tDCS and Functional Connectivity

9

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9.1 Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive transcranial brain stimulation (NTBS) technique in which the cortical excitability of the human brain is modulated by weak direct currents applied via scalp electrodes [37]. Numerous studies have been conducted with both healthy subjects and patients with neurological disorders (such as stroke and Parkinson's diseases) and psychiatric disorders (such as major depressive disorder [MDD] and schizophrenia) [36, 50, 72, 73]. However, the mechanisms of tDCS effect are not fully understood. Therefore, one way is to investigate the modulation of functional connectivity by combining tDCS with brain imaging techniques.

Functional magnetic resonance imaging (fMRI) measures the blood-oxygen-level-dependent (BOLD) signal which is a proxy of neuronal activation [58]. In order to evaluate the tDCS effect, functional connectivity is studied either task-based or during resting states. Task-based functional connectivity can be investigated by administering an appropriate task according to the respective research question during fMRI. The resting-state fMRI (rsfcMRI), on the other hand, is used to measure the functional integration of neural networks when participants are asked not to follow any particular thoughts or tasks. During the resting state, the human brain still exhibits organized activity across distant regions, and this activity can be recorded by changes in fluctuations of the BOLD signal [95]. In the resting state, previous studies have used seed-based analysis, independent component analysis (ICA), and graph analysis to extract major networks of activation, such as default mode network (DMN) [91], salience network [86], and central executive network [93]. The DMN is one of the most frequently investigated resting-state network in clinical research such as Alzheimer's disease [12], schizophrenia [62], and major depressive disorder [32]. The DMN locates its major hubs in medial prefrontal cortex, posterior cingulate cortex, and angular gyrus [3]. These regions are significantly less activated while performing cognitive tasks in comparison with resting state [85], and it has been suggested that they are related to self-referential thinking, theory of mind, and moral decisions [11, 80]. Wörsching et al. [102] from our group published a comprehensive review on prior research combining prefrontal tDCS and multimodal MRI.

In this chapter, we critically review the effects of motor cortex as well as prefrontal tDCS on functional connectivity in healthy subjects and patients with neurological and psychiatric disorders using both resting-state and task-based fMRI paradigms.

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9.2 Motor Cortex

9.2.1 Effects of Anodal tDCS

tDCS of motor regions may modulate motor cortex excitability including motor evoked potentials [51] and motor performance [47]. For example, anodal tDCS applied to the primary motor cortex (M1) shows an increase of neuronal activity in the ipsilateral hemisphere not only directly at M1 [49] but also in premotor regions [83] in the primary sensorimotor cortex (SM1) [40, 48] and in the supplementary motor area (SMA) [49]. However, the neuronal effect of motor tDCS is not only observed in regions close to the electrodes but also in distant areas via trans-synaptic paths. For example, tDCS with the anode over M1 modulates neuronal activity also at neighboring regions, that is, inducing an increase of activity within the parietal cortex [84]. Moreover, anodal M1 tDCS may reduce functional connectivity between SM1 and the rest of the brain [84] and increase functional connectivity between M1 and thalamus [83]. These findings suggest that tDCS exerts effects on corticocortical connectivity. Thus, tDCS appears to be an effective mediator for modulating brain function not only focally under the electrodes but also within networks involving distant intracortical as well as subcortical regions [38].

Finally, but importantly, it should be mentioned that the anodal stimulation side of tDCS does not always have a facilitating effect. For example, Amadi et al. [2] reported no significant changes in resting-state connectivity with anodal M1 tDCS. Furthermore, Antal et al. [4] found a reduced BOLD signal at the supplementary motor area (SMA) during finger tapping. Although tDCS with the anode over motor regions is a topic, which has been rather extensively studied compared to others, its effects are not yet fully understood and need further research.

9.2.2 Effects of Cathodal tDCS

Conversely, it is hypothesized that tDCS with the cathode over motor cortex regions exerts opposite effects to anodal tDCS, that is, reduces motor cortical excitability. Cathodal tDCS over the left motor cortex leads to a decrease in neuronal activity at the underlying area, as is the case with SMA [6]. Moreover, a global decrease in functional connectivity [6] as well as between the cortical and subcortical areas [82] are reported. However, as it was the case for anodal stimulation, the direction of the effect is not always the same. Cathodal tDCS on M1 could also increase resting-state functional connectivity on both motor and non-motor networks. For example, Amadi et al. [2] showed that cathodal left M1 tDCS leads to an increase of BOLD signal between the left- and right-hand regions of M1 and between left and right supplementary motor area (SMA). Additionally, increased functional connectivity within motor and default mode network was also observed, supporting the hypothesis that diminished top-down control may contribute to the impaired motor performance induced by cathodal tDCS [2]. Another study suggested that cathodal left M1 tDCS could enhance regional connectivity in the dorsolateral-M1 region [83].

