13 Precision Targeting of Neural Networks with tDCS Informed by Brain Mapping

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13.1 Introduction

Transcranial direct current stimulation (tDCS) is applied via surface electrodes attached to the scalp. The induced electrical field in the targeted cortex is thought to cause tonic shifts in the membrane potentials of cortical neurons that remain below firing threshold. This subthreshold effect on axonal excitability is thought to alter the intrinsic firing rate of the stimulated neurons in the brain and thereby the signaling in neural networks. By reversing aberrant signaling in those neural networks that are affected by neurological and neuropsychiatric conditions, tDCS offers a low-cost treatment option. The current state of evidence suggests moderate treatment effects in mental disorders, for example, depression [1], and in ameliorating motor and cognitive symptoms in nonprogressive (e.g., stroke [2, 3]) and progressive neurological disorders ([4]; see also [5] for review). The treatment effects of tDCS show substantial interindividual but also intraindividual variations. This variability hampers the clinical application of tDCS as therapeutic intervention [6]. In this chapter, we argue that the personalization of tDCS is critical to the future advancement of tDCS as a scientific and therapeutic tool. By tailoring the tDCS intervention to the individual brain, one can render tDCS more precise and induce more reliable and robust aftereffects. Taking a brain network perspective, we highlight how the combination of tDCS and brain imaging can reveal basic insights into the mechanism of action of tDCS and inform the personalization of tDCS.

13.1.1 Identifying and Targeting Dysfunctional Large-Scale Brain Networks

Genetic, environmental, and neurodevelopmental factors play important roles in the manifestation of psychiatric syndromes [7]. The interplay and extent of these factors are thought to alter molecular pathways in the cell as well as the functional interplay between neurons and surrounding glia at the micro-circuit level, for instance by altering

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neurotransmitter release or neuronal firing patterns. However, it is the resulting large-scale circuit dysfunction that ultimately causes mental dysfunction and psychiatric symptoms [8] (Fig. 13.1). Emotional, cognitive, and self-reflective mental functions critically rely on the integrated activity and connectivity of large-scale brain circuits. This implies that a clinically relevant mental dysfunction (e.g., excessive anxiety or fear) first emerges, when aberrant processes at the cellular and micro-circuit level produce a significant dysfunction of the macro-scale brain circuit that underpins the affected brain function (e.g., affective limbic brain circuit of emotional processing). This implies that the way a psychiatric disorder affects large-scale functional brain networks determines which behavioral dimensions are impaired and how they are impaired.

Figure 13.1 illustrates the complex etiology of psychiatric disorders. Polygenetic and neurodevelopmental factors lead to changes in multiple neurotransmitter systems and alters micro-circuit activity in multiple brain regions. The spatial expression of these micro-scale changes affects to a varying extent the activity and connectivity of several large-scale brain networks. The individual profile of large-scale brain circuit dysfunction determines the type and severity of symptoms that characterize the patient's clinical phenotype (i.e., the specific expression of symptoms and course of the disorder in an individual patient).

Pharmaceutical therapies with molecular and cellular targets are currently the first-in-line treatment but inherently lack "circuit specificity," impacting on all large-scale brain networks that express the molecular target structure (Fig. 13.1).

