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Review article

# Imaging transcranial direct current stimulation (tDCS) of the prefrontal cortex—correlation or causality in stimulation-mediated effects?

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ABSTRACT

Transcranial current stimulation approaches include neurophysiologically distinct non-invasive brain stimulation techniques widely applied in basic, translational and clinical research: transcranial direct current stimulation (tDCS), oscillating transcranial direct current stimulation (otDCS), transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS). Prefrontal tDCS seems to be an especially promising tool for clinical practice. In order to effectively modulate relevant neural circuits, systematic research on prefrontal tDCS is needed that uses neuroimaging and neurophysiology measures to specifically target and adjust this method to physiological requirements. This review therefore analyses the various neuroimaging methods used in combination with prefrontal tDCS in healthy and psychiatric populations. First, we provide a systematic overview on applications, computational models and studies combining neuroimaging or neurophysiological measures with tDCS. Second, we categorise these studies in terms of their experimental designs and show that many studies do not vary the experimental conditions to the extent required to demonstrate specific relations between tDCS and its behavioural or neurophysiological effects. Finally, to support best-practice tDCS research we provide a methodological framework for orientation among experimental designs.



**Contents**



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## 1. Introduction

Transcranial current stimulation (tCS) represents an array of non-invasive brain stimulation (NIBS) techniques, including transcranial direct current stimulation (tDCS), oscillating transcranial direct current stimulation (otDCS), transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS). tDCS is the most commonly applied NIBS technique in neuroscience and clinical research. Early experimental studies of direct current stimulation (DCS) in animals were carried out in the 1960s (Bindman et al., 1963; Bindman et al., 1962; Creutzfeldt et al., 1962; Purpura and McMurtry, 1965). DCS was reintroduced as tDCS in clinical neurophysiology 15 years ago (Nitsche and Paulus, 2000) and serves as a non-invasive and painless tool for neuromodulation (Nitsche et al., 2008) that is generating increasing interest among neuroscientists and clinical practitioners (Bestmann et al., 2015; Dubljevic et al., 2014). Research lines addressing these different interests and needs have been developing largely independently. This review critically appraises this evolution by focussing on the prefrontal cortex (PFC) as a key target region for clinical applications in neurocognitive and psychiatric research.

In tDCS, a weak electrical current is passed through the skull via two surface electrodes and reaches cortical areas, flowing from the anodal to the cathodal pole (Edwards et al., 2013; Miranda et al., 2006a). The electrical current is determined by the applied voltage at both electrodes divided by the total resistance through the head/body from one electrode to the other. Because part of the current is absorbed by the skin, skull and cerebrospinal fluid (CSF) (Miranda et al., 2006a; Zaghi et al., 2010), only a fraction of the applied current reaches the brain parenchyma (Wagner et al., 2007). Stimulation protocols up to a stimulation intensity of 2 mA and a stimulation duration of about 30 min (Bikson et al., 2016; Nitsche et al., 2003b,c) are considered as safe (Fregni et al., 2006a,b,c,e; Iyer et al., 2005; Nitsche et al., 2003b).

Depending on stimulation polarity, tDCS may induce excitatory or inhibitory effects on motor cortex excitability, often referred to as the paradigm of non-focal plasticity (Nitsche et al., 2003a,b,d; Nitsche and Paulus, 2000). Studies using an intensity of 1 mA found that neurophysiological parameters, such as motor-evoked potentials (MEP), increase when the anode is placed over the relevant cortical region (i.e. anodal stimulation) but decrease when the current flow is reversed (i.e. cathodal stimulation) (Been et al., 2007; Edwards et al., 1993; Nitsche et al., 2008; Nitsche and Paulus, 2000, 2001; Paulus, 2004). In the parameter space, however, dose-response relations do not appear to be linear, e.g. anodal tDCS with an intensity of 2 mA and a duration exceeding 20 min may lead to decreased cortical excitability (Monte-Silva et al., 2013). Moreover, bipolar tDCS montages, which are often used in prefrontal settings, are thought to exert net effects beyond the cortex regions close to the electrodes; these effects consist of both anodal facilitation and cathodal inhibition (Bikson et al., 2010). Usually, excitability changes can outlast the end of stimulation by an hour or longer (Bindman et al., 1962; Nitsche et al., 2003d; Nitsche and Paulus, 2000; Ohn et al., 2008). The duration of post-stimulation effects is determined by the stimulation duration, stimulation intensity and number of treatment sessions (Nitsche et al., 2003d; Nitsche and Paulus, 2000, 2001). Again, the respective dose-response relations underlying these aftereffects are likely to be non-linear (Monte-Silva et al., 2013). Furthermore, studies have indicated inter- and intra-individual variability in response to tDCS at varying current intensities (Chew et al., 2015; Lopez-Alonso et al., 2014; Lopez-Alonso et al., 2015).

Early research on tDCS mainly concentrated on stimulation of the motor cortex M1 (Stagg and Nitsche, 2011; Utz et al., 2010), because M1 stimulation produces a highly reproducible measurable output, i.e. MEPs. The first studies on tDCS in humans targeted the motor cortex and found decreased training-induced plasticity after both anodal and cathodal tDCS (Rosenkranz et al., 2000), improvement of implicit motor learning as a result of anodal stimulation (Nitsche et al., 2003e), and reduced cortico-spinal excitability as a consequence of cathodal tDCS (Nitsche et al., 2003e).

Regarding neurophysiological mechanisms of action, tDCS has been hypothesised to shift resting membrane potential towards de- or hyperpolarisation, depending on whether anodal or cathodal tDCS is applied (Nitsche et al., 2008). However, the exact mode of action is not completely understood (Ardolino et al., 2005). Early animal experiments demonstrated changes in spontaneous discharge rates of cortical neurons in the brain parenchyma adjacent to the electrode, thereby providing support for the aforementioned subthreshold modulation of resting membrane potential (Bindman et al., 1962; Purpura and McMurtry, 1965a,b). Mathematical models also indicate changes in the probability of spontaneous neuronal firing as a result of transmembrane potentials in neurons (Ardolino et al., 2005; Miranda et al., 2006c; Wagner et al., 2007; Zaghi et al., 2010) or in glial cells (Ruohonen and Karhu, 2012) being directed to de- or hyperpolarisation. Furthermore, MEP studies in which tDCS effects are systematically modulated by pharmacological interventions provide evidence for synaptic modifications after tDCS, i.e. for non-focal plasticity in the human brain. Different ionic and molecular events have shown to be evoked by tDCS as well. Among others, alterations have been observed in hydrogen and calcium concentrations, levels of cyclic adenosine monophosphate (cAMP), protein synthesis, *N*-methyl-D-aspartate (NMDA) receptor efficacy (Ardolino et al., 2005; Gartside, 1968; Hattori et al., 1990; Islam et al., 1995; Liebetanz et al., 2002; Nitsche et al., 2003a, 2004; Wagner et al., 2007) and brain bioenergetics (Binkofski et al., 2011; Clark et al., 2011; Rango et al., 2008).

Accordingly, neuroimaging studies of M1 tDCS provide evidence for enhanced cortical excitability in regions structurally or functionally connected with the anode (Boros et al., 2008; Nitsche et al., 2005). Initial studies that combined electroencephalography (EEG) with tDCS showed reduced power in low-frequency bands after

anodal stimulation, whereas the opposite pattern was observed for cathodal stimulation (Ardolino et al., 2005; Marshall et al., 2004). The first study comparing blood oxygenation level-dependent (BOLD) signals in functional magnetic resonance imaging (fMRI) before and after stimulation revealed a lasting signal decrease in the supplementary motor area (SMA) during a sequential finger opposition task after 5 min of cathodal stimulation of the left motor cortex (Baudewig et al., 2001). By means of $H_2^{15}O$ positron emission tomography (PET) of regional cerebral blood flow, Lang et al. (2005) found anodal tDCS over the left M1 to increase regional cortical blood flow (rCBF) in widespread cortical and subcortical areas compared to cathodal tDCS, while cathodal compared to anodal tDCS led to a reduction of metabolic activity in the corresponding areas. More recently, two magnetic resonance spectroscopy (MRS) studies reported reduced gamma-aminobutyric acid (GABA) (Stagg et al., 2009) and increased glutamine and glutamate in response to anodal tDCS over M1 (Clark et al., 2011).

Neurophysiological effects of tDCS may be associated with or even causally related to behavioural changes. Neuroimaging studies often include behavioural measures which may demonstrate the behavioural relevance of neuromodulatory findings. Different monitoring levels for tDCS effects exist and temporal relations vary between independent (tDCS) and dependent measures and among several dependent measures. TDCS can be applied on- or offline and behavioural and neurophysiological measures can be recorded simultaneously or consecutively. Because the combination of tDCS and certain outcome measures is mostly of correlative nature, straightforward interpretations of tDCS effects on both behavioural and physiological levels may be difficult. Thus, not only the combination of several monitoring levels, namely behavioural, neurophysiological and neuroimaging variables, that are simultaneously recorded before, during (i.e. online) and after tDCS stimulation, but also the general design of the respective studies in terms of control and comparator conditions is important (see Fig. 1). The design of comparator conditions potentially allows robust analysis of interactions between different conditions (active vs. sham) and outcome criteria, which may improve the explanatory power of tDCS studies. Such comparator conditions, however, depend on the tCS method, e.g. polarity is a major variable in tDCS and may serve to demonstrate the specificity of an intervention, whereas frequency and phase are particularly critical for tACS (see Fig. 2). Comparator conditions across tCS methods include the stimulation condition (active vs. sham), the timing (online, offline or combined) and selected target regions, i.e. the electrode placement/montage. In tCS, unless an extracephalic electrode is used both electrodes can be regarded as separate targets, i.e. we use the wording "1st target" or "2nd target", depending on the a priori hypotheses of the authors. Consequently, the position of either the 1st or 2nd electrode or of both electrodes can be changed and the effects of these different targets can be compared with each other. Unfortunately, the use of the above mentioned parameters varies considerably, leading to heterogeneous results, impaired reproducibility, less meaningful conclusions and reduced comparability between studies.

## 2. The prefrontal cortex as a target for tDCS in psychiatric disorders

Regions other than M1, e.g. the PFC, are of major interest as potential targets for a therapeutic application of tDCS in neurocognitive and psychiatric disorders. So far, tDCS has been shown to influence excitability or behavioural performance or both when applied to non-motor cortex regions comprising regions involved in sensory (visual and somatosensory), affective and cognitive functions (for review see Been et al., 2007). Currently, research is increasingly focussing on PFC stimulation sites, which are involved in more complex cognitive domains and may also provide an avenue for future development towards a therapeutic application. In this regard, the effects of prefrontal tDCS on learning and automaticity (motor and categorisation learning), memory (working memory [WM], long-term memory, episodic and declarative memory), decision making, mood, attention/vigilance, language, executive functions (problem solving, mental flexibility, inhibition, planning, impulsivity), emotion processing and regulation, semantic processing (language comprehension and naming, processing of action, congruence detection), verbal fluency, pain perception, social behaviours, food craving and risk taking have been studied in healthy volunteers (for review see Tremblay et al., 2014). Because of its resultant behavioural relevance and because prefrontal dysfunctions are associated with a variety of neurological and psychiatric diseases, prefrontal tDCS holds promise as a means of improving impaired brain function in neurological (for review see Flöel, 2014) and psychiatric diseases (Fregni and Pascual-Leone, 2007; Iyer et al., 2005; Kuo et al., 2014). Clinical applications of prefrontal tDCS have been investigated in patients with disorders of consciousness (Thibaut et al., 2014), chronic pain (Arul-Anandam et al., 2009; Valle et al., 2009), Parkinson's disease (Boggio et al., 2006; Fregni et al., 2006d), major depression (MD) (Boggio et al., 2008; Brunoni et al., 2013; Dell'Osso et al., 2012; Ferrucci et al., 2009; Ho et al., 2014; Kalu et al., 2012; Loo et al., 2012; Loo et al., 2010; Martin et al., 2013, 2011; Palm et al., 2012; Rigonatti et al., 2008), schizophrenia (Barr et al., 2012; Bose et al., 2014; Brunelin et al., 2012; Fitzgerald et al., 2014; Nawani et al., 2014; Vercammen et al., 2011), craving (Boggio et al., 2009, 2008; Conti and Nakamura-Palacios, 2014; da Silva et al., 2013; Nakamura-Palacios et al., 2012), attention deficit hyperactivity disorder (ADHD) (Prehn-Kristensen et al., 2014) and tinnitus (Frank et al., 2012; Vanneste and De Ridder, 2011; Vanneste et al., 2011, 2010).