9.2.3 Effects of Dual tDCS

In addition to unilateral stimulation of motor regions, bihemispheric or "dual" tDCS of left and right M1 has been investigated as well, for example, combined positioning of the anode over the nondominant motor cortex and of the cathode over the dominant motor cortex. This approach was found to improve performance significantly more than unihemispheric or sham tDCS [97] and facilitates motor recovery in chronic stroke patients [57]. Bihemispheric tDCS is thought to upregulate excitability of ipsilesional motor regions via anodal stimulation while concurrently downregulating contralesional motor regions via cathodal stimulation after stroke [57]. Therefore, Lindenberg et al. [56] investigated the effect of bihemispheric tDCS impacts on motor system activity and connectivity. Measuring neural correlates of dual and unihemispheric tDCS in healthy older subjects, they found that dual but not only anodal tDCS enhanced resting-state

connectivity of the left dorsal posterior cingulate cortex. Furthermore, dual tDCS showed stronger activations in bilateral M1 than anodal tDCS alone, regardless of whether participants used their left or right hand during the motor task. These results indicated that bihemispheric tDCS can induce complex networks modulations on left and right M1, including interhemispheric interactions and areas associated with motor control in the dorsal posterior cingulate cortex [56]. A further study showed that bilateral M1 tDCS (anode over right M1, cathode over left M1) induces the decrease in interhemispheric functional connectivity during stimulation. On the other hand, an increase in intracortical functional connectivity within right M1 was also observed [87]. These studies suggest that the dual tDCS is a potentially more powerful method in order to modulate functional connectivity.

9.3 Prefrontal tDCS

The prefrontal cortex plays a pivotal role in executing complex cognitive functions. Moreover, it is considered as a part of brain that, in addition to many functions, also determines the personality of individuals [67]. Previous studies have shown that anodal tDCS over the dorsolateral prefrontal cortex (DLPFC) can improve performance in various cognitive domains, including verbal skills, executive functions, and working memory in healthy subjects [16, 30, 35, 99]. Though we can observe the effects of prefrontal tDCS on multiple functional levels, the understanding of its neurophysiological action is still limited.

9.3.1 Prefrontal tDCS and Cognitive/Executive Functions

Prefrontal tDCS has been shown to be effective in modulating higher cognitive and executive performance such as verbal fluency [15], decision-making [19], and risk behavior [23]. Nevertheless, the neural basis of functional improvement remains unclear. Several combined tDCS-fMRI studies have addressed this neurofunctional relationship. For example, it is known that tDCS over the DLPFC modulates risk-taking behavior [8, 23, 103]. Weber et al. [99] showed that dual DLPFC tDCS (anode over F4 and cathode over F3 according to the 10–20-EEG system) reduces connectivity between right ACC and the rest of the brain, and the right ACC activity is positively correlated with risk behavior. Another example is anodal tDCS over the inferior frontal gyrus (IFG), that is, a region controlling the semantic retrieval process [96], which improves verbal function [52, 64]. The neurofunctional correlation of verbal improvement seems to be related to the reduced activity observed in the prefrontal cortex, especially at IFG, during the semantic word generation task [66]. Interestingly, anodal IFG tDCS reduces the hyperactivity in bilateral frontal cortices in elderly subjects. This may be associated with a neuronal mechanism corresponding to the temporal reversal of age-related verbal functional decline [65]. Furthermore, increased connectivity between IFG and other major hubs in language networks (such as bilateral inferior parietal, dorsolateral, medial prefrontal regions, and the left middle temporal gyrus) may represent a neuronal mechanism of language performance enhancement [66].

Working memory (WM) in healthy subjects showed a small but significant improvement after anodal tDCS of the left DLPFC, as suggested by a recent meta-analysis of 31 studies in healthy volunteers, when stimulation was coupled with WM training [61]. In contrast, stimulation alone did not show a significant difference after correction of the publication bias. In an early neurophysiological study, we observed similar effects, that is, a significant reduction of mean current densities for the delta band in the left subgenual PFC, the anterior cingulate, and the left medial frontal gyrus, in parallel with effects on n-back performance at a higher working memory load (2-back), while the less challenging memory performance at 0- and 1-back did not show superiority over sham treatment [44, 45].

