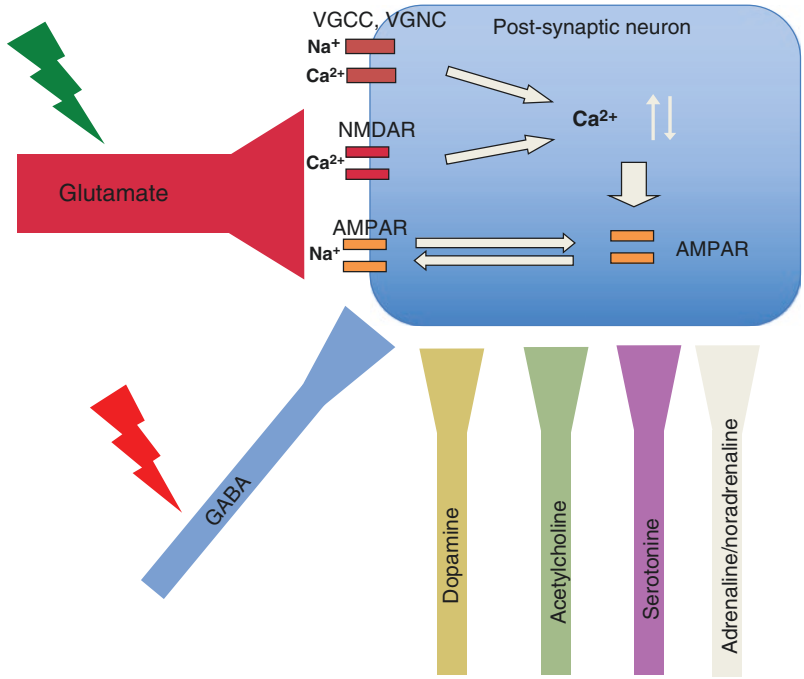

Fig. 3.2 Mechanisms and modulatory effects of tDCS-generated glutamatergic plasticity. In this figure, the main plasticity mechanism of glutamatergic synapses and the modulatory impact of other neurotransmitters and ion channels are displayed. As far as explored, tDCS has an enhancing effect on glutamatergic neurons (green arrow) [55, 121], while several studies showed that they reduce GABA activity (red arrow) [61, 122]. The release of glutamate activates NMDA receptors, which have calcium (Ca^{2+}) channel properties, if it is sufficiently strong. Depending on the amount of the consecutive intraneuronal calcium increase, enzyme cascades are activated which result in post-synaptic insertion or removal of glutamatergic AMPA receptors. The amount of post-synaptic AMPA receptors determines if a given activation of a pre-synaptic neuron results in supra-threshold post-synaptic activation. Thus, a modification of AMPA receptor density is the main basis for LTP and LTD. The activity of voltage-dependent calcium channels contributes to intracellular calcium alterations and the activation of sodium (Na^+) channels to the resting membrane potential, which affect the probability that NMDA receptors are activated and presynaptic activity results in a post-synaptic action potential. Various neurotransmitters such as GABA, dopamine, acetylcholine, serotonin, adrenaline and noradrenaline influence these principal mechanisms of action in a complex, sometimes non-linear way via their specific receptors, and they also have an impact on glutamatergic receptors and ion channels

a slight prolongation of cathodal tDCS-induced excitability diminution and a conversion of anodal tDCS-induced after-effects from facilitation into excitability reduction [78]. At least for anodal tDCS, these effects depend on activation of nicotinic receptors, since nicotine and the nicotinic α4β2 agonist varenicline had a similar effect on tDCS-induced plasticity [79, 80]. Recently it could furthermore be shown that this modulation depends on glutamate and calcium influx [81].

For serotonin, activation by a selective serotonin reuptake inhibitor (SSRI) facilitated and prolonged the after-effects of anodal tDCS and converted plasticity induced by cathodal stimulation into facilitation [82]. This effect was further enhanced after long-term application of SSRI [83]. Similar effects are obtained by enhancing of noradrenergic tone via the noradrenaline reuptake inhibitor reboxetine [84].