Anatomically targeted analyses of NIBS methods, including tDCS, in neuropsychiatric diseases have generated promising results (Fox et al., 2014; Fox et al., 2012). However, studies of prefrontal tDCS in a clinical setting that used both clinical and neurophysiological information as outcome measures are rare and included heterogeneous patient groups (for overview see Table 1). Moreover, quantitative, qualitative and long-term benefits have not yet been validated. Thus, the aim of this article is to provide an overview on tDCS studies of the PFC that used neuroimaging and neurophysiological techniques at different monitoring levels and that combined methodical approaches. Because prefrontal tDCS seems to be a promising tool for future clinical application, we concentrate on studies targeting the prefrontal cortex. However, as tDCS cannot be regarded as anatomically focal NIBS approach, we also include studies targeting other frontal regions.

## 3. Computational models of prefrontal tDCS

Studies face two main challenges when applying tDCS, i.e. when transferring current to a region of interest. First, landmarks on the skull do not necessarily correspond to underlying brain targets (Seibt et al., 2015). Second, current flow distribution and electric field intensity depend on electrode positioning and individual head anatomy (skull structure and brain anatomy) (Datta et al., 2011) as well as on structural and functional connections (Rosso et al., 2014). Thus, electric current does not necessarily peak under the electrode (Datta et al., 2009; Dmochowski et al., 2011, 2013) and may diffuse to areas outside the region directly beneath it (Datta et al., 2009; Dmochowski et al., 2011; Nelson et al., 2014). In particular, the relative placement of the cathode with respect to the anode determines the amount of current reaching brain tissue (Datta et al., 2008; Miranda et al., 2006a; Weaver et al., 1976 Miranda et al., 2006a; Weaver et al., 1976), electric field intensity within the region of

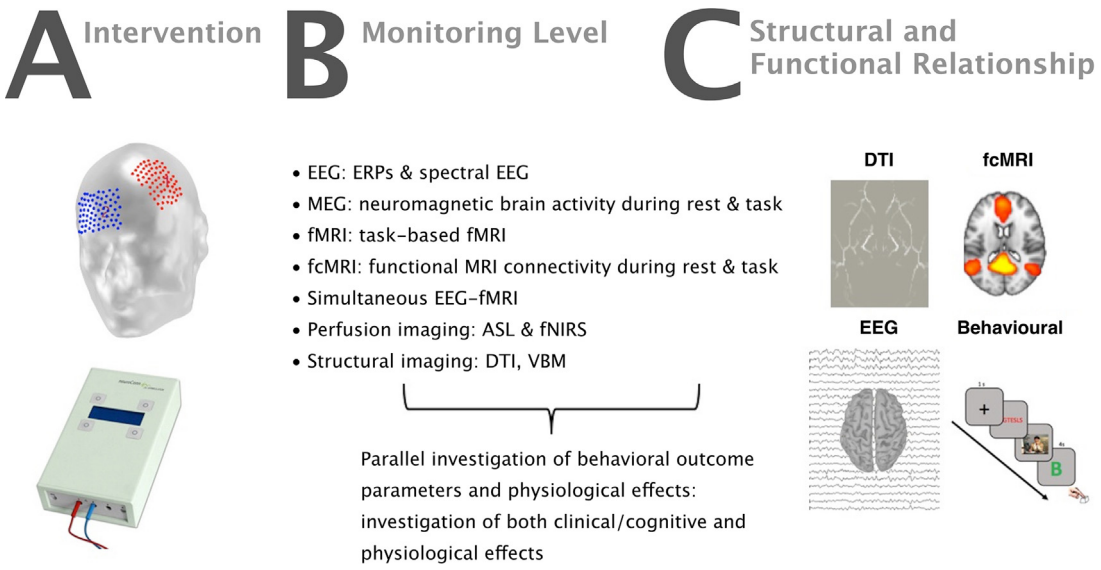


**Fig. 1.** A) tDCS/tACS application with 35 cm swamp electrodes. The anode is placed in a dorsolateral prefrontal position (electrode position F3), the cathode in a supraorbital one (electrode position Fp2). The head model was created with Matlab/Comets (Jung et al., 2013). B) Different neurophysiological methods that may serve as dependent measures. C) Possible relationships between different neurophysiological outcome measures (behavioural: a delayed working memory task with emotional distraction). ASL = arterial spin labelling, DTI = diffusion tensor imaging, EEG = electroencephalography, ERP = event-related potential, fcMRI = functional connectivity MRI, fMRI = functional magnetic resonance imaging, fNIRS = functional near-infrared spectroscopy, MEG = magnetoencephalography, VBM = voxel-based morphometry.

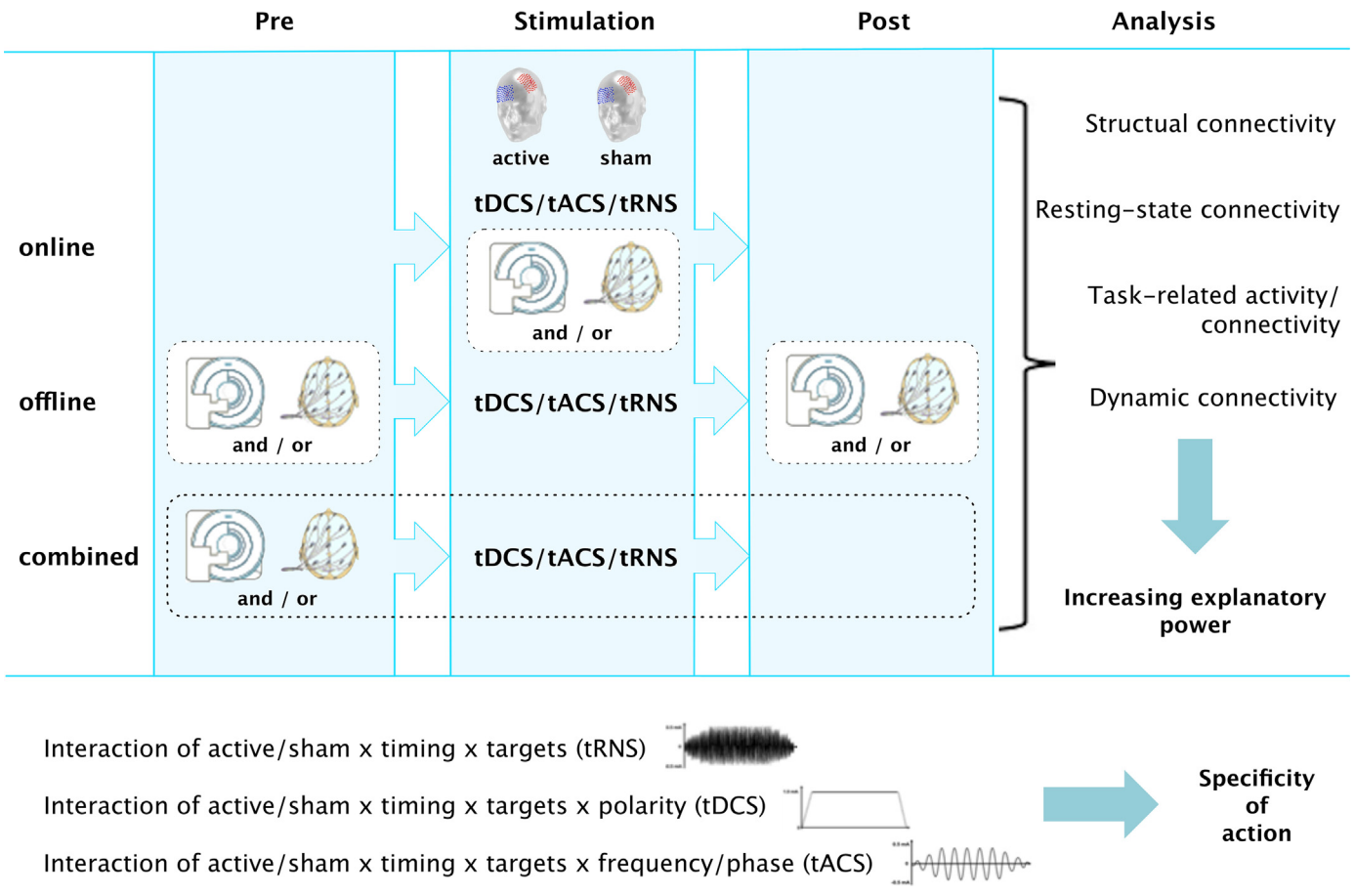


**Fig. 2.** Different combinations of tDCS/tRNS/tACS with functional magnetic resonance imaging (fMRI) and/or electroencephalography (EEG) that consider different stimulation factors: stimulation conditions (sham/active), timing of recording with respect to stimulation (online/offline/combined), targets (number of different electrode montages), polarity (anodal/cathodal, only for tDCS) and frequency/phase (only for tACS). tACS = transcranial alternating current stimulation, tDCS = transcranial direct current stimulation, tRNS = transcranial random noise stimulation. For tDCS (unless an extracephalic electrode is used), both electrodes can be regarded as targets, i.e. we use the wording 1st or 2nd target in accordance with the a priori hypotheses of the authors.

**Table 1**
Studies that investigated the effects of transcranial direct current stimulation (tDCS) on clinical outcomes and neurophysiological parameters.

| Study | Target measure(s) | Assessment | Condition(s) & polarity* | Design | *n* | Targets** | | Current [mA]/duration [min] | Specific interaction*** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st electrode | 2nd electrode | | |
| Nakamura-Palacios et al. (2012) | • ERPs<br>• alcohol-related and neutral sounds<br>• clinical outcomes (FAB and five items of OCDS) | combined | anodal tDCS<br>sham tDCS | crossover | 49<br>(alcohol-dependent patients during subacute abstinence period) | left DLPFC (F3) | right supra-deltoid area | 1/20 | active/sham × timing × target |
| | Results | (post-pre) tDCS > (post-pre) sham: ↑ mean amplitude of P3 at Fz associated with alcohol-related sounds, effect not seen for neutral sounds → change more pronounced in Lesch IV alcohol-dependent patients;<br>post tDCS > sham in Lesch IV alcohol-dependent patients only: ↑ FAB performance | | | | | | | |
| Vanneste et al. (2011) | • rs EEG<br>• tinnitus loudness and tinnitus-related distress | offline | cathodal tDCS | | 45<br>(tinnitus patients) | left DLPFC (F3) | right DLPFC (F4) | 1.5/20 | timing × target |
| | Results | responders > non-responders: ↑ gamma band activity in right primary and secondary auditory cortex and right parahippocampus + ↑ functional connectivity in gamma band between right DLPFC and right parahippocampus as well as right DLPFC and subgenual ACC | | | | | | | |
| Vanneste and De Ridder (2011) | • rs EEG<br>• tinnitus intensity and tinnitus-related distress | offline | cathodal tDCS<br>sham tDCS | crossover | 12<br>(patients with tinnitus, responding to tDCS) | left DLPFC (F3) | right DLPFC (F4) | 1.5/20 | active/sham × timing × target |
| | Results | post tDCS > BL (= pre tDCS + pre sham) & post tDCS > post sham: suppression of tinnitus intensity and tinnitus-related distress;<br>post tDCS > pre tDCS: ↑ activity in the pregenual ACC for alpha1 frequency band and ↓ activity in the right A1 for beta3 and gamma frequency band, ↓ gamma connectivity between right DLPFC, pregenual ACC, parahippocampus bilaterally and right A1, ↑ theta connectivity between these areas, ↓ correlation of activity in DLPFC and between ACC, parahippocampus, A1 and DLPFC between theta and alpha and beta, ROI analysis: gamma activity ↑ in right DLPFC and ↓ in left DLPFC;<br>post sham > pre sham: no significant differences in brain activity | | | | | | | |
| Pereira et al. (2013) | • rs fMRI<br>• phonemic and semantic verbal fluency | offline | anodal tDCS | crossover | 16<br>(patients with Parkinson's disease) | • left DLPFC (F3)<br>• left TPC (P3-T5) | right supra-orbital area | 2/20 | active/sham × timing × targets (1st) |
| | Results | post DLPFC tDCS > post TPC tDCS: ↑ functional connectivity in task-related networks and deactivation task-related networks (DMN), ↑ performance on phonemic fluency task, after adjusting for baseline phonemic performance | | | | | | | |
| Volpato et al. (2013) | • rs fMRI<br>• psychopathological symptoms (clinical scales) | offline | cathodal tDCS<br>sham tDCS | crossover | 1<br>(patient with severe OCD and comorbid mood and anxiety disorders) | left DLFPC (F3) | posterior neck-base | 2/10 (5 sessions for each condition) | active/sham × timing × target |
| | Results | BL patients > controls: interhemispheric asymmetry with hyperactivation of the left and hypoactivation of the right anterior neural circuits;<br>post tDCS > pre tDCS: no effect on symptoms of OCD, ↓ depression and anxiety, ↓ of interhemispheric imbalance;<br>no effect of rTMS → no placebo effect | | | | | | | |
| Conti and Nakamura-Palacios (2014) | • ERPs<br>• cue-reactivity | offline | cathodal tDCS<br>sham tDCS | parallel | 7 + 6<br>(patients addicted to crack-cocaine) | left DLPFC (F3) | right DLPFC (F4) | 2/20 | active/sham × timing × target |
| | Results | post sham > pre sham: ↑ activity in ACC during exposure to crack-related images;<br>post tDCS > pre tDCS: ↓ ACC activity after visualisation of drug cues | | | | | | | |
| da Silva et al. (2013) | • ERPs<br>• cue-reactivity<br>• cognitive and frontal executive functions<br>• craving<br>• depressive and anxiety symptoms<br>• quality of life<br>• relapse | offline | anodal tDCS<br>sham tDCS | parallel | 6 + 7<br>(alcohol-dependent patients) | left DLPFC (F3) | right supra-deltoid area | 2/20<br>(once a week for 5 consecutive weeks) | active/sham × timing × target |
| | Results | post tDCS > post sham: depressive symptoms ↓, craving ↓, blocking of increase in neural activation triggered by alcohol-related and neutral cues in PFC, trend to ↑ change in executive functions, trend for ↑ relapses | | | | | | | |
| Palm et al. (2013) | • rs fMRI<br>• clinical scales | offline | anodal tDCS | | 1 (patient with paranoid schizophrenia) | Left DLPFC (F3) | right supra-deltoid area | 2/20 (twice a day on 10 weekdays) | timing × target |