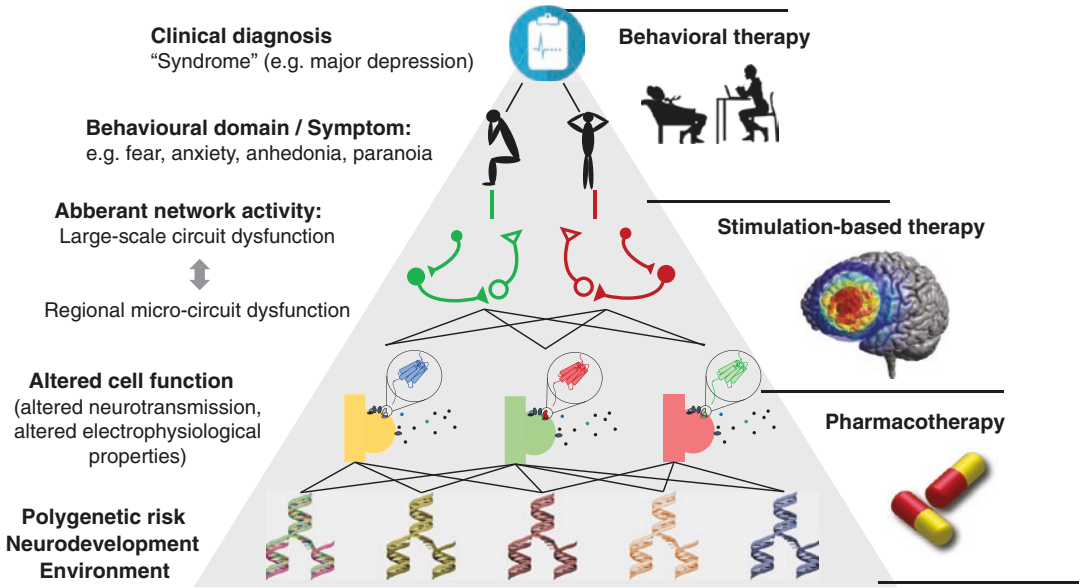

Fig. 13.1 Multilevel neurobiological framework of the pathogenesis and treatment of brain disorders
Psychiatric and neurologic disorders have a poly-causal origin. Multiple genetic factors and environmental exposures lead to multiple alterations of cellular pathways. The molecular changes at the cell level give rise to dysfunction in neuronal micro-circuits and large-scale brain circuits. The disease-related circuit dysfunctions (network level) are ultimately causing a range of symptoms in a given patient which leads to a clinical diagnosis (syndrome level). The black lines illustrate the polygenetic contribution to changes in neurotransmission and the polycausative molecular background leading to abnormal signaling in neural networks. The vertical green and red lines denote the close relationship between network signaling and a behavioral expression within specific domains of functions or cluster of symptoms. While pharmacological therapies have molecular targets and aim at improving cellular biology, therapeutic interventions are tailored to the symptoms expressed in a given patient. Brain stimulation therapies have an intermediate target, because they primarily are geared to improve the regional and network dysfunction that leads to a clinical dysfunction

Furthermore, the causative relation between their molecular targets and the therapeutic effect is often blurred. This is illustrated by the delayed clinical response to antidepressant pharmacotherapy which contrast with the immediate action at the cellular level (e.g., inhibition of serotonin reuptake from the synaptic cleft) [9]. Behavioral interventions such as cognitive behavioral therapy or motor training are also relatively non-selective. They usually engage multiple brain networks to a variable degree, and the magnitude of functional engagement of the various networks can be expected to vary from patient to patient. Transcranial brain stimulation techniques, such as tDCS, complement pharmacological and behavioral therapies, because they offer the opportunity to selectively target large-scale circuit dysfunction in a symptom-causing brain network, opening up interesting possibilities for a patient-specific "personalized" treatment. Of note, tDCS can be combined with pharmacological and behavioral interventions to manipulate circuit activity in the stimulated target network (see below).

The classical approach to investigate circuit-dysfunction in mental disorders is to identify syndrome-related changes in functional brain circuit activity and connectivity based on group comparisons between "affected" and "healthy" persons. The last decades have witnessed a paradigm shift away from grouping patients according to clinical diagnosis toward focusing on general domains of human functioning in order to enable a better mechanistic understanding of mental health and illness. The National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc) has been proposed as an open, matrix-like framework, which aims to identify the varying degrees of dysfunction in general psychological and neurobiological systems, currently focusing on six domains: negative valence systems, positive valence systems, cognitive systems, systems for social processes, regulatory (arousal) systems, and sensorimotor systems. The RDoC framework links genetic, molecular, and cellular aspects of neural systems with behavioral dimensions. Critically, circuit abnormalities in large-scale neuronal networks are seen as the causal link between aberrant neural systems and the resulting dysfunctional behavior. The RDoC framework has important implications for the therapeutic use of tDCS in mental disorders [10]. If one has identified a specific property of the brain network that causes a specific symptom, the individual expression of this circuit-biotype can guide the stratification and personalization of neuromodulatory tDCS.

13.1.2 Neuromodulation of Large-Scale Brain Circuits with tDCS

The traditional view is that tDCS has immediate polarity-dependent effects on intrinsic neural excitability. When given continuously for several minutes, tDCS may produce longer lasting polarity-specific shifts in intrinsic neuronal activity in the stimulated brain regions. Such polarizing effects have been shown in invasive recordings of cortical neuronal activity, while the cortex was exposed to a DC current running perpendicular to the cortical layers [11]. In humans, polarity-dependent, neuromodulatory effects of tDCS on cortical excitability were first demonstrated in the human motor cortex [12]. Placing one electrode over the motor hand area and the other electrode over the contralateral supraorbital region, bipolar tDCS can induce lasting changes in corticospinal excitability [12].

How Does tDCS Stimulate Neurons in the Brain?