These studies show a prominent and complex impact of neuromodulators on tDCS-induced plasticity, which might, for example, be relevant for treatment of patients suffering from neurological and psychiatric diseases, where neuromodulator activity is often pathologically altered and counteracted upon by pharmacological intervention.

tDCS Effect on Cortical Regions Other than M1

Most of the above-mentioned studies were performed in the human primary motor cortex, but the effects of tDCS are not restricted to this region. In the last years, numerous studies have been conducted, which show a similar functional or physiological impact of tDCS on a multitude of cortical regions. Neurophysiological effects have been demonstrated for the visual cortex, where anodal and cathodal tDCS have similar effects on cortical excitability as motor cortex stimulation; however, antagonistic effects were also observed when the return electrode was positioned at the neck [29]. tDCS over the visual cortex results in shorter duration of the after-effects, as compared to stimulation over M1 with identical stimulation protocols. For tDCS of the somato-sensory cortex, anodal tDCS increased respective SEP amplitudes for at least 60 min after stimulation in one study [85], and cathodal tDCS reduced those in another one [86]. For auditory cortex stimulation, anodal tDCS over the temporal and cathodal tDCS over the temporo-parietal cortex enhanced the respective evoked potentials [87]. The recent development of concurrent TMS-EEG recordings allows the investigation of physiological mechanisms of tDCS via direct monitoring of cortical excitability. Anodal tDCS increased mean field power of TMS-evoked cortical potentials both during and following tDCS over the posterior parietal cortex, and also the dorsolateral prefrontal cortex [88, 89], although results are somewhat heterogeneous at present [90]. Such methodological advance will further contribute to the understanding of tDCS physiology into larger detail. Finally, it has been demonstrated that tDCS can also affect the spinal cord and the cerebellum [91]. For the latter, its complex folding seems to result in antagonistic effects dependent on the depth of penetration, which makes sense, given the relationship of tDCS effects from the relation of electrical field and neuronal orientation [92].

Inter-Regional Effects of tDCS

Apart from the regional effects of tDCS under the stimulation electrodes, remote effects on topographically distant cortical and subcortical areas were described relatively early [34]. However, it was unclear whether those effects are caused by physiological spreading of cortical activity or by physical current spread. Simulation studies, although not physiologically validated so far, are in favour for at least a partial contribution of spread of current flow [36]. In addition, physiological effects of tDCS on remote areas have been described. Premotor anodal tDCS enhances intracortical facilitation of M1, most probably due to the activation of premotor-primary motor cortex afferents [60], and combined dorsal premotor and supplementary motor area (SMA) stimulation alters motor and somatosensory evoked potentials [93]. For parietal cortex stimulation, anodal tDCS enhanced, but cathodal tDCS reduced MEP amplitudes. Moreover, anodal tDCS over the posterior parietal cortex increased both ipsilateral M1 intracortical inhibition and facilitation, as well as parietal-motor cortical connectivity [94].

Furthermore, anodal tDCS over the posterior parietal cortex increased cortico-cortical potentials elicited by TMS in both local and surrounding and contralateral regions [89].

Recently, functional connectivity approaches have been applied to explore cortical network alterations induced by tDCS. For motor cortex stimulation under resting conditions, an fMRI study revealed that nodal minimum path length increased after anodal tDCS over M1, which means that functional connectivity of this area with topographically distant regions of the whole brain significantly decreased. In contrast to this generally reduced whole brain connectivity of M1, functional connectivity was enhanced between the primary motor cortex on the one hand and premotor and superior parietal areas on the other hand [95]. In another study, cathodal tDCS of the primary motor cortex increased functional connectivity between the stimulated M1 and the contralateral M1 and premotor cortices [63]. A similar effect of tDCS was described for anodal stimulation combined with motor practice in an EEG study, where functional connectivity was enhanced between primary motor, premotor and sensorimotor areas in the high gamma band [96]. Moreover, anodal tDCS of the primary motor cortex alters cortico-subcortical connectivity of the motor cortex at rest. Specifically, it was shown to enhance connectivity with the ipsilateral caudate nucleus and thalamus [97]. Alterations of intrinsic motor cortex connectivity by tDCS have also been demonstrated: cathodal stimulation increased local connectivity, most likely due to cortical noise reduction accomplished by the respective excitability and activity diminution, while anodal tDCS enhanced long-distance connectivity within this area [97]. Therefore, it can be concluded by the results of these studies that motor cortex tDCS alters the connectivity of large parts of the motor network.