Table 1 (*Continued*)

| Study | Target measure(s) | Assessment | Condition(s) & polarity* | Design | *n* | Targets** | | Current [mA]/duration [min] | Specific interaction*** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st electrode | 2nd electrode | | |
| | Results | post tDCS > pre tDCS: improvement in psychopathology, functional connectivity in anterior part of DMN ↓ | | | | | | | |
| Nawani et al. (2014) | • ERPs: corollary discharge abnormalities<br>• auditory hallucinations assessed with the AHRS | offline | anodal tDCS | crossover | 5 (schizophrenia patients with refractory auditory verbal hallucinations) | left DLFC (point midway between F3 and FP1) | left temporo-parietal junction (point midway between T3 and P3) | 2/20 (twice a day on 5 consecutive days) | timing × target |
| | Results | post tDCS > pre tDCS: ↓ AHRS scores;<br>pre tDCS: no significant difference between N1 amplitudes generated in talk and listen conditions<br>→ N100 amplitude during listening significantly greater than during talking in healthy participants whereas not significantly different in patients;<br>post tDCS: in patients, ↓ amplitude of N100 during talk than during listen | | | | | | | |
| Powell et al. (2014) | • ERPs<br>• spectral EEG<br>• visual WM | offline (post only) | anodal tDCS<br>sham tDCS | crossover<br>double blind | 14<br>(patients with MD episode) | left DLPFC (F3) | lateral aspect of right orbit (F8) | 2/20 (+ additional 15 sessions) | active/sham × timing × target |
| | Results | post tDCS > postsham: N2 amplitude ↓ and theta activity over frontal areas ↓ during memory retrieval of medium load, alpha activity over parietal areas ↑ during maintenance of high load | | | | | | | |
| Ulam et al. (2014) | • spectral EEG<br>• neuropsychological functions | offline | anodal tDCS<br>sham tDCS | parallel<br>double blind | 13 + 13<br>(TBI patients in acute or subactue stage of recovery) | left DLPFC (F3) | right supra-orbital site (Fp2) | 1/20 (on 10 consecutive days) | active/sham × timing × target |
| | Results | post tDCS > pre tDCS: after 1st session: theta ↓, after 10 sessions: delta ↓ & alpha ↑;<br>post sham > pre tDCS: no significant changes;<br>post tDCS > post sham: greater correlation delta ↓ – performance ↑, participants with excess slow EEG activity in initial recordings greater improvement on neuropsychological tests | | | | | | | |
| Hoy et al. (2015) | • spectral EEG<br>• WM (n-back) | offline (post only: 0, 20, 40 min) | anodal tDCS<br>sham tDCS | parallel<br>(condition) + crossover<br>(post assessment) | 16 + 13 + 12<br>(schizophrenia patients) | F3 | supra-orbital | 1 & 2/20 | active/sham × timing × target |
| | Results | 2 mA:<br>post tDCS 40 min > post tDCS 0 min: gamma event-related synchronisation ↑ in left DLPFC;<br>post tDCS 20 min > post tDCS 0 min: WM ↑, correlation performance ↑ – gamma event-related synchronisation ↑;<br>postsham 40 min > post sham 0 min: gamma event-related synchronisation ↓ | | | | | | | |
| Meinzer et al. (2014) | • task fMRI<br>• rs fMRI<br>• semantic word retrieval | online | anodal tDCS<br>sham tDCS | crossover<br>double-blind | 18<br>(MCI patients)<br>18<br>(matched HCs) | left ventral IFG<br>(intersection of T3-F3, F7-C3, and F7-F3) | right supra-orbital region | 1/20 | active/sham × timing × target |
| | | during sham: MCI patients > HCs: ↓ correct responses, ↑ activity in bilateral prefrontal regions, widespread connectivity changes including medial frontal and lateral fronto-temporal cortices, bilateral sensorimotor regions and right cerebellum;<br>during tDCS > during sham: MCI patients ↑ performance to level of HCs, ↓ task-related hyperactivity, reversal of abnormal connectivity pattern;<br>during tDCS for patients > during sham for HCs: comparable activity levels and connectivity patterns → "normalisation" in patients | | | | | | | |
| Reinhart et al. (2015) | • spectral EEG<br>• colour discrimination task (stop signal) | offline | anodal tDCS<br>sham tDCS | crossover | 19 (schizophrenia patients)<br>18 (matched HCs) | medial-frontal cortex (FCz) | centre of right cheek | 1.5/20 | active/sham × timing × target |
| | Results | BL: patients > HCs: post-error slowing ↓, on error minus correct trials asynchronous and low-power central midline theta oscillations (4–8 Hz);<br>post tDCS > post sham: ↑ intertrial phase coherence of medial-frontal theta in both groups, post-error slowing ↑ in patients, ↑ accuracy in both groups, ↑ connectivity between medial-frontal and fronto-lateral sites in patients;<br>post sham: in HCs: coupling theta response – trial-to-trial post-error adjustment, in patients: no theta phase synchrony on error relative to correct trials, weaker synchrony relative to controls<br>post tDCS: in patients, prediction of single-trial fluctuations in post-error RT by peak theta phase-coherence values, prediction of post-error slowing by Cz-F4 theta synchrony<br>→after tDCS, patients comparable to sham baseline level of HCs in terms of temporal consistency of central midline theta waves across trials, in terms of post-error behavioural adjustments and connectivity | | | | | | | |

A1 = primary auditory cortex, ACC = anterior cingulate cortex, AHRS = Auditory Hallucinations Rating Scale, BL = baseline, DLPFC = dorsolateral prefrontal cortex, EEG = electroencephalography, ERP = event-related potential, exp. = experiment, FAB = Frontal Assessment Battery, fMRI = functional MRI, mA = milliamperes, HC = healthy control, IFG = inferior frontal gyrus, MCI = mild cognitive impairment, min = minutes, MD = major depression, OCD = obsessive compulsive disorder, OCDS=Obsessive Compulsive Drinking Scale, ROI = region of interest, rs = resting state, rTMS = repetitive transcranial magnetic stimulation, RSN = resting state network, TBI = traumatic brain injury, tDCS = transcranial direct current stimulation, TPC = temporo-parietal cortex, ↑ = increase, ↓ = decrease.

* Polarity = tDCS condition according to the main hypothesis of the respective study (e.g. in a study investigating the main effect of anodal tDCS on verbal fluency the condition is described as "anodal tDCS/sham tDCS").

** Targets = electrode montages, 1st and 2nd electrode = terms to indicate where the anodal and cathodal stimulation electrode is placed by referring to the given stimulation polarity (i.e. for anodal stimulation, the anode refers to the first electrode, for cathodal stimulation, the cathode refers to the first electrode).

*** Specific interaction = see Fig. 2.

interest (Bai et al., 2014; Datta et al., 2011; Galletta et al., 2015) and the pattern of current flow, i.e. brain areas stimulated (Bai et al., 2014; Galletta et al., 2015). For example, several groups have successfully applied tDCS with one electrode on the scalp and a second at an extracephalic position (Plewnia et al., 2015), inferring that this may lead to more defined stimulation (Wolkenstein and Plewnia, 2013). However, the current flow or electrical field between both electrodes may be even harder to determine and physical models would be warranted. Because there is no inactive electrode in tCS, the terms "active" and "reference" or "return" electrode seem somewhat misleading. Thus, in this review we use the terms "1st" and "2nd" electrode throughout the text and tables. To outline our theoretical assumptions, we summarise the main hypotheses derived from such computational models, which still require experimental validation by preclinical research in animals, in vivo neurophysiological recordings in humans or functional neuroimaging.

Across studies, standard electrode montages for prefrontal tDCS, such as dorsolateral prefrontal cortex (DLPFC) targeted montages (EEG 10–20 system: F3-F4 or F3-Fp2), were found to be suitable for DLPFC stimulation on the basis of the respective models (Bai et al., 2014; DaSilva et al., 2015; Datta et al., 2011; Nelson et al., 2014; Neuling et al., 2012). Importantly, less shunting occurred and a higher amount of current entered the brain with increasing inter-electrode distance (Bai et al., 2014). If a higher current strength reaches the brain, other brain areas outside the region close to the electrode may be stimulated more effectively (mainly other frontal areas such as the cingulum and the orbitofrontal cortex (OFC) and medial neuroanatomical regions, e.g. the mesencephalon, cerebellum and hippocampus) (Bai et al., 2014; DaSilva et al., 2015; Datta et al., 2011; Galletta et al., 2015; Nelson et al., 2014; Neuling et al., 2012). At the same time, increasing the distance between electrodes, which is particularly relevant e.g. for extracephalic montages, leads to a loss of electric field magnitude in the DLPFC (Bai et al., 2014; DaSilva et al., 2015). Because regions with higher electrical fields are more likely to show a response, Datta et al. (2011) argue that the selection of electrode montages should be based on current maximisation in the target regions. Smaller electrode sizes may compensate for the trade-off between widespread stimulation and electric field intensity. The impact that changes in electrode size or orientation have on electric field intensity and distribution needs to be considered as potentially critical. Whereas displacement of the electrode by 1 cm did not have any significant impact on current flow in one study (Bai et al., 2014), another study (Woods et al., 2015) showed that even small drifts in electrode positions (also about 1 cm) significantly changed the distribution of the electric field across the brain as well as the peak electric field intensity.

It has also been shown that current density may cluster in local hot spots, depending on individual anatomical variations, and thus influence inter-individual efficacy (Bai et al., 2014). A very recent study indicates that current flow patterns can be optimised by adjusting tDCS electrode placement according to the individual anatomy (Seibt et al., 2015). Using high-resolution Finite Element Models, Seibt et al. (2015) investigated the impact of individual head anatomy and different positioning approaches on brain current flow in five participants by evaluating seven different electrode positions, all of which nominally targeted the left DLPFC. Analyses revealed a significant inter-individual variability in terms of positioning of the electrodes (guided via different systems or rules) on the one hand and brain current flow on the other. Two approaches increased electrical field intensity and precise excitation of the target region, namely maximising the distance between the electrodes and increasing the proximity of the electrodes to thinner skull structures. Furthermore, on the basis of these criteria the authors have suggested an improved system for electrode positioning (OLE System), which is easy to use (because it does not require functional imaging, mapping or neuro-navigation) and which permits accurate electrode placement (Seibt et al., 2015). Thus, to improve localisation it is preferable to use a standardised procedure for electrode positioning, e.g. the OLE System mentioned above.