9.3.2 Prefrontal tDCS and Resting-State Network

Several researchers investigated whether prefrontal tDCS modulates resting-state network connectivity as well. For example, [44, 45] showed that anodal tDCS over the left DLPFC increases functional connectivity in both the default mode network (DMN) and in left and right frontoparietal network (FPN). Likewise, when anodal electrode was placed over either the left or right DLPFC, DMN components showed reduced synchrony, whereas the anticorrelated network (AN) showed increased synchrony [80]. The AN is associated with cognitive processing when attention to the external environment is required, and it is known to anticorrelate with DMN activity [28, 70]. Furthermore, Park et al. [79] also found that left DLPFC anodal tDCS increases DLPFC connectivity to the right hemisphere and decreases DLPFC connectivity to the brain regions around the stimulation site in the left hemisphere. These findings suggest that prefrontal tDCS modulates resting-state functional connectivity at the primary stimulation site and at connected brain regions. Wörsching et al. [100] investigated a priori hypotheses on specific effects of prefrontal tDCS montage using multimodal fMRI in 32 healthy participants. After tDCS with an F3 cathode/ F4 anode montage, functional MRI connectivity decreased in the medial part of the left PFC at rest [100]. In addition, regional brain activity during a delayed working memory-retrieval task (DWM) decreased in this area more strongly after negative than neutral distraction, and responses to DWM tasks were faster, regardless of distractor type [100] (Fig. 9.1).

9.4 Therapeutic Application of tDCS

tDCS has been proposed as an effective intervention in alleviating symptoms of neurological disorders such as Parkinson's disease [29] and chronic pain [5] as well as psychiatric disorders such as depression [71], schizophrenia [9], and addiction [59]. However, despite its enormous potential, tDCS still requires many efforts such as large randomized controlled clinical trials (RCTs) and individualized development of NTBS treatment to achieve a broader clinical implementation. Individualization of treatment is an important and challenging factor in this regard, as there are distinct individual response patterns to frontal tDCS due to, for example, individual anatomical features, gender, or age. One reason, among many others, is that we do not understand the neural underpinnings of stimulation-enhanced neuromodulation in relation to the individual pathology. Therefore, combined tDCS-fMRI studies need to be extended to clinical populations in order to investigate the mechanisms of tDCS treatment in comparison of health and disease.

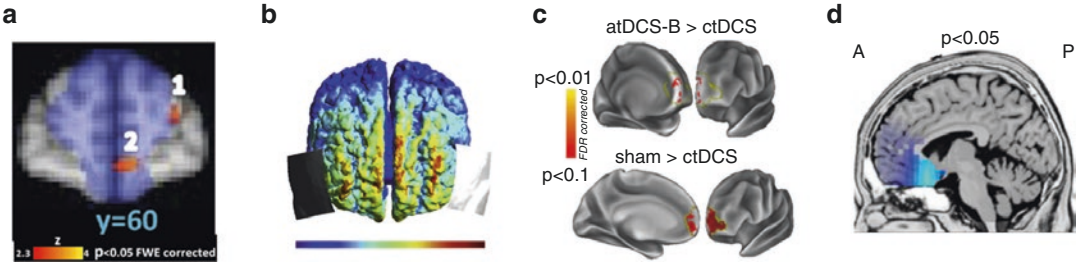

Fig. 9.1 In pilot studies, we observed direct effects of prefrontal tDCS on medial prefrontal areas. Shown here for (**a**) functional MRI connectivity at rest [45], (**b**) simulation in depressed patients using T1-weighted anatomies [14], (**c**) functional MRI connectivity at rest with different tDCS montages [100], and (**d**) EEG at rest [44]. Electrode localization for (**a**) F3-Fp2, (**b**) F3-F4, F4-F3, (**c**) F3-F4, and (**d**) F3-Fp2, 2 mA intensity, 20 minutes stimulation