Beyond tDCS of the motor cortex, stimulation of the dorsolateral prefrontal cortex has been demonstrated to induce widespread alterations of functional connectivity, including the default mode network and attention-related networks in healthy subjects [98, 99]. A study conducted by Mainzer and co-workers showed that respective connectivity alterations are brain state-dependent. Whereas anodal tDCS over the left inferior frontal gyrus under resting conditions enhanced functional connectivity of a network associated with language processing, respective stimulation reduced respective connectivity in a language task and improved performance, thus suggesting that tDCS conducted during task performance enhanced the efficacy of processing [100].

To summarise, in addition to its regional effects under the stimulation electrodes, tDCS has prominent effects on functional networks at both cortical and subcortical levels. The relevance of these network alterations for cognition and behaviour needs to be explored in more detail in future studies.

3.3 tACS

It is well established that sensory and association areas of the brain are organised in a distributed manner. This segregation requires efficient communication mechanisms allowing the brain to integrate information both within and across different areas to guide behaviour. The question is, how can the human brain achieve this relatively fast and efficient integration of information? A prominent hypothesis suggests that neural oscillations play a fundamental role in cognitive functions supporting both neural communication and plasticity. Despite the large amount of empirical data, so far the majority of these studies have provided only correlative evidence for the impact of neural oscillations on cognitive performance, whereas its causal role is still to be determined. In order to probe the causal neurophysiology underlying function and behaviour of neural oscillations, tACS has emerged as a promising technique to achieve this goal.

tACS is a variant of tES, which modulates oscillatory brain activity via application of alternating currents with sinusoidal waveforms. Growing evidence from human research suggests that, during stimulation, oscillatory brain activity, as measured with electro-encephalography (EEG) and more recently with magneto-encephalography (MEG), phase-locks to

rhythmic trains of stimulation [101, 102]. tACS is presumed to affect neuronal membrane potentials by subthreshold (i.e. no action potential generation) oscillatory electrical stimulation with specific frequencies and to interact with ongoing rhythmic cortical activities. Interestingly, the observed entrainment effects are more prominent when the frequency of stimulation matches the dominant frequency of the stimulated structure [103]. However, for specific stimulation frequencies, also neuroplastic excitability modifications have been described [104–107]. By its modulating effect on task-related oscillatory brain activity, tACS appears to be a useful tool to investigate the causality of physiological phenomena for cognition and behaviour. In this section, we discuss the possible physiological effects of tACS as well as examples of its effects on cognition and behaviour.

3.3.1 tACS Protocols and Effects

The application of tACS employs a similar set-up as conventional tDCS, except for the polarity of stimulation. While anodal or cathodal stimulation in case of tDCS describes the constant polarity of an electrode during the whole intervention and determines the direction of effects, the polarity of the two electrodes in tACS alternates every half cycle. The efficacy of tACS is mainly determined by the intensity, frequency and phase of the stimulation protocol, which result in modulation of cortical excitability and/or oscillations.