Computational models for other tCS methods, e.g. tACS, are also available (Manoli et al., 2012); however, for prefrontal stimulation these models are not as elaborated as those for tDCS. Although one may be tempted to assume that the distribution of the electrical fields in tACS or tRNS resembles that of the field in tDCS, this is not clear on either the macro- or microstructural level and requires further research.

In sum, electrode montages are a critical factor to consider for the clinical application of tDCS. Before choosing tDCS electrode sizes and montages, one has to hypothetically define how the action of tDCS may be transmitted to target regions or networks by considering the critical issues.

## 4. Overview on functional-connectivity imaging: about regions and targets

There is increasing evidence that electric current induced by tDCS influences activity in brain regions distant from the site of stimulation. This may originate from two events: First, the applied current is not spatially focal but flows between the two electrodes. Depending on the distance between the anode and cathode, the current passes through a considerable number of functionally and anatomically distinct parts of the brain and thus potentially also affects other regions. Second, tDCS can elicit activity in regions that share connections with but are distant from the target region. Such long-distance effects of prefrontal stimulation as a result of existing inter-regional connections can be addressed by analysis of spontaneous network organisation, so called resting-state networks (RSN).

In past studies, RSNs were reliably reproducible across thousands of healthy volunteers and patients with major depression (Biswal et al., 2010; Iwabuchi et al., 2015; Kaiser et al., 2015). Structural connections of white matter density underlie the most prominent RSNs (van den Heuvel and Hulshoff Pol, 2010; van den Heuvel and Sporns, 2013). A very recent study demonstrated that medial-frontal and frontal-parietal connectivity is highly reliable, with a recognition rate of up to 99% when data obtained on two separate days from 126 healthy volunteers were analysed (Finn et al., 2015). A meta-analysis focusing on task-based neuroimaging experiments, which are publically accessible at the BrainMap database, indicates that RSNs are highly relevant to behaviour (Laird et al., 2011). Frontal-parietal connectivity was highly correlated with cognitive functions such as WM (Laird et al., 2011). For this reason, the impact of prefrontal tDCS on RSNs may entail important information about its specific mechanisms of action.

### 4.1. Studies investigating tDCS effects on resting-state connectivity

TDCS-induced connectivity changes found in fMRI studies comparing RSN configurations before and after prefrontal tDCS may reflect a state of enhanced alertness. Two studies report that functional connectivity between the PFC and anatomical distant regions is increased (see Table 2). This holds true for RSNs associated with externally directed attention, (Boly et al., 2008; Corbetta and Shulman, 2002; Fox et al., 2006) or cognitive engagement (Lewis et al., 2009; Mazoyer et al., 2009; Turken et al., 2008), such as the frontal parietal network (FPN) (Keeser et al., 2011a; Pena-Gomez et al., 2012). With regard to the default mode network (DMN), which is ascribed a role in passive monitoring of the external envi-

**Table 2**
Studies that investigated the effects of transcranial direct current stimulation (tDCS) on the resting brain.

| Study | Target measure(s) | Assessment | Condition(s) & polarity* | Design | *n* | Targets** | | Current [mA]/duration [min] | Specific interaction*** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st electrode | 2nd electrode | | |
| Keeser et al. (2011a) | rs fMRI | offline | anodal tDCS<br>sham tDCS | crossover<br>double blind | 13 | left DLPFC (F3) | right supraorbital region | 2/20 | active/sham × timing × target |
| | Results | BL: four RSNs, corresponding to DMN, left and right FPNs, SRN;<br>post tDCS > post sham: ↑ coactivation in frontal parts of the DMN, parts of the left and right FPN and right PCC, ↑ coactivation outside RSNs within anodal ROI in frontal gyrus | | | | | | | |
| Pena-Gomez et al. (2012) | rs fMRI | offline (post only) | anodal tDCS<br>sham tDCS | crossover | 10 | left DLPFC (F3)<br>right DLPFC (F4) | contralateral supraorbital region | 2/20 | active/sham × timing × targets (1st and 2nd) |
| | Results | post tDCS (left and right) > post sham: ↑ temporal functional connectivity between prefrontal and parietal regions (which are components of the AN), ↓ spatial robustness of the DMN | | | | | | | |
| Park et al. (2013) | rs fMRI | offline | anodal tDCS<br>sham tDCS | parallel | 25 + 14 | left DLPFC (F3) | right supraorbital region | 1/20 | active/sham × timing × target |
| | Results | post tDCS > post sham: ↑ connectivity of left DLPFC - right hemisphere, ↓ left DLPFC connectivity to brain regions around the stimulation site | | | | | | | |
| Stagg et al. (2013) | brain perfusion using ASL | combined | Exp. 1:<br>anodal tDCS<br>cathodal tDCS<br>Exp. 2:<br>sham tDCS | crossover (polarity) + parallel (condition) | 12 for each exp. | left DLPFC (F3) | right supraorbital region | 1/20 | active/sham × timing × target × polarity |
| | Results | during anodal tDCS > pre tDCS: ↑ coupling left DLPF – right DLPFC and left sensorimotor cortex, ↓ coupling left DLPFC – thalami bilaterally/brain stem/cerebellum;<br>post anodal tDCS> pre tDCS: ↑ functional connectivity left DLPFC – primary sensorimotor cortices bilaterally | | | | | | | |
| Hone-Blanchet et al. (2015) | MRS | combined (during and post) | anodal tDCS<br>sham tDCS | crossover<br>double-blind | 15 | left DLPFC (F3) | right DLPFC (F4) | 1/30 | active/sham × timing × target |
| | Results | during anodal tDCS > during sham: ↑ prefrontal NAA, ↑ striatal glx, no differences in prefrontal or striatal GABA level;<br>post anodal tDCS > post sham: no differences in glx, NAA or GABA levels in left DLPFC; during tDCS > post tDCS: ↑ NAA in left DLPFC | | | | | | | |

AN = attention network, ASL = arterial spin labelling, BL = baseline, DLPFC = dorsolateral prefrontal cortex, DMN = default mode network, exp. = experiment, FPN = frontal parietal network, GABA = gamma-aminobutyric acid, glx = glutamine, mA = milliamperes, min = minutes, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, NAA = N-acetyl Aspartate, PCC = posterior cingulate cortex, ROI = region of interest, rs-fMRI = resting state functional MRI, RSN = resting state network, SRN = self-referential network, tDCS = transcranial direct current stimulation, ↑ = increase, ↓ = decrease.

* Polarity = tDCS condition according to the main hypothesis of the respective study (e.g. in a study investigating the main effect of anodal tDCS on verbal fluency the condition is described as "anodal tDCS/sham tDCS").

** Targets = electrode montages, 1st and 2nd electrode = terms to indicate where the anodal and cathodal stimulation electrode is placed by referring to the given stimulation polarity (i.e. for anodal stimulation, the anode refers to the first electrode, for cathodal stimulation, the cathode refers to the first electrode).

*** Specific interaction = see Fig. 2.

ronment (Ghatan et al., 1995; Gilbert et al., 2007; Gusnard et al., 2001b; Hahn et al., 2007; Shulman et al., 1997) and in internal mentation (Buckner et al., 2008; Gusnard et al., 2001a), results are ambiguous. Keeser et al. (2011a) report increased coactivations in frontal parts of the DMN, whereas Pena-Gomez et al. (2012) found diminished spatial robustness of the DMN. Nevertheless, increased connectivity within frontal parts of the DMN, as reported by Keeser et al. (2011a), could entail poorer large-scale network integrations. In view of this functional segregation, Pena-Gomez et al. (2012) have proposed that tDCS guides the brain towards a state optimal for supporting (upcoming) cognitive demands. By facilitating the balance between DMN deactivation and FPN activation, anodal tDCS may reallocate cerebral resources, thereby acting as a priming mechanism. In addition, a study by Park et al. (2013) indicates that tDCS subserves information transmission by increasing interhemispheric connectivity, potentially leading to enhanced cognitive performance. In sum, studies combining prefrontal tDCS and resting-state fMRI show that prefrontal tDCS modulates resting-state connectivity in the human brain by inducing changes in functional connectivity both close to the stimulation sites and in distant brain regions, again suggesting that tDCS is not spatially focal. What is more, RSN analyses have the potential to identify stimulation sites where tDCS may exert its clinical effects (Fox et al., 2014).

### 4.2. Comments and future directions

Although all studies concentrating on resting-state modulations in response to prefrontal stimulation relied on a data-driven independent component or seed-based analyses, to further clarify the impact of tDCS on network structures graph-based data approaches, comprising centrality and graph-wide metrics, should be considered. Graph theory offers certain advantages. Above all, it is purely explanatory (Zuo et al., 2012) and does not rely on any a priori assumptions (Lohmann et al., 2010; Margulies et al., 2010) such as the structure of a single network. Consequently, it allows tDCS effects to be characterised on more complex network structures (see Meinzer et al., 2012, 2013, 2014; Weber et al., 2014) independently of a priori specifications of the number of components and substantial a posteriori selection of valid topologies, thereby allowing connections to be made between central brain regions ("hubs") subserving different cognitive processes (Lohmann et al., 2010). In addition, network topologies can be described via graph theoretical analyses. According to graph theory, human functional brain networks during resting wakefulness equate to a small-world organisation (Achard et al., 2006), which describes a network topology of high local clustering, short path length and few long-distance connections (Watts and Strogatz, 1998). Enabling both specialised processing among local connections and information transfer across distant regions (Sporns et al., 2004), a small-world topology represents an optimal structure for large-scale brain networks (Bassett and Bullmore, 2006). With regard to prefrontal tDCS, it may be of interest to evaluate whether this pattern can be modulated in the same way, as standard functional connectivity analyses suggest.

## 5. Overview on task-related imaging: the behavioural level

Purely physiological studies are important for investigating neuronal mechanisms underlying tDCS effects. Brain oscillations (Jacobson et al., 2012), brain perfusion (Stagg et al., 2013), amount of oxyhemoglobin (Merzagora et al., 2010), brain bioenergetics (Rae et al., 2013) and functional connectivity (see above) have shown to be susceptible to tDCS of the PFC. Although these studies have suggested possible behavioural implications, they lack direct evidence for a functional relevance of the entrained neuromodulatory effects of tDCS. Vice versa, purely behavioural studies can verify an impact of prefrontal tDCS on higher cognitive processes (see Introduction) but neglect concurrent effects on a physiological level. In order to obtain a deeper understanding with regard to the functional relevance of tDCS-induced neuromodulatory effects, cognitive tasks can be included in the experimental design of neurophysiological studies. Because we are concentrating on prefrontal tDCS, behavioural paradigms that involve and evoke activity within frontal areas – particularly within the area covered by the stimulation electrode of interest – are of relevance.

### 5.1. tDCS effects on task-related brain activity: task-fMRI studies

Neural correlates of tDCS-induced performance facilitation or inhibition can be detected on the basis of task fMRI. The assessment of BOLD signal changes in response to a cognitive task before and after or during prefrontal tDCS allows for simultaneous monitoring of tDCS effects on both a neurophysiological and behavioural level, thereby enabling direct comparisons between both measures. So far, only two studies have applied this method in combination with prefrontal tDCS (see Table 3). In response to anodal tDCS, both studies proved an increase in the behaviour of interest, neurophysiological changes associated with the observed behaviour and a relation between both outcomes (Chib et al., 2013; Holland et al., 2011). Especially the third finding indicates that prefrontal tDCS can drive behaviourally relevant brain regions towards a state associated with improved cognitive processing. Holland et al. (2011) targeted the inferior frontal cortex (IFC) with 2 mA for 20 min and demonstrated both behavioural and neural facilitation effects during this time. Compared to a sham condition in the same study, participants' performance of an overt picture-naming task improved during anodal tDCS, while the BOLD signal in the left frontal cortex, including Broca's area, decreased. Moreover, faster naming responses and BOLD signal reductions in Broca's area correlated significantly (Holland et al., 2011). A classical fMRI pre-post between-subject design, including anodal tDCS of the ventro-medial PFC (VMPFC) and simultaneous cathodal stimulation of the right DLPFC (2 mA, 15 min), demonstrated increases in participants' appraisals of facial attractiveness. In addition, when compared with an active sham condition (anode: right DLPFC, cathode: VMPFC), higher attractiveness ratings were associated with upregulated activity in the ventral midbrain, and connectivity of this area with the VMPFC increased. Again, prefrontal-midbrain connectivity positively correlated with attractiveness ratings (Chib et al., 2013).