The mechanisms through which tDCS affects neural spiking and patterns of network activity are still to be determined, but they are likely to be dose dependent. Current tDCS protocols produce relatively low currents in the cortical tissue. Approximately, 75% of the current that is applied to the scalp is shunted along low-resistance pathways (e.g., fluid, bone, skin, and subcutaneous tissue), while only 25% of the current pass through the brain [13–15]. Therefore, tDCS does only cause subtle effects on the membrane potential of cortical axons. These subtle polarizing effects may add stochastic noise to ongoing

activity (see [16]) and "tune" the level of ongoing (intrinsic) neuronal activity but are too weak to trigger action potentials. Thus, the weak intracranial currents cannot evoke synchronized extra activity in the stimulated cortex.

The intensity of the intracranially induced electrical field is highest at the gyral crowns and relatively weak in the gyral sulci [14]. Neuromodulatory effects of tDCS on the excitability and activity of cortical neurons are therefore more likely to occur in cortical regions close to the surface [17]. Depending on the orientation of the electrical field with respect to the axon, tDCS induces slight changes in the membrane potential, which in turn can alter neuronal excitability. The direction of polarization depends on the orientation of the axonal structures with respect to the orientation of the induced electrical field and is illustrated in Fig. 13.2. Changing the orientation of the induced electrical field relative to the main neuron's soma-dendritic axis, from parallel to perpendicular, substantially changes which axonal structures are polarized as well as the strength and direction of the polarizing effects. The immediate or acute effects on axonal excitability may change how efficient the neuron interacts with connected neurons, for instance by changing synaptic or ephaptic couplings or the interaction of both (see [18] for review). Due to the complex biophysical-neurophysiological interactions, the functional impact of tDCS on the targeted brain networks cannot be simply accounted for by polarity-dependent increase or decrease in neuronal excitability and consequently neural activity.

From a network perspective, tDCS can modulate not only task-specific activity below the electrodes, but also the connectivity within large-scale network [19]. The polarization of neurons during tDCS not only changes how they process information but also their propensity to undergo plastic changes (see [20]). The common notion is that tDCS evokes lasting after-effects at the site of stimulation by inducing prolonged changes in intrinsic circuit activity in the stimulated regional microcircuits [21]. In addition, tDCS may also change the integration of neuronal activity in large-scale bran networks by changing inter-regional functional coupling of the stimulated brain region with other remote network nodes [22].

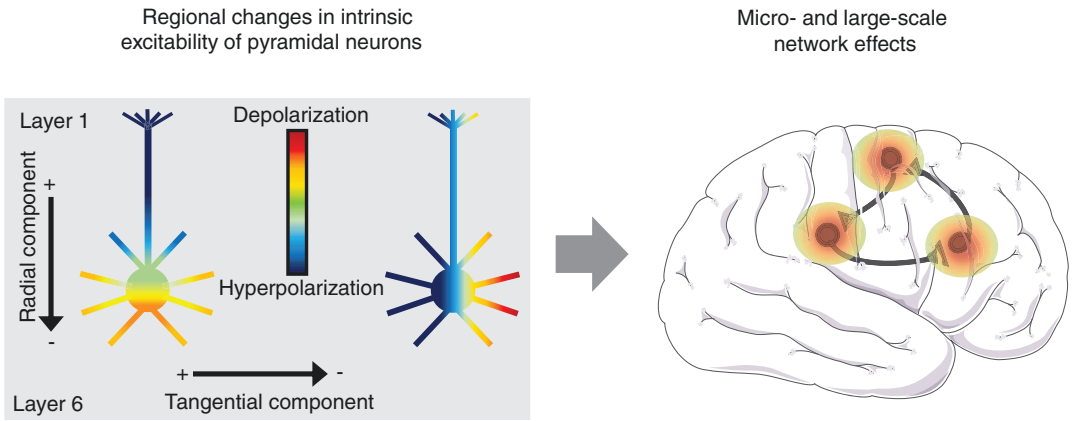

Fig. 13.2 Interactions of tDCS with brain function: from the single-cell level to signal integration in large-scale brain networks
Exposed neuronal compartments are depolarized or hyperpolarized dependent on orientation relative to the electric field. The left panel illustrates the polarization of a pyramidal cell depending on a current flow. Below the anode, the radial component of the electric field depolarizes basal neural compartments and hyperpolarized apical dendrites, whereas a radial component excites axonal kinks and bends. The neuronal effects, that is, on membrane potential, are miniscule but augment and tune ongoing activity in neural networks (left panel), which leads to behavioral and clinical effects