Physiological Effects of tACS

Similar to tDCS, tACS is assumed to not induce cortical activity, but to modulate spontaneous activity via sub-threshold membrane polarisation. One potentially relevant effect is modulation of spontaneous oscillatory activity. In accordance, computational modelling suggests that external electric stimulation with a relatively low amplitude, as applied in tACS, is indeed sufficient for synchronising oscillatory activity of neural networks [108]. Animal studies demonstrated synchronisation of neuronal spike activity corresponding to the externally applied frequency of oscillations within different frequency bands [109], a phenomenon termed entrainment. While the results of that initial investigation were promising, tACS was applied in rodents at current intensities that would be prohibited in humans. Thus, the question remains as to whether conventional current intensities applied in humans have the capability of inducing entrainment in vivo and during wake states. A recent study presented data from non-human primates, a highly realistic model of the human brain, demonstrating that tACS reliably entrains the spiking activity of single neurons in awake monkey. Crucially, this entrainment was shown to be limited to the frequency of stimulation and the vicinity of the targeted brain region [110]. With increasing electric field strength, more neurons were entrained to the stimulation frequency. Importantly, concurrent electric field recordings demonstrated that these spike timing changes occur in a field regime that are practicable in humans (i.e. electric fields <0.5 mV/mm, which are achievable in humans for tACS intensities between 1 and 2 mA). Together, these results provide compelling evidence that tACS applied at conventional intensities in humans have the capability of genuinely inducing entrainment of neural oscillations.

Regarding studies in humans, when tACS is applied within the individual alpha frequency for 10 min over the occipital lobe, the corresponding spectral power was facilitated, and this effect outlasted the intervention [111, 112]. Likewise, it was shown that by prefrontal stimulation in the gamma frequency range, but not at other frequencies, during REM sleep, where gamma band activity is presumed to have important functional relevance, brain activity in these frequencies was enhanced [113]. Similar effects were obtained for beta frequency stimulation of the motor cortex, where it was also shown that the oscillatory aftereffects depended on glutamatergic mechanisms, because block of NMDA receptors abolished these [114]. Thus, taken together, these studies deliver evidence for a modulatory effect of tACS on spontaneous cortical oscillatory activity.

Beyond its impact on oscillatory brain activity, tACS can also affect cortical excitability. These effects seem critically to depend on stimu-

lation frequency and intensity and differ between online and after-effects. For the primary motor cortex, online effects on cortical excitability were selectively obtained by 20 Hz stimulation, but not by tACS within other physiological frequency bands. Since 20 Hz is the predominant frequency in the resting motor cortex, this result fits nicely with the modulatory impact of tACS on oscillatory brain activity [115]. For after-effects, even longer tACS durations (2–10 min) within similar frequency ranges showed no effect on MEPs with a peak-to-peak stimulation amplitude of 1 mA [104, 116]. Enhancing, however, stimulation intensity to 2 mA and stimulation duration to 15 min resulted in neuroplastic excitability enhancement lasting for at least 60 min after the end of stimulation and respective after-effects dependent on the activity of NMDA receptors [114]. For other frequency bands, already lower stimulation intensities and durations induce neuroplasticity. tACS over M1 with 140 Hz and 0.63 A/m^2 for 10 min significantly enhanced cortical excitability during and after stimulation [106]. In the same study, lower stimulation intensity with 0.25 A/m^2 resulted in a decrease of excitability. Interestingly, hippocampal plasticity is closely related to respective oscillations, which might explain the relatively high propensity of this frequency band for plasticity induction. With even higher frequency stimulation outside the physiological range of brain oscillations, including stimulation frequencies between 2 and 5 kHz, tACS (0.2 A/m^2 for 10 min) induces MEP enhancements lasting for more than 1 h [117]. The respective mechanisms of these stimulation frequencies are not well explored. To summarise, tACS may non-linearly alter cortical excitability during and after intervention. The presence and direction of this effect depends on stimulation frequency, intensity and duration.