### 5.2. tDCS effects on fMRI-charactrerised behavioural tasks

Likewise, some approaches recorded tDCS-evoked performance changes and the neuronal basis underpinning the behavioural findings independently of each other and then pulled the findings together (see Table 3). After showing that a BOLD response in a certain area is associated with a certain cognitive process during task execution, those studies compared behavioural outcomes after real and sham tDCS to the previously identified area. Because they observed tDCS-induced intensifications of this cognitive process, the authors suggest a link between both measures. In their view, tDCS supported activity within the region of interest and thus increased the use of the behavioural parameter (Nihonsugi et al., 2015; Xue et al., 2012). In our opinion, findings of behavioural and physiological modulations as a consequence of tDCS should be interpreted carefully if both dependent variables are recorded separately but linked ex post. Only investigations of both behavioural and physiological effects during (online) or directly after (offline) NIBS offer the possibility to make explicit assumptions about neu-

**Table 3**
Studies that used functional magnetic resonance imaging (fMRI) to investigate tDCS effects on task-related brain activity.

| Study | Target measure(s) | Assessment | Condition(s) & polarity* | Design | *n* | Targets** | | Current [mA]/duration [min] | Specific interaction*** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st electrode | 2nd electrode | | |
| Holland et al. (2011) | • task fMRI<br>• overt picture-naming | online | anodal tDCS<br>sham tDCS | crossover | 10 | left IFC (FC5) | right frontopolar cortex | 2/20 | active/sham × timing × target |
| | Results | during tDCS > during sham: behavioural and neural facilitation effects: spoken naming responses ↑, BOLD signal in left frontal cortex, including Broca's area ↓;<br>during anodal tDCS: in ventral premotor cortex, correlation naming RTs ↑ - BOLD responses ↑ | | | | | | | |
| Xue et al. (2012) | • task fMRI<br>• GF during a matching pennies game | offline (post only) | anodal tDCS<br>sham tDCS | crossover | 18 per exp. | left lateral PFC (intersection of F3-T3 line and F7-C3 line) | left cheek | 1.5/10 | active/sham × timing × target |
| | Results | strong BOLD response in left lateral PFC to the current outcome preceded use of GF strategy 10 s later;<br>post tDCS > post sham: ↑ use of GF strategy, decisions more "sticky" | | | | | | | |
| Chib et al. (2013) | • task fMRI<br>• attractiveness ratings | offline | anodal tDCS<br>cathodal tDCS<br>sham tDCS | parallel | 99 (separated in 6 stimulation groups) | • ventro-medial PFC (halfway between Fp1 and Fp2)<br>• right DLPFC (F4)<br>• vertex (Cz) | • right DLPFC (F4)<br>• vertex (Cz)<br>• left DLPFC (F3) | 2/15 | active/sham × timing × targets (1st and 2nd) × polarity |
| | Results | post anodal tDCS of VMPFC and simultaneous cathodal stimulation of right DLPFC (main stimulation group) > pre tDCS: attractiveness ratings ↑;<br>post tDCS in main stimulation group > post active sham (anode: right DLPFC, cathode: VMPFC): correlation activity in ventral midbrain – attractiveness ratings ↑, VMPFC - ventral midbrain connectivity ↑<br>→ correlation prefrontal/midbrain connectivity ↑ – attractiveness ratings ↑ | | | | | | | |
| Nihonsugi et al. (2015) | • task fMRI<br>• trust game task: intention-based (guilt) vs. outcome-based (inequity) decisions | online | anodal tDCS<br>sham tDCS | crossover (tDCS exp.) + parallel (2 exp.: fMRI and tDCS)) | 41 (fMRI) + 22 (tDCS) | peak voxel in right DLPFC | Oz | 2/5 min before task, lasting until end of task | active/sham × timing × target |
| | | fMRI: correlation ↑ activity right DLPFC – amount of guilt, correlation ↑ activity right amygdala ventral striatum – amount of inequity;<br>during tDCS > during sham: ↑ guilt, no difference between reward and inequity<br>→ participants with larger ↑ in guilt in tDCS condition, higher cooperation ratio | | | | | | | |

ACC = anterior cingulate cortex, BOLD = blood oxygenation level dependent, exp. = experiment, fMRI = functional magnetic resonance imaging, GF = gambler's fallacy, IFC = inferior frontal cortex, mA = milliamperes, min = minutes, PFC = prefrontal cortex, tDCS = transcranial direct current stimulation, tRNS = transcranial random noise stimulation, TSST = Trier Social Stress Test, RT = reaction time, VMPFC = ventro-medial PFC, WM = working memory, ↑ = increase, ↓ = decrease.

* Polarity = tDCS condition according to the main hypothesis of the respective study (e.g. in a study investigating the main effect of anodal tDCS on verbal fluency the condition is described as "anodal tDCS/sham tDCS").

** Targets = electrode montages, 1st and 2nd electrode = terms to indicate where the anodal and cathodal stimulation electrode is placed by referring to the given stimulation polarity (i.e. for anodal stimulation, the anode refers to the first electrode, for cathodal stimulation, the cathode refers to the first electrode).

*** Specific interaction = see Fig. 2.

rophysiological mechanisms and their functional relevance. Still, the relation between the independent variable (tDCS) and the dependent measures remains correlative and a causal role of tDCS for the observed measure cannot necessarily be inferred.

### 5.3. tDCS studies combining different imaging methods

Increasing the number of monitoring levels, however, could make interpretations more meaningful. If tDCS is shown to affect different physiological measures which are related to each other as well as to a behavioural outcome, the respective experiment may have a higher explanatory power. Three studies have integrated task-related with resting-state imaging measures, thereby making use of three different monitoring levels (see Table 6). Two consecutive studies by the same group showed very nicely that anodal prefrontal tDCS improves performance via two mechanisms: neural priming of the relevant brain region during task execution and connectivity strengthening in task-relevant networks during rest. Connectivity was quantified with a graph-based approach, i.e. Eigenvector Centrality Mapping, in order to characterise network structures across the entire brain that are sensitive to tDCS without a priori assumptions. The aim of this group was to test the potential of tDCS to improve semantic word retrieval (Meinzer et al., 2012, 2013). In their first study, they used a within-subject design and applied anodal and sham tDCS during acquisition of resting-state and task-fMRI data. Compared to sham tDCS, active tDCS resulted in improved semantic word generation, task-related activity reductions in the left ventral inferior frontal gyrus (IFG) – the area beneath the anodal electrode (cathode placed at the right supraorbital region) – and increased connectivity in regions overlapping with the language network (Meinzer et al., 2012). Using the same study design and electrode montage, in their follow-up study the authors compared 20 healthy elderly adults with 20 matched younger adults serving as controls. During 20 min of anodal tDCS, the elderly adults' performance improved up to the level of their younger controls. Moreover, in the elderly adults, task-related hyperactivity, as found during the sham condition in the bilateral prefrontal cortices, anterior cingulate gyrus and precuneus, declined and resting-state data moved from enhanced anterior and reduced posterior functional brain connectivity to a more "standard" connectivity pattern (Meinzer et al., 2013). Interestingly, another study could not prove an impact of tDCS on behavioural variables of the Balloon Analog Risk Task (BART), although in the active group task-related activity increased in the right DLPFC and anterior cingulate gyrus (ACC) in response to losses and, during rest, blood perfusion in the OFC and right caudate as well as connectivity of the right ACC to the rest of the brain decreased (Weber et al., 2014). Such inconsistent results may be due to the fact that the study did not use an established paradigm but used tDCS to elucidate the neurophysiological correlates of a task. Otherwise, this is again a study that implemented graph metrics to describe resting-state modulations after prefrontal stimulation. By this means, the authors demonstrate an association between risk taking and network structure. Eigenvector centrality of the ACC decreased in response to tDCS, while this centrality measure was positively correlated with risk seeking. Equally, eigenvector centrality of the DLPFC correlated negatively with risk seeking, and loss-related activity within this region was influenced by tDCS (Weber et al., 2014).

## 6. Overview on EEG tDCS and ERP tDCS: dynamic issues

EEG recordings allow ongoing neural activity during rest or task execution to be captured with a higher temporal yet poorer spatial resolution. Event-related spectral perturbations (ERSP) or event-related potentials (ERP) can characterise tDCS-related changes in frequency or amplitude and latency, respectively (Achermann and Borbely, 2003; Dijk and Lockley, 2002). EEG studies show that tDCS-induced facilitations of higher-order cognitive processes are accompanied by modulations of their associated electrophysiological correlates. From those findings, one may conclude that tDCS operates on a neuronal level. Depending on the behaviour of interest, both neural enhancement through anodal stimulation and neural decrement through cathodal tDCS seem to either support or interfere with optimal performance.

### 6.1. Studies using spectral EEG to investigate tDCS effects on task-related and resting brain activity

In most ERSP studies, specific frequencies associated with attention and alertness (for review see Herrmann et al., 2015), such as beta and theta, increased in response to anodal tDCS, confirming the potential of tDCS to support higher-order cognitive processes (see Table 4). Baseline frequency scalp distributions during cognitive measures of WM, congruence detection (Balconi and Vitaloni, 2012), emotional valence (Maeoka et al., 2012) and attention (Miller et al., 2015) have been contrasted with post-stimulation assessments. After anodal stimulation, WM performance increased (Lu et al., 2015; Zaehle et al., 2011) and emotional valence ratings of unpleasantness for unpleasant pictures decreased (Maeoka et al., 2012), while there was no impact on behavioural performance during sustained attention (Miller et al., 2015). Electrophysiological modulations referred to elevated oscillatory power in the theta and alpha band (Zaehle et al., 2011) or increased spatiotemporal pattern similarity (STPS) (Lu et al., 2015) and augmented F3 beta band EEG power, with a congruent reduction in alpha band EEG power (Maeoka et al., 2012). After cathodal stimulation, Balconi and Vitaloni (2012) found speeded reaction times (RT) for incongruous conditions, along with enhanced alpha activity. One study failed to prove an influence of tDCS on EEG power during task execution or on task performance itself. However, during a period of rest immediately after tDCS and before the task, they found increased frontal-midline theta amplitude as compared to the sham condition. According to a standardised low resolution electromagnetic tomography analysis (sLORETA) this effect was localised to right prefrontal and left medial prefrontal brain areas (Miller et al., 2015).

### 6.2. Studies using ERPs to investigate the effect of tDCS on task-related brain activity

The effect of tDCS on ERP profiles has also been investigated in several studies (see Table 5). Behavioural improvement after anodal (i.e. response inhibition, face encoding, forced-choice target discrimination, visual search, WM) (Cunillera et al., 2015; Lafontaine et al., 2013; Reinhart and Woodman, 2014, 2015; Zaehle et al., 2011) or cathodal stimulation (i.e. congruence detection) (Balconi and Vitaloni, 2014) was reported, with most studies finding corresponding modulations in electrophysiological deflections (Balconi and Vitaloni, 2014; Cunillera et al., 2015; Lafontaine et al., 2013; Reinhart and Woodman, 2014, 2015; Zaehle et al., 2011). For example, in a follow-up study, Balconi and Vitaloni (2014) replicated their previous results (Balconi and Vitaloni, 2012) and related this finding to a reduced N400 component (Balconi and Vitaloni, 2014). Three independent studies by Lafontaine et al. (2013), Zaehle et al. (2011), and Reinhart and Woodman (2014) compared both anodal and cathodal stimulation to sham and showed that the effects induced by anodal tDCS on both a cognitive domain and its corresponding electrophysiological correlate can be reversed through cathodal stimulation of the same area. Those findings again argue for a polarity-specific effect of tDCS, with a specific impact on both electrophysiological and behavioural parameters. One study found

**Table 4**
Studies that used spectral electroencephalography (EEG) to investigate tDCS effects on task-related and resting brain activity.