9.4.1 Neurological Disorders

Stroke

tDCS over motor cortex can be used to treat neurological patients with motor disorders. For example, stroke patients benefit more from rehabilitation of motor skills when dual tDCS (anode over the lesion and cathode over the non-lesion hemisphere) is administered over M1 during motor training [53, 55]. Such effects were reported to be maintained for intervals of 1 week [55] up to several months [1], and improvement of performance may even reach out to an untrained task as well [55]. However, as to the neuronal mechanisms of this effect, Lefebvre et al. [55] suggested that the permanent behavioral enhancement induced by tDCS is associated with activity of the ipsilesional motor skill learning network, which has a main hub in premotor regions [27, 33]. More recently, it was reported that tDCS increases activity in the ipsilesional motor and premotor cortex during movement of the affected hand [1]. Additionally, Lefebvre et al. [54] showed that connectivity between M1 and the dorsal premotor cortex (PMd) is stronger in the lesioned hemisphere before dual tDCS treatment, but enhanced in the *non-lesion* site after treatment. Moreover, functional connectivity appears to increase between somatomotor network regions as well as within motor and premotor cortex [54]. Motor tDCS studies overall show both local effect within the motor cortex and network effect between motor regions and other areas as discussed.

Language Deficits

The interest in using tDCS for neurorehabilitation of stroke patients has led tDCS-fMRI research also to another target region, that is, Broca's area. Broca's area is located around the posterior region of left inferior frontal gyrus and is involved in speech production [7]. tDCS over Broca's area has been found to improve naming performance of aphasia patients [35, 43, 63]. Neuronal correlates of these functional changes were investigated by several researchers, leading to heterogeneous results at first glance. Holland et al. [35] observed that anodal tDCS over the left inferior frontal cortex during an overt picture-naming fMRI study reduced neuronal activity in Broca's area while performance in naming pictures improved in aphasic stroke patients. In contrast, Marangolo et al. [63] showed that bilateral tDCS (anode over left Broca) with simultaneous speech training increased functional connectivity in the left hemisphere of chronic stroke patients. These results may be explained by an interaction between neural priming and main effects [20]. In one study [35], the functional scan was obtained during task performance, whereas Marangolo et al. [63] investigated resting-state fMRI after a 3-week treatment period. One may hypothesize that neuronal activity decreased in the study by Holland et al. [35] due to repeated picture naming tasks, and this regional priming effect transcended the global hemispheric effect of anodal tDCS which was shown by Marangolo et al. [63]. Either way, these findings provide converging evidence from functional imaging and behavioral data that tDCS exerts effects on regional brain function at lesion sites, which may improve patients' cognitive recovery.

Patients with Parkinson's disease (PD) may also have verbal fluency problems such as phonemic and semantic fluency deficits due to dissociable processes mediated by different cortico-striatal circuits involving left frontal and temporal regions [94]. Therefore, Pereira et al. [81] investigated the differential effects induced by tDCS (2 mA, 20 min) over frontal and temporo-parietal areas on verbal fluency networks in patients with PD. Patients underwent a verbal fluency paradigm inside an fMRI scanner and received anodal tDCS over left DLPFC and temporo-parietal cortex (TPC) in a counterbalanced order with the cathode placed over the right supraorbital area. ICA showed that functional connectivity in verbal fluency and task-related deactivation networks is significantly better with tDCS over left DLPFC than with TPC. In addition, DLPFC tDCS also improved performance on the phonemic fluency task.

9.4.2 Psychiatric Disorders

Schizophrenia

tDCS has been demonstrated to exert therapeutic effects in a number of psychiatric disorders. Several research groups have combined tDCS with neuroimaging techniques to investigate the mechanisms of its putative therapeutic action. For example, the application of tDCS as treatment of negative symptoms and auditory verbal hallucination (AVH) in schizophrenia is a field that is relatively well tested. With regard to negative symptoms, Orlov et al. [76] showed that anodal tDCS over the left DLPFC (2 mA, 30 min, cathode over the right supraorbital area) in schizophrenia patients induces a positive correlation between increased activation in the medial frontal cortex and consolidated working memory (n-back) performance 24 hours after tDCS. Regarding executive functions, behavioral improvement with Stroop task was associated with reduced activity in the anterior cingulate cortex after prefrontal tDCS, which is known for response conflict processing [46, 68]. Auditory hallucinations, which are common positive symptoms of schizophrenia, are known to be associated with abnormal hyperactivity in the left temporo-parietal areas (Wernicke's area), left inferior frontal areas (Broca's area), and in their right homologues [41]. Several studies have shown that cathodal tDCS over the left temporo-parietal junction (TPJ) and anode over the left DLPFC may reduce AVH symptom in schizophrenia patients [24, 89, 90]. The neural representation of AVH reported by Mondino et al. [69] included specific areas for inner speech production and monitoring; in particular, a decrease in resting-state functional connectivity between left TPJ and left anterior insula as well as right inferior frontal gyrus and an increase between left TPJ and left angular gyrus, left DLPFC, and precuneus was observed. A study on the effect of prefrontal tDCS in schizophrenia with predominantly negative symptoms investigated the effect of prefrontal tDCS on both negative and positive symptoms under double-blind conditions. Clinically, there were remarkable effects in the group receiving active tDCS treatment [78]. The results of this proof-of-concept study show that prefrontal tDCS added to stable antipsychotic medication can improve negative symptoms of schizophrenia in severely affected patients, as demonstrated by the significant change in scores on the Scale for the Assessment of Negative Symptoms (SANS). These effects were associated with a change in intrinsic resting network activity, particularly an increase in functional connectivity in the insular cortex [78]. However, it must be added that the sample size was very small, and the gender distribution differed between active and sham tDCS.