13.2 Precision tDCS: How to Tailor tDCS-Based Research to the Individual Brain

The vast majority of tDCS research applies the same tDCS regime to a group of individuals to study and modulate brain function, matching the electrode positions and current intensity across individuals (Fig. 13.3). Such one-size-fits-all approach is inherently imprecise as it does not consider interindividual variations in brain structure and function (brain-trait features) and ignores the fact that tDCS effects critically depend on the "brain state" at the time of stimulation (brain-state features). We therefore argue that the tDCS community should thrive toward a personalization of tDCS that tailors the tDCS intervention to the individual brain anatomy and function. Personalization and precision can only be achieved by leveraging the explanatory potential offered by brain imaging techniques. This applies equally to the neuroscientific and therapeutic use of tDCS in humans. Only a comprehensive use of neuroimaging can unravel the underlying neuromodulatory mechanisms of tDCS at the brain circuit level. The combination of tDCS and brain mapping can lead to neurobiologically informed, causal models that can predict how tDCS will change the function of targeted brain networks and thereby improve target symptoms. The potential contributions of brain mapping to the personalization and optimization of tDCS interventions are illustrated in Fig. 13.4. We elaborate in the following sections how brain mapping can guide precision tDCS providing illustrative examples from the literature. This

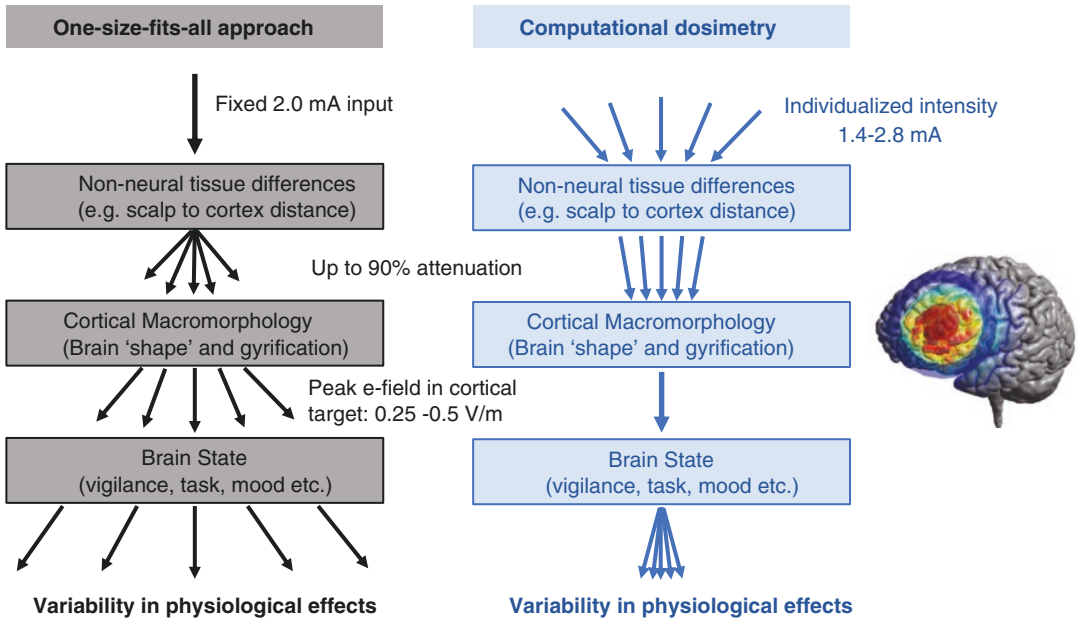

Fig. 13.3 The impact of individualized computational dosimetry
The left panel illustrate the variability in the physiological outcome when applying a *one-size-fits-all* tDCS protocol. Both stabile individual traits such as nonneural tissue properties (top boxes) and cortical anatomy (middle boxes) as well as rapidly changing brain states (bottom boxes) contribute to the variability. The right panel depicts the effect of individualizing the dose using sMRI-based computational models of the electric field. The variability caused by interindividual differences in stable anatomical traits can be accounted for by adjusting the individual tDCS setup (montage, current intensity), but variability caused by differences in the state of targeted and interconnected neural networks are still present. To minimize these, online imaging-based state control is needed (not illustrated here). Values for input intensity, attenuation, and electric field strength are taken from [26, 47]