| Study | Target measure(s) | Assessment | Condition(s) & polarity* | Design | *n* | Targets** | | Current [mA]/duration [min] | Specific interaction*** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st electrode | 2nd electrode | | |
| Balconi and Vitaloni (2012) | • spectral EEG<br>• congruence detection | offline | cathodal tDCS<br>sham tDCS | crossover | 34 | left DLPFC | right supraorbital region | 2/15 | active/sham × timing × target |
| | Results | post tDCS > pre tDCS: alpha ↑ for incongruous actions, RTs ↓ in response to incongruous condition; no effect for sham | | | | | | | |
| Maeoka et al. (2012) | • spectral EEG<br>• subjective reports of SAM oddball paradigm (unpleasant, neutral, pleasant pictures) | offline | anodal tDCS<br>sham tDCS | crossover | 15 | left DLPFC (F3) | right supraorbital region | 1/20 | active/sham × timing × target |
| | Results | post tDCS > post sham: beta band power ↑ and alpha band power ↓ in F3 during unpleasant pictures, SAM ratings for emotional valence ↑ (= ↓ of unpleasantness) for unpleasant pictures | | | | | | | |
| Jacobson et al. (2012) | • resting EEG power spectrum | offline (post only) | anodal tDCS<br>sham tDCS | crossover | 11 | right IFG (crossing point between T4-Fz and F8-Cz) | lateral OFC (above left eyebrow) | 1.5/15 | active/sham × timing × target |
| | Results | post tDCS > post sham: power of theta band ↓ in right IFG but not in lateral OFC | | | | | | | |
| Lu et al. (2015) | • EEG: STPS<br>• recognition memory of visual forms | offline (post only) | anodal tDCS<br>sham tDCS | crossover (condition) + parallel (stimulation site) | 20 + 17 (control exp.) | · left IFG (FC5)<br>· visual cortex (Oz) | contralateral OFC | 1.5/20 | active/sham × timing × targets (1st) |
| | | remembered items > forgotten items: ↑ self-STPS in two temporal clusters (right frontal region and left posterior region), ↑ global-STPS in right occipital region;<br>post prefrontal tDCS > post sham: ↑ number of remembered items, ↑ self-STPS, but not between-STPS;<br>post occipital tDCS > post sham: no effect on RTs or memory performance or STPS | | | | | | | |
| Miller et al. (2015) | • spectral EEG<br>• attention performance (Go/No-Go) | offline (post only) | anodal tDCS<br>sham tDCS | crossover | 8 | anterior frontal midline-site (Afz) | off scalp stimulation: under chin | 1/15 | active/sham × timing × target |
| | Results | post tDCS > post sham: ↑ frontal–midline theta amplitude during period of rest → sLORETA analysis: effect in surface EEG localised to right prefrontal and left medial prefrontal brain areas, no impact on behavioural performance during sustained attention task | | | | | | | |

EEG = electroencephalography, exp. = experiment, IFG = inferior frontal gyrus, mA = milliamperes, min = minutes, OFC = orbitofrontal cortex, RT = reaction time, SAM = Self-Assessment Manikin, sLORETA = standardised low resolution electromagnetic tomography, STPS = spatiotemporal pattern similarity, tDCS = transcranial direct current stimulation, WM = working memory, ↑ = increase, ↓ = decrease.

* Polarity = tDCS condition according to the main hypothesis of the respective study (e.g. in a study investigating the main effect of anodal tDCS on verbal fluency the condition is described as "anodal tDCS/sham tDCS").

** Targets = electrode montages, 1st and 2nd electrode = terms to indicate where the anodal and cathodal stimulation electrode is placed by referring to the given stimulation polarity (i.e. for anodal stimulation, the anode refers to the first electrode, for cathodal stimulation, the cathode refers to the first electrode).

*** Specific interaction = see Fig. 2.

**Table 5**
Studies that used event-related potentials (ERPs) to investigate tDCS on task-related brain activity.

| Study | Target measure(s) | Assessment | Condition(s) & polarity* | Design | *n* | Targets** | | Current [mA]/duration [min] | Specific interaction*** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st electrode | 2nd electrode | | |
| Zaehle et al. (2011) | • spectral EEG & ERPs<br>• WM (2-back) | offline (post only) | anodal tDCS<br>cathodal tDCS<br>sham tDCS | crossover | 16 | left DLPFC (F3) | left mastoid | 1/15 | active/sham × timing × target × polarity |
| | Results | (post anodal tDCS—post sham) > (post cathodal tDCS—post sham): WM performance (d') ↑ and oscillatory power ↑ in theta, alpha and lower beta bands under posterior electrode sites;<br>(post anodal tDCS—post sham) > control group: non-significant d' increase;<br>(post cathodal tDCS—post sham) > control group: WM performance (d') ↓ (weaker d' increase);<br>post anodal tDCS > both post cathodal tDCS and post sham: ↑ N1 latencies;<br>post anodal tDCS > post cathodal tDCS: total power in theta, alpha and lower beta bands under posterior electrode sites;<br>post cathodal tDCS > post sham: oscillatory power ↓ in theta and alpha bands under posterior electrode sites, ↓ P3 latencies at Pz | | | | | | | |
| Balconi and Vitaloni (2014) | • ERPs<br>• congruent/incongruent object-related actions (Exp. 1) or sentences (Exp. 2) | offline | cathodal tDCS<br>sham tDCS | crossover (condition) + parallel (task) | 30 + 28 | left DLPFC (F3) | right supraorbital region | 2/15 | active/sham × timing × target |
| | Results | post tDCS > both pre tDCS and post sham: in Experiment 1, ↓ N400, ↑ ERs, and RTs ↓ in response to incongruent conditions;<br>sLORETA: difference between congruent versus incongruent conditions for sham stimulation → localisation of source of this differential activation to the pFC | | | | | | | |
| Bellaïche et al., 2013 | • ERPs<br>• post-error slowing (Erikson flanker Task) | offline | anodal tDCS<br>cathodal tDCS<br>sham tDCS | parallel | 17 + 15 + 16 | horizontally over Fpz | between inion and Oz, also in a horizontal direction | 1/22 | active/sham × timing × target × polarity |
| | Results | post cathodal tDCS > both post anodal tDCS and post sham: Pe amplitudes ↓, but no effect for ERN | | | | | | | |
| Lafontaine et al. (2013) | • ERPs<br>• face encoding | offline (post only) | anodal tDCS<br>cathodal tDCS<br>sham tDCS | crossover | 11 | right DLPFC (F4) | left DLPFC (F3) | 1.5/15 | active/sham × timing × target × polarity |
| | Results | post anodal tDCS > other conditions: N170 ↓ (= RS), P3a amplitudes ↑, ↑ recognition RT<br>→ tDCS condition effect on N170 amplitude reflects differential RS between active tDCS conditions during the first five repetitions of stimuli<br>→ tDCS condition effect specific to right hemisphere where face stimuli are preferentially processed;<br>post cathodal tDCS > other conditions: N170 amplitude and RTs ↑, delay in P3a latency | | | | | | | |
| Reinhart and Woodman (2014) | • ERPs<br>• forced choice target discrimination with stop signals and feedback | offline (post only) | anodal tDCS<br>cathodal tDCS<br>sham tDCS | crossover (condition) + parallel (4 consecutive exp.) | 18+ 18 + 10+ 18 | medial-frontal cortex (FCz) | right or left cheek | 1.5/20 | active/sham × timing × target × polarity |

Table 5 (*Continued*)

| Study | Target measure(s) | Assessment | Condition(s) & polarity* | Design | *n* | Targets** | | Current [mA]/duration [min] | Specific interaction*** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st electrode | 2nd electrode | | |
| | Results | post cathodal tDCS > post sham: performance-monitoring activity ↓, behavioural adjustments after an error ↑, learning ↓;<br>post anodal tDCS > post sham: performance-monitoring activity ↑, behavioural adjustments after an error ↑, learning ↑ → improvement of cognition for 20 h;<br>no change in potentials indexing mechanisms of perceptual or response processing | | | | | | | |
| Cunillera et al. (2015) | • ERPs<br>• Response inhibition (Go/No-Go and SST) | online | anodal tDCS<br>sham tDCS | crossover | 23 | crossing point between T4-Fz and F8-Cz | crossing point between T3-Fz and F7-Cz | 1.5/20 | active/sham × timing × target |
| | Results | during anodal tDCS > during sham: RTs ↓ in Go trials, no effect on SSRT, amplitude ↓ of inhibitory P3 in NoGo and Stop-correct inhibited trials | | | | | | | |
| Reinhart and Woodman (2015) | • ERPs<br>• visual search | offline (post only) | anodal tDCS<br>sham | crossover (condition) + parallel (stimulation site) | 18 + 18 + 18 | • medial-frontal region (FCz)<br>• right parietal (P2) | centre of the right cheek | 2/20 | active/sham × timing × targets (1st) |
| | Results | post prefrontal tDCS > post sham:<br>• RTs ↑, such that search RTs reached floor levels within a single trial, N2-posterior-contralateral mirrored single-trial RT effects → attentional tuning (deployment of covert attention to the possible target in a search array)<br>• ↑ negativity of anterior P1 (index of long-term memory) across same-target trials, neural index of WM unchanged-<br>• change in individual participant's anterior P1 amplitude across same-target runs after stimulation highly predictive of accelerated rates at which participants searched through subsequent visual search array;<br>post parietal tDCS > post sham: ↑ perceptual processing of search array elements (search for targets ↑), but only on trials in which target colour appeared contralateral (i.e., in the left visual field) to location of the stimulating electrode on the head, no effect on overall tuning of attention or memory representations controlling search performance | | | | | | | |

d' = D-prime, EEG = electroencephalography, ERN = error-related negativity, ERP = event-related potential, exp. = experiment, h = hours, mA = milliamperes, min = minutes, OFC = orbitofrontal cortex, Pe = error-positivity, RS = repetition suppression, RT = reaction time, sLORETA = standardised low resolution electromagnetic tomography, SST = Stop-Signal Task, WM = working memory, ↑ = increase, ↓ = decrease.

* Polarity = tDCS condition according to the main hypothesis of the respective study (e.g. in a study investigating the main effect of anodal tDCS on verbal fluency the condition is described as "anodal tDCS/sham tDCS").

** Targets = electrode montages, 1st and 2nd electrode = terms to indicate where the anodal and cathodal stimulation electrode is placed by referring to the given stimulation polarity (i.e. for anodal stimulation, the anode refers to the first electrode, for cathodal stimulation, the cathode refers to the first electrode).

*** Specific interaction = see Fig. 2.

**Table 6**
Studies that investigated the effects of transcranial direct current stimulation (tDCS) by combining different imaging methods.

| Study | Target measure(s) | Assessment | Condition(s) & polarity* | Design | *n* | Targets** | | Current [mA]/duration [min] | Specific interaction*** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st electrode | 2nd electrode | | |
| Meinzer et al. (2012) | • rs fMRI<br>• task fMRI<br>• semantic word retrieval | online | anodal tDCS<br>sham tDCS | crossover | 20 | left ventral IFG (intersection of T3-F3, F7-C3, and F7-F3) | right supraorbital region | 1/17 | active/sham × timing × target |
| | Results | during tDCS > during sham: word-retrieval ↑ and ↓task-related activation in left ventral IFG (area specifically implicated in semantic retrieval processes), ↑ connectivity of left IFG and additional major hubs overlapping with the language network | | | | | | | |
| Meinzer et al. (2013) | • rs fMRI<br>• task fMRI<br>• semantic word retrieval | online | anodal tDCS<br>sham tDCS | crossover | 20 (healthy elderly adults)<br>20 (matched younger adults) | left ventral IFG (intersection of T3-F3, F7-C3, and F7-F3) | right supraorbital region | 1/20 | active/sham × timing × target |
| | Results | during tDCS > during sham: improvement of performance up to level of younger controls, task-related hyperactivity ↓ in bilateral prefrontal cortices, anterior cingulate gyrus, precuneus, more "youth-like" connectivity pattern during rs-fMRI | | | | | | | |
| Weber et al. (2014) | • task fMRI<br>• rs fMRI (ASL)<br>• BART | offline | anodal tDCS<br>sham tDCS | parallel | 22 + 11 | right DLPFC (F4) | left DLPFC (F3) | 1.5/15 | active/sham × timing × target |
| | Results | network analysis: whole-brain connectivity of right ACC positive correlation with number of pumps participants were willing to make on the BART, whole-brain connectivity of right DLPFC negative correlation with pumps on the BART; post tDCS > post sham: ↓ resting blood perfusion in OFC and right caudate, ↑ task-related activity in the right DLPFC and ACC in response to losses but not wins or increasing risk, ↓ connectivity between right ACC and rest of brain | | | | | | | |
| Keeser et al. (2011b) | • rs EEG<br>• ERPs<br>• WM (n-back) | offline (post only) | anodal tDCS<br>sham tDCS | crossover<br>double blind | 10 | left DLPFC (F3) | right supraorbital region | 2/20 | active/sham × timing × target |
| | Results | post tDCS > post sham: left frontal delta activity ↓, ↓ mean current densities for delta band in left subgenual PFC, anterior cingulate, left medial frontal gyrus, effect strongest for first 5 min, in n-back error rate ↓, accuracy ↑, RT ↓, P2 and P3 amplitudes ↑ for 2-back condition at electrode Fz, for time window 250–450 ms ↑ activity in left parahippocampal gyrus for 2-back condition | | | | | | | |
| Wirth et al. (2011) | • rs EEG<br>• ERPs<br>• SI-effect | combined (during + post) | anodal tDCS<br>sham tDCS | crossover | 20 | left DPFC (halfway between F3 and AF3) | extra-encephalic on right shoulder | 1.5/37 | active/sham × timing × target |
| | Results | during tDCS > during sham: behavioural SI-effect ↓, electrophysiological SI-effect ↑ over left compared to right temporal scalp-electrode sites → superior tuning of neural responses within language-related generators; post tDCS > post sham: delta activity ↓ during picture naming and resting state → neural disinhibition | | | | | | | |

ACC = anterior cingulate cortex, ASL = arterial spin labelling, BART = Balloon Analog Risk Task, DLPFC = dorsolateral prefrontal cortex, EEG = electroencephalography, ERP = event-related potential, exp. = experiment, fMRI = functional MRI, IFG = inferior frontal cortex, mA = milliamperes, min = minutes, OFC = orbitofrontal cortex, PFC = prefrontal cortex, ROI = region of interest, rs = resting state, RT = reaction time, SI = semantic interference, tDCS = transcranial direct current stimulation, ↑ = increase, ↓ = decrease.