Major Depressive Disorder

Numerous fMRI studies focused on functional connectivity at rest in major depressive disorder (MDD) patients. Bidirectional changes of connectivity in distinct regions, circuits, and networks have been reported compared to controls. For a therapeutic application of NIBS, that is, particularly rTMS as focal stimulation approach, these alterations were conceptualized as guidance for target sites on the group as well as on the individual level [21, 92]. In contrast, tDCS as nonfocal means for cortex stimulation may need another approach, where functional targeting is achieved by other specific interventions (e.g., cognitive tasks). For instance, working memory and sustained attention training are common cognitive tasks for depression treatment, since these tasks are associated with DLPFC activity [10]. In the first place, however, connectivity changes elicited by tDCS need to be better understood on the background of specific pathophysiological changes observed in MDD.

Some regions, such as the basal amygdala, show reduced functional connectivity with the medial orbitofrontal cortex, which is involved in reward; and the dorsolateral amygdala had relatively reduced connectivity with the lateral orbitofrontal cortex in MDD [17]. However, numerous studies suggest that the prefrontal cortex (PFC) is one of the most promising areas for connectivity-based target sites for NTBS. Among many findings, decreased whole brain functional connectivity homogeneity as proxy to voxel-wise changes of functional connectivity patterns

between the medial prefrontal cortex (MPFC) and the left angular gyrus has been reported in MDD [98], as well as a reduced default mode network (DMN) connectivity to the frontal pole in late-life depression [31]. Correlation coefficients also suggested an increased connectivity at the dorsomedial prefrontal cortex (DMPFC) in patients with MDD when compared to healthy subjects [88].

Very recently, two studies investigated gray matter (GM) volume as well as functional connectivity of the PFC in relation to the antidepressant response to tDCS within a large randomized placebo-controlled study, that is, the Escitalopram versus Electric Current Therapy for Treating Depression Clinical Study (ELECT-TDCS) [13, 14]. The main finding was a positive association between improvement of depression after treatment compared to baseline and the size of the GM volume in PFC subregions, which was only observed in the tDCS, but neither in the escitalopram nor in the placebo group [14].

In contrast, there was no significant association between resting-state connectivity within a priori defined regions of the PFC and the change in depression scores after tDCS treatment. A possible interpretation for these divergent findings would be that rsfcMRI rather reflects "brain states" [104] of the patients, while structural MRI data may provide trait measures. However, further interpretation is hampered by the small sample size of the cohort.

9.5 Effect Variability and Test-Retest Reliability of tDCS

Test-retest reliability (TRT) and variability of tDCS-induced effects has been one of the major topics of discussion. Opitz et al. [75] demonstrated the importance of precise tDCS electrode placement and suggested that less than 1 cm accuracy is required in order to achieve a sufficient reliability. Padberg et al. [77] employed a specially manufactured cap in order to assure the precise electrode placement over the DLPFC for a multicenter trial. However, even though accuracy of the electrode positions is ensured, inter- and intraindividual variability can be affected by many other factors too.

In order to measure the variability of tDCS effects on M1 excitability, standardized MEPs (i.e., peak-to-peak MEP amplitude of 1 mV prior to tDCS or fixed output of the stimulator) or recruitment curves were compared after each tDCS session. With this approach, a significant interindividual [18, 34] as well as intraindividual variability [18, 22] of MEP amplitudes were observed. However, Madhavan et al. [60] and Jamil et al. [39] reported a higher reliability (i.e., intraclass correlation coefficients [ICC] of 0.6–0.9) for intraindividual responses after 1 mA anodal tDCS.