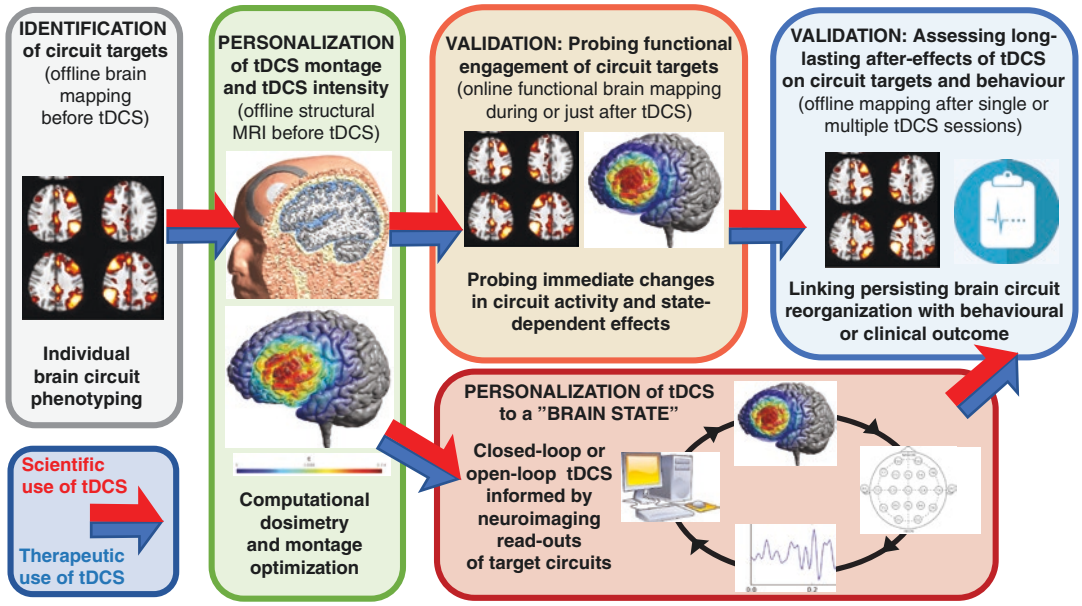

Fig. 13.4 Brain mapping informs precision tDCS
Brain imaging is necessary and sufficient to enable and ensure precision tCDS stimulation. Identifying the circuitry phenotype and adjusting stimulation intensity to the individual brain increases the likelihood of changing signaling (exclusively) in the affected networks. Only through online validation as well as state-informed and controlled stimulation can target engagement be ensured. Offline validation provides mechanisms of actions underlying the therapeutic effects of tDCS, which informs future application

does not only entail neuroimaging informed planning of a tDCS intervention at the individual level (i.e., personalization), but also identifying intrinsic brain states that are more susceptible to the neuromodulatory effects of tDCS (i.e., state dependency).

13.2.1 Identification of Brain Circuit Targets with Offline Brain Mapping Before tDCS

Task-related and task-free functional MRI (fMRI) or EEG/MEG studies can reveal spatiotemporal patterns of functional integration in large-scale networks that are consistent at the group level. Hence, researchers can use this information to identify cerebral regions that constitute a promising target for a tDCS intervention, for instance, because a given region shows strong functional engagement in an experimental task that probes the brain function of interest (Fig. 13.4). However, not only regional brain *activity* and inter-regional *functional connectivity* (identified with fMRI, EEG/MEG or PET) but also *structural connectivity* (revealed by structural MRI, diffusion sensitive MRI, and changes in the neurochemical profile, evidenced by magnetic resonance spectroscopy (MRS) or PET can assist researchers in the decision on which brain region to target with tDCS. Since reproducibility of functional brain mapping studies is often poor, one may apply meta-analytical tools such as activation likelihood estimation (ALE) to identify brain regions that express a brain activity profile consistently across many studies [23]. An illustrative example for neuroimaging-guided target selection is the left dorsal prefrontal cortex (dlPFC) as cortical target for transcranial stimulation therapies in major depression disorder (MDD). This region is chosen because it expresses local functional (hypoactivity) and structural (reduced gray matter volume) abnormalities as well changes in functional connectivity to anterior cingulate cortex in MDD [24]. Moreover, local metabolic changes in the shape of reduced regional GABA

and glutamine (GLX) have been revealed in several prefrontal cortical regions with MRS [25].

How can the knowledge provided by brain mapping studies be used in practice when planning a tDCS study? Let us assume that a range of task-related fMRI studies point to an abnormality "X" in cortical region "Y," and the hypothesis is that by applying anodal tDCS to region "Y," a symptom "Z" will improve. One option is to extract the peak location derived from the group-based activation maps, at which abnormality "X" is maximally expressed in region "Y" and use this peak as "hot spot" for tDCS targeting. An alternative option is to perform task-related fMRI in the participants before the tDCS intervention and use the individual activation pattern in cortical region "Y" as individual "hotspot" for tDCS targeting.

13.2.2 Personalization of tDCS: Computational Dosimetry and Montage Optimization

Modeling of the tDCS-induced electrical field can be used to reduce individual differences in current field distribution and intensity. The effects of individualized dosing are illustrated in Fig. 13.3. Modeled e-fields corresponds well to intracranial measurements and are preferable to both one-size-fits-all approaches and unifactorial corrections based on, for example, scalp to gray matter distance (see [26]). A recent post-hoc analyses of the clinical outcome following 10 weeks of tDCS treatment in the ELECT trial underscores the clinical potential of electrical field modeling to inform the dosing of tDCS [27]. Improvements in negative affect scaled positively and linearly with the modeled electrical field strength in bilateral DLFPC and ACC. In contrast, no relation between the induced electrical field strength and positive affect or anxiety was found. The results suggest the existence of a therapeutic range that is associated with positive outcomes, and future studies may use this knowledge to prospectively adjust the necessary dose (i.e., current intensity) to reach the target range with the help of electrical field modeling.