tACS Effects on Cognition and Behaviour

The modulatory impact of tACS on oscillatory cortical activities has an impact on cognition and behaviour. Numerous studies were conducted for uni-regional tACS to explore the relevance of oscillatory activity of a specific area for performance. A couple of studies were performed in the visual domain. For visual perception, stimulation with beta or alpha frequency significantly reduced phosphene thresholds in illuminated or dark conditions, respectively [118]. Since beta frequencies are predominant in illuminated surroundings, whereas alpha frequencies dominate under light deprivation, this study suggests that tACS can modulate visual perception via its impact on naturally occurring cortical oscillations. In another study with tACS over V1, contrast perception was enhanced under high gamma (60 Hz) frequency stimulation, while spatial attention remained unchanged [119], underscoring the region-specific effect of tACS. Beyond visual areas, other cortical modalities have also been shown to be affected by tACS. Somatosensory tactile perception was enhanced specifically with tACS over the sensory cortex in the alpha (10–14 Hz) and high gamma (52–70 Hz) range [115]. For the motor system, 20 Hz tACS slowed down voluntary movement, but 70 Hz stimulation enhanced motor performance [120, 121]. Interestingly, a more recent study combined tACS and fMRI to reveal the neural mechanisms underlying these tACS-driven motor performance improvements [122]. This study showed that a remote area relative to the location of the target electrode – the dorsomedial prefrontal cortex (dmPFC) which is known to be engaged in cognitive and motor control – regulates the tACS-induced behavioural changes. More specifically, this study revealed that these changes not only result from activity modulations underneath the stimulation electrode but also reflect compensatory modulation within connected and functionally related brain networks. Another study showed increased behavioural variability following 10 Hz tACS [123] and also facilitated motor sequence learning, but only when applied at alpha frequency, which is associated with the inhibition of irrelevant stimuli during cognitive tasks [121, 124]. In addition to relative elementary cognitive processes, tACS was employed to alter more complex functions. Working memory performance was altered by tACS in the theta frequency range (6.5 Hz) over the left DLPFC

[125], and sleep-dependent consciousness levels were affected by tACS in the gamma frequency range [113] (Fig. 3.3). Similarly, rhythmic stimulation with gamma frequency over the left middle frontal gyrus enhanced fluid intelligence in another study [126].

In the above-mentioned studies, tACS was applied with standard frequencies across subjects. However, individual alignment of stimulation parameters to physiological oscillations might be also a promising approach. Cecere and co-workers (2015) explored the relevance of adjustment of tACS over V1 to individual oscillatory activity in a cross-modal sound-induced visual illusion task. tACS was applied with the individual alpha frequency or ±2 Hz. As compared to stimulation with individual alpha frequency, the deviating stimulation protocols enlarged or shrunken the illusion perception time window, demonstrating a critical impact of specific alpha frequency on this perceptual process.