For nonmotor regions, the assessment of intra- or interindividual variability is less established, and more complex measures, for example, modulation parameters for functional connectivity, had to be introduced. For example, Wörsching et al. [101] assessed individual responses to an active prefrontal tDCS over the three test sessions. This study showed a low test-retest reliability for the effects of 2 mA tDCS in terms of voxel-wise ICC of post-tDCS maps between sessions. Moreover, the distribution of voxel-wise ICC in the region of interest (ROI) analysis was shifted to lower TRT reliability after active, but not after sham tDCS. This result indicates that the neuromodulatory effects evoked by active tDCS are intra- and interindividually variable and may depend on brain state affected by various components such as time, mood, and hormone level. In sum, intra- as well as interindividual variation of tDCS effects have been reported and the underpinnings of this variability should be a focus for future research. This variation also hinders the use of tDCS paradigms for longitudinal assessment and a direct comparison of protocols [42]. Moreover, it emphasizes the need for even more standardized methods (e.g., by including electric field parameters) to account for this uncertainty. Notably, Madhavan et al. [60] reported that even lower interindividual variability and high test-retest reliability does not account for the reliability of tDCS clinical efficacy.

In order to account for these variabilities and to improve reproducibility, the importance of

open science needs to be emphasized. As technology improves, Platform as a Service (PaaS) products enable to convey software in a package (called container) using an open-source standard data interchange format, such as JSON. By sharing all available data, such as the version of the used analysis software and the exact computational method through the frame of open science, we may expect higher reproducibility of the each tDCS effect in the future.

9.6 Association Between Response Patterns and Baseline MRI Markers

Structural and functional MRI measures have been used to identify markers of clinical response to tDCS as individual prediction of therapeutic effects as an unmet need in the field. As outlined above, examples include gray matter volumes, cortical thickness, and DLPFC activation. The findings of Bulubas et al. [14] demonstrated that the antidepressant response to tDCS in the ELECT-TDCS trial was related to GM volumes of a left-sided PFC region at baseline. This relationship was intervention-specific for tDCS, that is, neither observed for escitalopram nor placebo. This finding converges with data from other pilot studies investigating such associations. The relationship with cortical thickness was also assessed by implementing a disruptive left prefrontal stimulation during a decision-making task [25, 26]. Filmer et al. [26] showed that an increased cortical thickness at the middle frontal sulcus and inferior frontal gyrus as well as a decreased thickness at the inferior frontal triangular gyrus were related to a higher disruption of the learning task after prefrontal anodal, but not cathodal stimulation. Furthermore, Filmer et al. [25] showed that performance inconsistency during anodal stimulation is not only related to cortical thickness in inferior frontal gyrus but also to prefrontal neurochemical response patterns measured by magnetic resonance spectroscopy. These studies show that both cortical anatomy and neurochemical difference influence individual variability in the effect of tDCS to the behavior.

Another example is the study by Nord et al. [74] who conducted task fMRI prior to prefrontal tDCS treatment in MDD. Greater activation of the left PFC during a working memory task (i.e., n-back) at baseline was correlated with a larger improvement of depression scores after tDCS treatment. This research line may develop tDCS toward a personalized treatment with individual adjustment of tDCS parameters, such as electrode localization and stimulation intensity, and thus improve its therapeutic effectiveness.

9.7 Conclusions and Future Directions

This chapter has given an overview on experimental and clinical studies that investigated changes of functional MRI connectivity in relation to nonfocal brain stimulation with tDCS. In the majority of studies, tDCS was used to induce changes in functional connectivity both at primary stimulation sites and connected brain regions. The results of these studies provide us with a better understanding of the brain's intrinsic networks and may serve to improve therapeutic effects of NTBS.

While most studies have focused on motor cortex and PFC regions, data for other brain areas (e.g., visual cortex) or other functional domains or systems (e.g., memory, executive, and visual) are very limited. In numerous studies, tDCS has been found to lead to an amelioration of clinical symptoms in neurological and psychiatric disorders; however, very few studies have included neuroimaging in order to elucidate mechanisms of tDCS action on a neuronal and system level. Further limitations we have identified in the field of functional connectivity research on tDCS are small sample sizes together with a large intra- and inter-individual variability of effects, a lack of test-retest designs, and active control conditions for comparison as well as systematic studies on the impact of stimulation parameters for establishing

dose-response relationships. Nevertheless, combining tDCS with multimodal neuroimaging appears to be a promising avenue for developing NTBS toward an effective array of interventions for an individualized treatment in neuropsychiatric disorders.

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