A precise model of the tDCS-induced electrical field is contingent on the ability to segment both neural and nonneural head tissues precisely. Hereinto, segmentations based on both T1- and T2-weighted sMRI have been demonstrated to outperform segmentations from T1 alone in terms of DICE scores and variability. Recent developments in automated segmentation pipelines have improved T1-based segmentations substantially [28], but the inclusion of T2-weighted brain scans is recommended to minimize fat-shift artifacts.

Modeling the tDCS-induced electrical field based on high-resolution anatomical head models can reveal interindividual and between-group variability in the tDCS-induced electric fields [29]. This has been shown for tDCS of the left dlPFC, a common target in brain stimulation studies designed to treat MDD. A recent study applied computational modeling to simulate the spatial distribution of tDCS-induced electric fields in 20 frontal regions, considering several bi-hemispheric, bi-polar tDCS and left-hemispheric, multielectrode tDCS montages [30]. Bi-hemispheric, bi-polar tDCS montages placed electrodes symmetrically over right and left dlPFC and produced comparable e-field strength in the left dlPFC and medial prefrontal cortex. In contrast, the multielectrode tDCS montages with a central electrode placed over left dlPFC produced a more local e-field in the targeted dlPFC. Depending on stimulation parameters, the magnitude and focality of tDCS-induced electrical fields varied considerably [30]. These findings suggest that individual modeling of tDCS protocols may substantially improve individual cortical targeting as well as standardizing therapeutic tDCS interventions across subjects. This also applies to scientific tDCS studies of human brain function that lack a therapeutic context. Here, electric field calculations can be used to compare and optimize different tDCS strategies for selective spatial targeting of the cortical region of interest [31].

Choosing the optimal montage for selective engagement of a specific region can be difficult. Concentric electrode or multielectrode montages with a central anode (or cathode) and surrounding cathodes (anodes) can increase the spatial

specificity at the expense of a reduced strength of the induced electrical field [32] which further increases the need for spatial guidance. Several automatized pipelines exist that enables reversed e-field modeling; that is, based on an anatomical target and a predefined electrical field intensity, the optimal montage within the safety limitation can be found (see [17]). An important notion is that even with careful brain imaging-guided electrode placement and individual computed dosing, the effect of ongoing activity in the target and interconnected network can still shape the neuronal effects of tDCS. Hence, modeling the tDCS-induced electrical fields in the brain is only a first step. Future work will need to implement anatomically realistic biophysical models that can be used to predict the effects of the induced electrical fields on axonal structures in terms of depolarization or hyperpolarization as well as the dependency of these de- or hyperpolarizing effects on physiological factors.

13.2.3 Probing Functional Engagement of Brain Circuit Targets by tDCS

As evident from early studies targeting the pericentral cortex, the effects of tDCS substantially depend on the functional state of the cortex at the time of stimulation, changing radically when stimulation is given when subjects are relaxed (idling state) or while they generate motor activity (active state) [33]. Both immediate- and after-effects of tDCS are emergent properties of the applied current (extrinsic variable) and the ongoing neuronal activity (intrinsic variable). The interaction between these variables explains the state dependency of the functional responses of both neural networks and individual neuronal compartments exposed to the e-field. In general, it is assumed that tDCS only engage those axonal compartments that are already active by adding stochastic noise to the system. However, opposing mechanisms may operate. Ongoing activity changes the biophysical properties of membranes such as decreased resistance, which in terms may augment hyperpolarization and antagonize depolarization by anodal stimulation (see [34] for discussion). This implies that regional and network effects most likely scale nonlinearly with the intensity of the locally induced electrical field strength and that this relationship depends on the brain state.

These uncertainties regarding the functional impact of tDCS on the target region motivate the need to assess the functional engagement of circuit targets with online functional brain mapping during or shortly after tDCS and to validate efficacy of stimulation as demonstrated in a recent study by Li et al. [35]. Using concurrent tDCS and fMRI, they found tDCS of inferior prefrontal gyrus to cause polarity-specific and state-dependent activity changes in remote cortical nodes of the default mode (DMN) and salience (SN) networks [35]. In regions active during a choice reaction time task, the largest accentuation of activity was found with cathodal stimulation that conversely attenuated regional activity across both networks when delivered during rest. Functional connectivity in the interrogated networks also changed with tDCS in a polarity- and task-specific manner. Whereas these results showcase the potential of brain imaging to probe the immediate impact of tDCS and thereby confirm functional engagement of the targeted brain networks. This is particularly important in all tDCS studies that do not stimulate motor cortex and thus cannot use MEP measurements as functional readout.