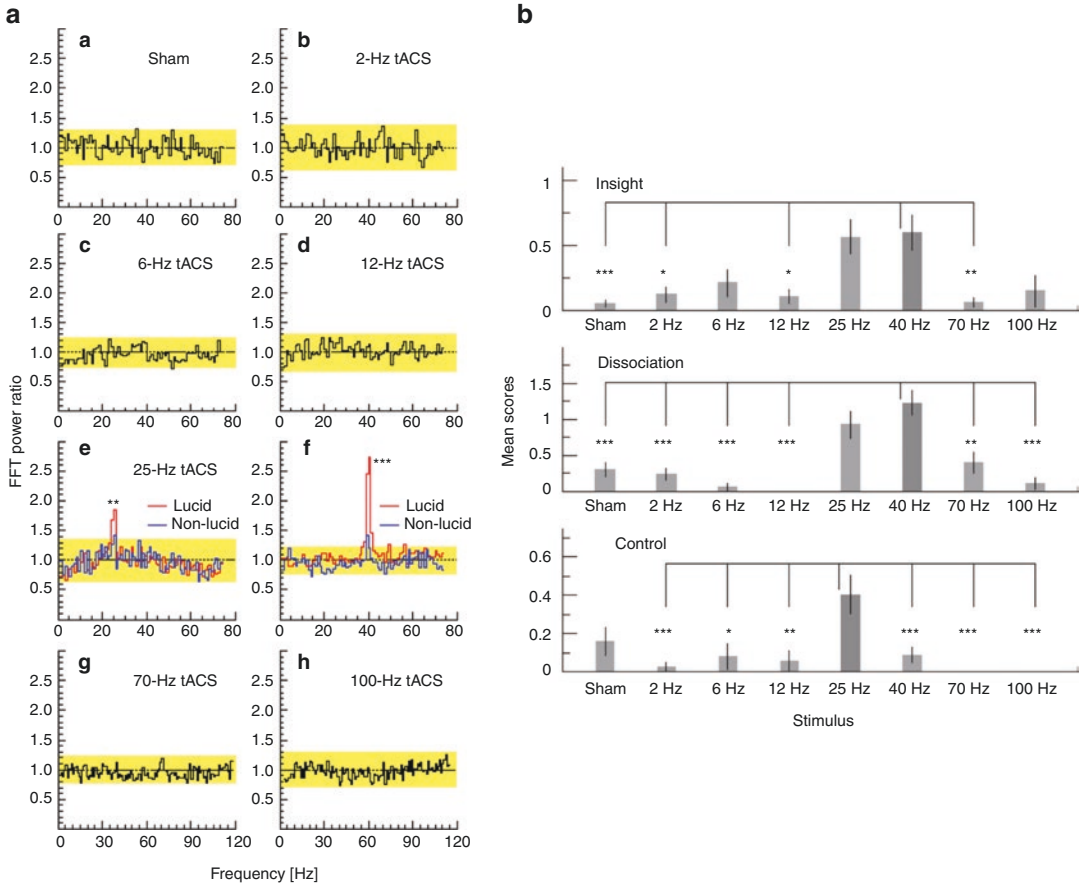

Fig. 3.3 Enhancing self-awareness during dreaming with high gamma tACS. (**a**) Grand average FFT power ratios of activity during (phase II) versus activity before stimulation (phase I) for the different stimulation conditions: sham, 2, 6, 12, 25, 40, 70 and 100 Hz (**a**–**h**). Yellow shading represents mean values ±2 s.e. Any excursions outside of this range are considered to be significant at least at the $P < 0.05$ level. Note that, with 40-Hz and 25-Hz stimulation, lucid dreams (red line) were accompanied by a significantly larger increase in the respective frequency band than non-lucid dreams (blue line). (**b**) Selected contrasts of mean scores (s.e.) for the LuCiD factors' insight, dissociation and control. The contrasts for insight and dissociation were strongest during stimulation with 40 Hz (40-Hz reference condition is shaded, top and middle frame). Control was increased most during stimulation with 25 Hz (25-Hz reference condition is shaded, bottom frame). $^{***}P < 0.001$, $^{**}P \leq 0.01$, $^{*}P \leq 0.05$. (Voss et al. [113], with permission of *Nature Neuroscience*)

Furthermore, individually adjusted tACS offers the potential to modulate peripheral and periodic motor movements such as tremor with individually adjusted frequency alignment [127]. In that study, stimulation was not only adjusted to individual frequency, but also phase-locked to oscillatory activity. tACS in phase with oscillatory activity enhanced, whereas antagonistic stimulation reduced tremor considerably, presumably via phase cancellation effects. Taken together, these studies show that tACS adjusted to physiological oscillations is able to modulate cognitive processes of different complexity in different domains, and that sophisticated approaches like individual adjustment of tACS frequency and phase-locked stimulation are promising approaches to improve insight about the relevance of regional oscillations for performance.