* Polarity = tDCS condition according to the main hypothesis of the respective study (e.g. in a study investigating the main effect of anodal tDCS on verbal fluency the condition is described as "anodal tDCS/sham tDCS").

** Targets = electrode montages, 1st and 2nd electrode = terms to indicate where the anodal and cathodal stimulation electrode is placed by referring to the given stimulation polarity (i.e. for anodal stimulation, the anode refers to the first electrode, for cathodal stimulation, the cathode refers to the first electrode).

*** Specific interaction = see Fig. 2.

an effect of cathodal tDCS on electrophysiological potentials associated with the error-monitoring system. However, this effect was not accompanied by a modulation of the associated behavioural measure: post-error slowing (Bellaïche et al., 2013).

### 6.3. Studies investigating tDCS effects with combined EEG approaches

In addition to task-related EEG, two studies included resting-state EEG recordings in their study design to enable comparisons between tDCS-related modulations in ongoing frequencies, evoked activity and behavioural performance. Their findings, which comprise reduced low frequency power at frontal sites as well as increased event-related activity along with behavioural improvements, again validate the assumption that prefrontal tDCS is able to positively influence cognitive processing (see Table 6). In a double-blind, sham-controlled within-subject design, Keeser et al. (2011b) recorded EEG at rest and in response to a n-back task after anodal tDCS over the left DLPFC, with the reference electrode attached to the right supraorbital region. Twenty minutes of tDCS at 2 mA resulted in suppression of left frontal delta activity as well as in enhanced P2- and P3-ERP amplitudes for the 2-back condition at electrode Fz. By means of sLORETA the reduction of mean current densities for the delta band could be localised to the left subgenual PFC, anterior cingulate and left medial frontal gyrus. The source of enhanced activity in the 2-back condition was detected in the left parahippocampal gyrus for the time window 250–450 ms. Those electrophysiological findings were associated with a reduction in the n-back error rate and RTs as well as with an increase in accuracy (Keeser et al., 2011b). High-density EEG enabled Wirth et al. (2011) to monitor online effects of tDCS on scalp electrophysiology while completing a semantic interference (SI) task in addition to post-tDCS assessments. Stimulation (1.5 mA) started 7 min before execution of the task and was then delivered for 30 min. Another picture-naming paradigm was conducted in the offline phase together with an eyes-closed resting EEG. Analyses comparing the active to sham condition revealed a decline in the behavioural SI effect accompanied by facilitation of the electrophysiological SI effect over the left compared to the right temporal scalp electrode sites during tDCS. Post-tDCS effects comprised reduced delta activity during both the picture-naming and resting state, which was interpreted by the authors as neural disinhibition (Wirth et al., 2011).

### 6.4. Further considerations: TMS-EEG to probe prefrontal tDCS activity

On a neurophysiological level, TMS can also elicit ERPs, functional variables which are supposed to be comparable to MEPs for probing M1 excitability (for review see Hill et al., 2016). Only one recent study by Cunillera et al. (2015) has applied this method to frontal brain regions. Beyond sham effects, this study revealed that amplitudes of transcranial magnetic evoked potentials (TEP) increased compared to baseline and sham after 15 days of stimulation of the right IFG (2 mA, 20 min) in aphasic patients. An advantage of this method is that individual excitability levels can be measured by TEPs, which may represent a variable for individually adjusting tCS. Another benefit is related to the fact that ERPs can be induced passively without an active contribution by the person undergoing the procedure, allowing application in severely impaired neurological or psychiatric patients (Cunillera et al., 2015). Finally, TMS-EEG might be also suitable to probe tDCS effects on cortical oscillations (Hill et al., 2016).

## 7. From correlation to higher explanatory power: considerations on how to optimise prefrontal tCS experiments

TCS methods are non-invasive interventions for inducing excitability changes in the brain. The balance between excitation and inhibition is capable of predicting behaviour (Smit et al., 2013), and there is an imbalance between excitation and inhibition in neuropsychiatric disorders such as Alzheimer disease (Montez et al., 2009). These excitability changes are subthreshold, which is why prefrontal tCS provides an indirect or correlative approach that relies on statistical relations between activity changes and experimental conditions. We suggest that prefrontal tCS studies can overcome this obstacle and that optimally meaningful conclusions can only be drawn if evidence for the observed effect is accumulated at different monitoring levels and if the effect is related to a specific interaction in the experimental design, including meaningful control conditions.

### 7.1. Levels of monitoring tDCS effects

Effectiveness of prefrontal tDCS has been reported for various cognitive domains and with a variety of methods ranging from purely behavioural or neurophysiological recordings over task-related physiological effects to the integration of different neurophysiological measures with functional data. In our view, study designs that utilise combined behavioural/neurophysiological measurements are preferable, because they allow evidence from different sources to be compared and merged, thus increasing the explanatory power of a study. Since it is of particular interest to address state-dependent interactions of tDCS-mediated effects, i.e. how tDCS-induced resting-state modulations affect task performance and brain activity and how tDCS effects on the resting state relate to tDCS effects on task-based data, it may be highly informative to include both task and resting-state paradigms.

Beyond that, there is one further level of complexity which has not been addressed so far but could be targeted for research on NIBS methods. Recent technical advances allow EEG and MRI to be simultaneously acquired and analysed and thus the advantages of both methods – the high temporal resolution of EEG and the high spatial resolution of MR imaging techniques – to be combined. On the basis of combined EEG and fMRI measurements, neural correlates of tDCS could be explored in more detail by studying both electrophysiological and metabolic entrainments.

### 7.2. Specificity in time

Experimental studies on tDCS also differ with respect to the temporal coherence between stimulation and the recording of outcome measures. Behavioural and physiological effects can be logged offline, i.e. after the stimulation period, or online, i.e. during the stimulation (see Fig. 2). The latter approach faces some obstacles because of practical issues, such as MRI compatibility of the stimulation equipment and interference of strong electrical artefacts with neurophysiological signals, especially with EEG. However, some studies have overcome these obstacles by either using a ring-electrode setup, which prevents tDCS-induced artefacts (Sehm et al., 2013), or implementing mathematical solutions for artefact rejection similar to EEG scanner artefact corrections (Mangia et al., 2014). Moreover, MRI-compatible stimulation systems are available. Combining tDCS with online neurophysiological measurements could inform us in more detail about the temporal resolution of this method – i.e. the starting point at which and the length of time for which tDCS influences cortical processing. Recent discoveries on dynamical neurophysiological aspects of RSNs question the assumption of network stationarity, which is

the basis for the characterisation of large-scale brain networks (for review see Hutchison et al., 2013; Khanna et al., 2015; Singer, 2013). Within-network functional connectivity has been shown to fluctuate on the order of subseconds – much more rapidly than previously assumed. Such rapid changing activity patterns are thought to subserve information processing in the cerebral cortex, which requires a flexible system to cope with and adapt to unpredictable external stimuli (Hutchison et al., 2013; Singer, 2013; Zalesky et al., 2014). Non-stationarity has been detected in RSNs derived from BOLD-signal time-series, magnetoencephalography (MEG) signals and resting-state EEG rhythms (for review see Hutchison et al., 2013). Consequently, with respect to time of stimulation both online and offline recordings should be incorporated into a tDCS study in order to trace the formation of tDCS-induced changes as well as tDCS after-effects.

### 7.3. Specificity of target regions

Regarding electrode positioning and control conditions, prefrontal tDCS can be applied bilaterally with both electrodes placed at the same position on the right and left hemispheres, unilaterally with the cathode or anode placed above the region of interest and the other electrode located at another region (e.g. supraorbital) on the contralateral hemisphere, or extracephalically with the reference electrode put on another part of the body, e.g. the shoulder (Brunoni et al., 2012). Because there is no consensus in terms of suitable stimulation montages for a certain variable under study, most findings are likely to be a function of the targeted brain areas. Therefore, awareness should be raised for this drawback and scientists should be encouraged to systematically evaluate montages with a proven value for the variable of interest. Systematically reversing and changing the electrode arrangement can identify the most effective target location. If montage specificity is given, i.e. other montages produce no, considerably less or qualitatively different effects for the variable under study, a direct effect of tDCS on that variable can be accepted with a high level of certainty. In this context, standardisation of montages should be considered as well (Seibt et al., 2015).

### 7.4. Optimised experimental designs

In sum, the specificity of stimulation action can be optimally demonstrated in space (e.g. electrode montage and polarity for tDCS), time (e.g. online, offline, combined) and function (e.g. behavioural or neurophysiological measures). Such specificity theoretically needs to be demonstrated for each single outcome variable (i.e. behavioural or neurophysiological). In contrast, combining monitoring levels does not improve specificity as such, but may clearly increase the explanatory power of the experiment (see Fig. 2). Still, most studies on tCS do not take advantage of the possibility to show specific interaction. Only seven out of 48 cited tCS studies used a combined design that considers both online and offline effects of the stimulation (Hone-Blanchet et al., 2015; Kirov et al., 2009; Marshall et al., 2011; Nakamura-Palacios et al., 2012; Stagg et al., 2013; Voss et al., 2014; Wirth et al., 2011). In 12 of the 48 tCS studies, electrode arrangement was systematically manipulated such that polarity and/or the use of several targets could be considered as an additional interaction factor or factor level (Bellaïche et al., 2013; Chib et al., 2013; Jausovec and Jausovec, 2014; Lafontaine et al., 2013; Lu et al., 2015; Pena-Gomez et al., 2012; Pereira et al., 2013; Reinhart and Woodman, 2014, 2015; Stagg et al., 2013; Voss et al., 2014; Zaehle et al., 2011). Only one out of 40 tDCS studies (Chib et al., 2013) and only two out of eight tACS/otDCS studies (Jausovec and Jausovec, 2014; Voss et al., 2014) maximally manipulated the independent variable, resulting in a four-way interaction with two levels on the factor target. Finally, only one study combined manipulation of the independent variable polarity with offline as well as online measurements (Stagg et al., 2013). Nevertheless, apart from two clinical trials of small sample size (Nawani et al., 2014; Palm et al., 2013; Ulam et al., 2014), all cited studies included a sham condition as placebo control.

### 7.5. tACS and otDCS for investigating oscillatory specificity

Methodical progress has provided neuroscientists with the possibility to directly examine stimulation-entrained neural activity and hence to introduce further levels of interaction: frequency and phase (see Fig. 2). Two alternative types of non-invasive brain stimulation techniques – otDCS and tACS – deliver sinusoidal currents to the scull at a specific frequency matched with the oscillation of interest. If this frequency is present in the brain, sinusoidal currents can directly and selectively influence ongoing rhythmic brain activity. This offers the advantage to experimentally modulate a cognitive process and ongoing brain oscillations at the same time and thus, in combination with electrophysiological recordings, to demonstrate a causal role of that EEG oscillation for the respective cognitive process under study (for review see Herrmann et al., 2015). For a summary of studies combining prefrontal tACS or otDCS with neuroimaging methods, see Table 7.