We wish to emphasize that the absence of changes in a neuroimaging readout during concurrent brain imaging and tDCS cannot be interpreted as a failure to engage the target node or network. Regarding BOLD-fMRI, the BOLD signal in a single voxel is an average signal that reflect the net effect of tDCS on a wide range of different neural compartments with different orientations and different neuronal populations, including excitatory and inhibitory neurons. The multitude of regional tDCS effects might very well oppose each other in terms of changing the BOLD signal and thereby cancel each other out, leaving the BOLD signal in that voxel unchanged. In addition, artifacts below the electrode may be mistaken as changes in neural activity, as evi-

dent from the BOLD signal changes under the stimulation electrodes observed during tDCS in cadavers [36] (but see also [37]). Independent of the imaging modality, non-transcranial off-target effects of tDCS may also confound the neuroimaging readout (see below).

13.2.4 Mapping tDCS-Induced After-Effects with Brain Imaging

Brain imaging conducted (before and) after tDCS can delineate functional changes at the regional and inter-regional level that underpin the behavioral and clinical after-effects of tDCS interventions. In basic science, this is a critical step toward establishing causal relationship between brain network features and behavioral variation in health (e.g., abilities) or disease (e.g., disabilities). The characterization of longer lasting (hours to weeks) after-effects on circuit targets and behavior is key to validation of tDCS efficacy (Fig. 13.4). Offline mapping after single or multiple tDCS sessions has the potential to link long-lasting brain circuit reorganization with behavioral or clinical outcomes at the single-person level. If a tDCS-induced reversal of aberrant brain activity predicts a mitigation of a preexisting disability, this corroborates a causal relation and validates the tDCS protocol and confirms efficient modulation of the tDCS target at the brain network level.

13.2.5 State-Informed tDCS to Achieve Contextual Precision

It is well known that the neuromodulatory effects of tDCS critically depend on the functional state of the targeted brain networks (i.e., the neuronal context) [35, 38], but the mechanistic rules that govern the state dependency of tDCS are poorly understood. Given the importance of state dependency, it should be a priority of tDCS research in the coming years to systematically study how the "neuronal context" of the targeted brain circuits frames the efficacy of tDCS and how tDCS can be aligned to the expression of a favorable brain state to achieve conceptual precision.

Modeling of the tDCS-induced electrical fields in the brain can be used to optimize spatial precision and standardize the electrical field in the target region across persons. Functional brain mapping can indicate functional engagement of the targeted brain network and its outlasting modulation by tDCS. While these are major milestones in the pursuit to realize precision tDCS, they cannot contribute to advance the contextual precision of tDCS. This requires the use of techniques that can extract information about the current brain state at high temporal resolution without significant temporal delay. One experimental strategy is to "standardize" the brain state during tDCS by asking the subjects to perform a well-defined task during tDCS. Another option is to record measures of the bodily state (respiration, pupillometry, sympathetic skin response) and use these bodily signals to adjust tDCS for instance by online tuning tDCS intensity according to fluctuations of these bodily signals. A third option is to directly record brain activity with electroencephalography (EEG). Because of its excellent temporal resolution, EEG can instantaneously extract fluctuations in the brain state of interest, and this information can be used to inform precision tDCS. The optimal hardware solution would be an integrated tDCS-EEG system that can record brain activity and apply tDCS simultaneously. For therapeutic applications, such integrated tDCS-EEG systems should be easy to operate and should allow home-based use and remote, web-based control.

Two control principles can be used for state-informed EEG-tDCS (Fig. 13.4). Firstly, one may adopt an open-loop approach that uses an EEG-based readout of the brain state of interest to ensure contextual precision of tDCS. For instance, subjects can be instructed to engage in a specific task that previously has been demonstrated to increase the neuromodulatory (after) effects of tDCS and treatment efficacy. In this setting, EEG could be used to monitor whether the task-related brain state is sufficiently increasing contextual precision of tDCS. Secondly, one

may adopt a closed-loop approach, in which the EEG-based readout of the brain state of interest is used in a rule-based adaptive fashion. For instance, if the oscillatory power expressed in the target network does not shift toward the target frequency, a closed-loop system could adjust tDCS variables to improve target engagement. If focal stimulation of one node does not achieve the desired state change in the target network, one may increase intensity stimulus intensity or increase the number of targeted brain regions by altering the weighting of current in a multielectrode tDCS setup (see [39]).