Beyond exploration of regional effects, tACS is suited to explore the relevance of oscillatory brain activity for task-relevant interactions between cortical areas. Specifically, tACS offers the opportunity to explore the causal relevance of functional oscillatory connectivity for task performance via combined stimulation of distant, but functionally connected cortical areas. A couple of studies demonstrated this effect for perceptual tasks. Anti-phasic tACS over parietal and occipital areas in the alpha frequency range (6–10 Hz), which increases a presumed inhibitory alpha effect, reduced the performance of a visual detection task [128]. Moreover, a phase-specific tACS effect was observed by anti-phasic (180-degree difference) 40 Hz stimulation bilaterally over the parieto-occipital junction. Here, motion perception was altered possibly via modulation of interhemispheric functional coupling in the gamma range [101, 129]. In the latter study, 4 × 1 tACS, with the same electrode montage as used in 4 × 1-tDCS, was applied in order to separately adjust different phase angles of the electrodes placed over the two hemispheres [101]. Beyond these elementary processes, also modification of more complex cognitive tasks was explored. For working memory performance, it was shown that parietal and frontal areas connect during task performance in the theta frequency range. In accordance with the hypothesis that synchronisation between both areas is causally relevant for task performance, synchronised stimulation with 6 Hz frequency improved reaction time, whereas antagonistic tACS diminished performance [130]. Likewise, interhemispheric anti-phase tACS over F3/F4 with slow-wave frequencies (0.75 Hz, current density 5.17 A/m^2) during a nap reduced activity in delta-frequency bands, which was correlated with impaired memory recall [131]. In a recent study, researchers aimed to identify a causal link between reduced frontotemporal brain oscillatory dynamics and working memory deficits in the elderly [132]. The investigators first conducted an EEG study where they found that phase–amplitude coupling in temporal regions correlated with working memory performance in the younger group but not in the older group. Moreover, theta-phase synchronisation between frontal and temporal regions – which is thought to reflect the influence of the frontal cortex on content processing and storage in temporal areas – was absent in the elderly group but not in the young group. These results suggested the possibility of a causal relationship between these neural signatures and working memory performance, which the authors explored in a subsequent tACS study. They applied tACS to strengthen frontotemporal theta-phase synchronisation [130] in the older adult group while they were performing the working memory task. tACS led to an improvement of working memory that resembled performance levels seen in younger subjects. These positive behavioural effects started about 10 min after the onset of stimulation and outlasted the stimulation period by about 1 h. Thus, these results provide novel evidence that non-pharmacological interventions based on tACS protocols could improve cognitive decline in healthy ageing.

Turning to examples at even higher cognitive processes, in an initial EEG study, it was demonstrated that gamma phase-coupling between the medial fronto-polar and superior parietal cortex correlated with the accuracy of making decisions based on subjective preferences [133]. This correlative evidence was causally confirmed with multi-site tACS, where it was shown that

transcranially inducing decoupling between the frontopolar and parietal regions identified in the EEG study indeed impaired the ability of human participants to correctly choose between alternatives containing primary rewards [134].

Taken together, tACS is able to modulate cognitive functions, and beyond regional modulation of oscillatory activity, also specific network alterations are suited to modify functional connectivity and performance.

3.4 General Remarks

Since tDCS and tACS have been re-introduced as tools to induce acute and neuroplastic alterations of cortical excitability and activity and to modulate cognitive processes, an increasing number of studies have been conducted to develop protocols enhancing the efficacy of stimulation and to explore the physiological basics of the effects. For tDCS, the determinants of efficacy, such as stimulation intensity, duration and repetition intervals, have been identified, and protocols which allow a relatively focal stimulation have been developed. It has been shown that the dependence of tDCS efficacy on these stimulation parameters is not linear in each case. Future work should focus on further optimising stimulation protocols, which will be important especially for clinical applications, where stable alterations of cortical excitability and activity are needed. Moreover, given the partial non-linearity of the effects, exploring optimal combinations of stimulation with performance would be an important, but not trivial, topic of future research. Since most of the studies reported in this review were conducted in the primary motor cortex, the transferability of the respective results to other cortical areas has yet to be explored. With regard to the mechanisms of action, pharmacological, TMS, EEG and functional imaging studies have revealed the main physiological mechanisms of tDCS, that is, the primary effect of membrane polarisation, the dependence of the after-effects from alterations of glutamatergic synapses and the complex alteration of tDCS-induced plasticity by neuromodulators. Furthermore, it became increasingly clear recently that the effects of tDCS are not only restricted to the area under the electrodes. The stimulation also induces alterations of connectivity within cortical and cortico-subcortical networks. As for tACS, experiments in both animals and humans, as well as results from computational simulation, increased insights into the basic physiology. However, the development of tACS protocols is still in a relatively early state as compared to tDCS. Further investigations including the combination of neurophysiological recordings and neuroimaging techniques will be desirable to improve mechanistic understanding. Although knowledge about the physiological basis of tDCS and tACS is incomplete, respective studies provide a basis, which might also be important for evaluating new fields of application in future.

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