Regarding tRNS, only one study has addressed the effect of this type of prefrontal stimulation on brain activity and arithmetic processing (Snowball et al., 2013) (see Table 3). Again, the whole range of possible interactions was not exploited because interaction factors referred to timing and active/sham.

## 8. How should we evaluate tDCS for therapeutic neuromodulation?

Application of stimulation currents to the PFC aims at enhancing higher-order cognitive processes. In combination with neuroimaging techniques such as fMRI or EEG, tCS can be used to demonstrate a link between a brain region and a cognitive process and to investigate the functional interactions between different brain areas. Consequently, tDCS is often used to further elucidate the functional role of certain brain regions for specific cognitive domains (for review see Filmer et al., 2014). A multitude of studies have described the application of prefrontal tDCS in various research fields dedicated to higher-order cognitive processes, such as memory and attention. At the same time, as demonstrated by clinical trials prefrontal tDCS holds great potential as a therapeutic intervention. However, to evaluate tDCS as a therapeutic tool its effectiveness needs to be systematically investigated.

First of all, the effect under investigation should comprise a mental activity typically impaired in psychiatric or neurological disorders. Ideally, the selection of the paradigm to measure the mental activity of interest should be based on a known behaviour-physiology relation, e.g. resembling the MEP paradigm for M1 tDCS. Next, the effects should be proven in healthy controls first and subsequently tested in patients. However, beyond translation from basic research, to improve knowledge about the potential benefits of tDCS researchers also need to consider experience from clinical applications because it can inform and influence basic research (reverse translation).

Researchers also need to take into account that the effect of the stimulation depends on the “dosage”. In clinical samples receiving tDCS for treatment, one parameter of this dosage is the number and timing of stimulation sessions. In contrast, all of the neuroimaging or neurophysiology studies reported here concentrated on post-stimulation effects of single sessions. Can we simply infer that consecutive tDCS sessions have an additive effect? What are the dynamical aspects of tDCS, i.e. what are the differences between

**Table 7**
Studies that investigated the effects of oscillating transcranial direct current stimulation (otDCS), transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) with electroencephalography (EEG).

| Study | Target measure(s) | Assessment | Condition(s) & polarity* | Design | n | Targets** | | Frequency [Hz]/duration [min] | Specific interaction*** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st electrode | 2nd electrode | | |
| Marshall et al. (2004) | • spectral EEG<br>• declarative (retention of word pairs) and non-declarative memory (mirror tracing) | offline | anodal otDCS<br>sham otDCS | parallel | 30 | F3 + M1 | F4 + M2 | 0.26 mA/cm$^2$/30 during SW-rich sleep and during wake retention interval | active/sham × timing × target × frequency |
| | Results | post otDCS > post sham:<br>during sleep: ↑ declarative memory, sleep depth ↑ toward the end of stimulation period, average power in the faster frequency bands (θ, α, β) ↓, slow oscillatory activity (< 3 Hz) ↑, mood ↑,<br>during wake retention interval: no effect on memory, mood ↑ | | | | | | | |
| Kirov et al. (2009) | • spectral EEG<br>• declarative memory (VLMT) and procedural memory | 1 st exp.: combined<br>2nd exp.: online<br>3rd exp.: online | anodal otDCS<br>sham otDCS | crossover (condition) + parallel (3 exp.) | 16 + 12 + 13 | bilaterally at fronto-lateral locations (F3 & F4) | both mastoids | 0.75/five 5-min epochs of stimulation separated by 1-min stimulation-free intervals | active/sham × timing × target × frequency |
| | Results | during otDCS > during sham: endogenous EEG oscillations (0.4-1.2 Hz) ↑ at frontal leads, EEG theta ↑, encoding of hippocampus-dependent memories ↑ when otDCS applied during learning (no enhancement of consolidation of memories when applied after learning) | | | | | | | |
| Marshall et al. (2011) | • spectral EEG<br>• declarative and procedural memory | combined | anodal theta-otDCS<br>sham theta-otDCS | crossover (condition) + parallel (stimulation NREM/REM) | 25 + 16 | bilaterally at fronto-lateral locations (F3 & F4) | both mastoids | sinusoidal stimulation between 0 and 260 μA/five 5-min epochs of stimulation separated by 1-min stimulation-free intervals | active/sham × timing × target × frequency |
| | | during otDCS > during sham during NREM: ↓ time in SWS, ↓ slow oscillations, ↓ slow frontal spindle activity;<br>post otDCS > post sham during NREM: rebound in slow oscillatory and slow frontal spindle activity, ↓ consolidation of declarative memory (recalled words-pairs);<br>during tDCS > during sham during REM: ↑ gamma activity;<br>post tDCS > post sham during REM: no effect on consolidation of either procedural skills or declarative pair-associate words | | | | | | | |
| Polania et al. (2012) | • delayed letter discrimination<br>• EEG | EEG exp.: offline<br>Behavioural Exp: offline (post only) | theta-tACS: synchronized (0°)<br>desynchronized (180°)<br>sham tACS | crossover | 18 | left DLPFC (F3) + left PPC (P3) | Cz | 6/14 | active/sham × timing × target × phase |

Table 7 (*Continued*)

| Study | Target measure(s) | Assessment | Condition(s) & polarity* | Design | n | Targets** | | Frequency [Hz]/duration [min] | Specific interaction*** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st electrode | 2nd electrode | | |
| | | EEG exp.:<br>post probe presentation > pre probe presentation: ↑ phase synchronisation at 4–7 Hz 200–500 msec after memory probe onset, correlation relative phase between DLPFC and PPC − RTs<br>Behavioural exp.:<br>post tACS synchronisation > post sham: ↓ visual memory-matching RTs;<br>post tACS desynchronisation > both post tACS-synchronisation and post sham: ↑ visual memory-matching RTs | | | | | | | |
| Reato et al. (2013) | SWO during sleep | offline (post only) | anodal otDCS<br>sham otDCS | parallel | 13 + 10 | bilaterally at F3 and F4 | mastoids (M1 and M2) | 0.75 with trapezoid waveform/25 plus four 1-min intervals without stimulation | active/sham × timing × target × frequency |
| | Results | post otDCS > post sham: ↓ homeostatic decay of SWO | | | | | | | |
| Snowball et al. (2013) | • NIRS<br>• arithmetic training | offline | real tRNS<br>sham tRNS | parallel<br>double blind | 25 | left DLPFC (F3) | right DLPFC (F4) | 20 (on 5 days) | |
| | Results | post tRNS > post sham: ↑ speed of both calculation- and memory-recall-based arithmetic learning, more efficient neurovascular coupling within left DLPFC;<br>6 months after training: tRNS > sham group: for calculation problems (old and new), ↓ peak latency and ↑ performance correlation calculation RTs - peak latency of changes in hemodynamic responses | | | | | | | |
| Jausovec and Jausovec (2014) | • WM<br>• ERP | offline (post only) | verum tACS<br>sham tACS | crossover (condition) + parallel (stimulation site) | 24 | • left parietal (P3)<br>• left DLPFC (F3) | above right eyebrow | individual determined theta frequency/15 | active/sham × timing × targets (1st) × frequency |
| | Results | post parietal tACS > post sham: ↑ WM storage capacity, ↓ P300 latency in left hemisphere<br>post prefrontal tACS > post sham: no influence | | | | | | | |
| Voss et al. (2014) | • sleep EEG<br>• dreaming/lucidity | combined | anodal tACS<br>sham tACS | crossover | 27 | F3<br>F4 | TP10<br>TP9 | 2, 6, 12, 25, 40, 100/during REM sleep | active/sham × timing × targets (1st and 2nd) × frequency |
| | Results | during 40/25-Hz tACS > pre tACS: influence on ongoing brain activity (power in lower and upper gamma frequency ↑);<br>post 40/25-Hz tACS > post sham: induction of self-reflective awareness in dreams, correlation gamma frequency ↑ – lucidity | | | | | | | |

DLPFC = dorsolateral prefrontal coretx, EEG = electroencephalography, exp. = experiment, fMRI = functional MRI, GF = gambler's fallacy, mA = milliamperes, min = minutes, msec = milliseconds, (N)REM = (non-) rapid eye movement, NIRS = near-infrared spectroscopy, otDCS = oscillating transcranial current stimulation, PFC = prefrontal cortex, PCC = posterior cingulate cortex, RT = reaction time, SW = slow wave, SWO = slow-wave oscillations, tACS = transcranial alternating current stimulation, tRNS = transcranial random noise stimulation, VLMT = verbal learning memory task, WM = working memory, μA = microamperes, ↑ = increase, ↓ = decrease.

* Polarity = tDCS condition according to the main hypothesis of the respective study (e.g. in a study investigating the main effect of anodal tDCS on verbal fluency the condition is described as "anodal tDCS/sham tDCS").

** Targets = electrode montages, 1st and 2nd electrode = terms to indicate where the anodal and cathodal stimulation electrode is placed by referring to the given stimulation polarity (i.e. for anodal stimulation, the anode refers to the first electrode, for cathodal stimulation, the cathode refers to the first electrode).

*** Specific interaction = see Fig. 2.

one and ten sessions? And how stable are effects across different sessions – is it always the same in the same person? Single stimulation sessions lead to changes in neuronal activity and it is possible that repeated stimulation sessions will increase the probability that the neuronal firing pattern occurs again in the future. To monitor these possible long-lasting tDCS-effects measurements of structural changes by means of Diffusion Tensor Imaging (DTI) and voxel-based morphometry (VBM) will be of particular interest.

Because of the high variability in tDCS responses between and within participants (Chew et al., 2015; Lopez-Alonso et al., 2014, 2015), the small sample sizes used in neuroimaging and NIBS studies are problematic. Gender can influence NIBS effects as well. For this reason, large sample sizes of $n > 50$ are warranted and single-subject results are needed beyond group analyses.

## 9. Conclusions

To conclude, even though sound and systematic investigations into methodological limitations, action mechanisms and functional relevance are clearly needed, prefrontal tDCS seems a feasible tool to influence cognition and, as a consequence, to improve cognitive deficits associated with psychiatric and neurological disorders. In our opinion (Antal et al., 2015), statements that claim little-to-no neurophysiological effect of tDCS (Horvath et al., 2015) are premature and inadequate. Indeed, reported effects are heterogeneous because of the large variety of methods, protocols and designs applied as well as the high variability in brain anatomy, cognitive and personality traits in healthy participants and psychiatric patients. Nevertheless, existing results are generally promising: All studies included in this review detected an effect on at least one monitoring level, with some studies even showing a relation between behavioural and neurophysiological indices.

## 10. Outlook

The current view that tDCS represents an established array of methods in cognitive neuroscience is justified and the potential of tDCS in clinical practice, such as the treatment of depression, is currently under systematic investigation. The reproducibility of prefrontal tDCS effects should be a major aim of future tDCS research in order to evaluate which effects are of enough value to be considered as therapeutically beneficial for patients. Through compliance with the proposed methodological landmarks, studies can contribute to the reliability and consistency of tDCS effects and allow the efficacy of tDCS to be elucidated. Moreover, for future research it is important to utilise neuroimaging and/or neurophysiology findings to evaluate the clinical response to prefrontal tDCS for therapeutic purposes. Very recently, it was shown that information on RSNs alone could predict the response to electroconvulsive treatment (van Waarde et al., 2015). On the other hand, computational models and in vivo recordings are necessary to understand the impact of tDCS on a neuronal level. Because the action of stimulation on neurons is not limited to simple excitation or inhibition, modulations of neural firing patterns and long-term consequences for neurotransmitter and receptor systems are poorly understood and have to be clarified before introducing tDCS as a therapeutic tool. So far, only one study has investigated the effects of prefrontal tDCS on neurotransmitter concentrations by means of MRS (see Table 2) (Hone-Blanchet et al., 2015).

In consideration of the above mentioned methodological issues, we are currently conducting a project consisting of several tDCS studies, each of which aims to recruit a meaningful number of cases, uses a double-blind sham-controlled crossover design and combines task-related and resting-state fMRI data with online and offline tDCS. Furthermore, we are planning one study that will apply combined EEG/fMRI measurements. The rational of this project is to identify the optimal electrode montage for achieving the best effects in WM capacity and its respective neuronal correlates by systematically manipulating the electrode arrangement. Subsequently, we aim to translate this design to psychiatric patients with depression because WM is known to be impaired in those patients.

Finally, imaging tDCS and broader imaging stimulation could both serve as important functional paradigm for challenging neuronal networks in terms of their plasticity in order to obtain further insights into network dynamics and directly identify potential therapeutic applications in neuropsychiatric disorders.

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