13.2.6 Mind Peripheral Effects When Personalizing tDCS!

When applying transcutaneous electric current, less than a quarter reaches the brain. Most of the current is shunted through more conductive superficial tissue which causes simultaneous costimulation of peripheral components of the nervous system in the head, including peripheral nerve fibers and peripheral receptors in the skin, eye (retina), or inner ear [40–42]. Peripheral costimulation is a relevant issue when using tDCS as a scientific or therapeutic tool, because it may contribute to the behavioral effects of tDCS and should be controlled for by "sham" stimulation [31]. Especially when using pseudo-monopolar (multielectrode or center-ring) montages, tDCS-induced excitation of the peripheral somatosensory system leads to sensory side effects, including itching, tingling, and burning sensations under the electrode. Depending on the electrode positions, bi-polar tDCS setups may cause vertigo or visual phenomena such as phosphenes during the ramping-up and ramping-down phase of tDCS (for further details on side effects, see [40]).

Peripheral costimulation during tDCS may contribute to therapeutic or behavioral aftereffects of tDCS and should be controlled for by "sham" tDCS that matches the peripheral costimulation without causing neurobiologically relevant brain stimulation [31]. The somatosensory effects of tDCS render it possible for the subjects to recognize when the tDCS is applied. This may unintentionally change their brain state during the intervention by, for instance, introducing expectancy or changing the emotional state. Even if somatosensory costimulation does not cause conscious perception, it may induce indirect brain modulation through a tonic change in afferent input to sensory brain networks.

Since conscious perception of costimulation may change overall alertness to a task and induce placebo effects, a realistic "sham tDCS" condition should be included in the experimental design. This is however challenging, because it is difficult in practice to match subjective experiences. Accordingly, real tDCS can often be distinguished from sham tDCS. When asked directly, subjects frequently report the strongest experience of, for example, skin sensations to be at the beginning of stimulation, corresponding with the ramping phase of the current. It cannot be excluded that some sensory receptors are more susceptible to the change in voltage gradient, rather than the gradient alone, meaning a shorter range between ramp-up and -down phase (as used in sham conditions) can be detected by the subject. It would therefore be too simplistic to assume that the sham stimulation induces the exact same peripheral effects as the real tDCS.

Some studies have tested the effect of applying numbing cream before stimulation, and found a reduction in the sensation of pain and other sensory modalities associated with nociceptive processing, such as tingling, sharpness, and pinching (specific receptor or fiber type has however not been reported) [43, 44]. Even though numbing cream can alleviate some mechanistic properties of pain and discomfort, there are still issues with the apparent ability to distinguish between tDCS and sham stimulation (placebo) [45, 46].

Modeling the tDCS-induced electrical field in the scalp may contribute to minimize peripheral effects. As mentioned previously in this chapter, recent developed computational models of current flow provide accurate estimations of induced electrical fields from tDCS. Toolboxes, such as SimNIBS, use individual MRI head anatomy for precise modeling of peripheral costimulation, for example, cutaneous stimulation. Electrical field

simulations can show how the field distribution differs in the cortex and skin depending on the electrode type, the number of electrodes and their position on the scalp. This, in terms, can help to minimize peripheral costimulation or to design sham tDCS conditions that only stimulate the peripheral extracranial neuronal structures, while sparing the cortex, thereby avoiding unwanted direct modulation of the target network. This might be achieved by placing smaller electrodes in proximity to each other. In conclusion, there is no simple solution that can fix the methodological issues caused by peripheral costimulation during tDCS. The inherent methodological challenges should not prevent one to take proper precautions to minimize peripheral costimulation and to ensure optimal sham-tDCS conditions based on individual simulation of the induced electrical fields outside the brain.

13.3 Conclusion and Perspectives

The combination of tDCS with a wide range of brain mapping techniques offers powerful opportunities to advance the scientific and therapeutic use of tDCS. The computational modeling of the tDCS-induced electrical field distribution in the brain is already well established and an important step toward personalization of dosing and increased spatial precision (Fig. 13.3). Future research will expand the precision tDCS approach by mapping and modeling the biophysical-neurobiological interactions and their state dependency. This research will yield insights which can be used to ensure functional precision and to personalize tDCS to the individual properties of the stimulated functional brain networks (Fig. 13.4).

Conflict of Interest Hartwig R. Siebner has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark and Lundbeck AS, Denmark, and as editor-in-chief (Neuroimage Clinical) and senior editor (NeuroImage) from Elsevier Publishers, Amsterdam, the Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany and from Gyldendal Publishers, Copenhagen, Denmark.

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