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The effect of transcranial direct current stimulation (tDCS) on working memory in schizophrenia.

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III. List of abbreviations

AeCi	Anodal-excitation / cathodal-inhibition
BDNF	Brain-derived neurotrophic factor
cAMP	Cyclic adenosine monophosphate
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CONSIST	Cognitive and Negative Symptoms in Schizophrenia Trial
CRN	Correct response negativity
CRT	Cognitive remediation therapy
DALY	Disability-adjusted life year
dlPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
HD-tDCS	High definition tDCS
ICF	Intracortical facilitation
MCCB	MATRICS Consensus Cognitive Battery
MEG	Magnetoencephalography
MEP	Motor evoked potential
MMN	Mismatch negativity
NMDA	N-methyl-D-aspartate
PAS	Paired associative stimulation
PFC	Prefrontal cortex
rTMS	Repetitive transcranial magnetic stimulation
SICI	Short-interval intracortical inhibition
SMD	Standardized mean difference
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
WHO	World Health Organization

1. Introduction

1.1 Schizophrenia

Schizophrenia is a serious psychiatric disorder associated with a variety of psychological symptoms. The disorder has been described very early in the history of humankind and still is the subject of popular discourse (Kyziridis, 2005). The median point prevalence is 4.6 per 1000 inhabitants (McGrath et al., 2008) and the disorder occurs predominantly between the ages of 15 and 35, with men being affected about three to four years earlier than women (Häfner et al., 2013).

The term schizophrenia itself is a neologism from the ancient Greek verb σχίζειν (split) and the noun φρήν (diaphragm), the place where, according to ancient belief, the soul lives. German psychiatrist Paul Eugen Bleuler introduced the term into the psychiatric discourse in the 20th century.

The psychopathological profile of schizophrenia consists of several symptom dimensions. The so-called positive symptoms are psychotic symptoms, such as hallucinations or delusions. These are most prominently displayed during psychotic exacerbations in which about two thirds of patients respond to adequate pharmacological treatment (Meltzer, 1997). Even without drug intervention, the resolution of a psychotic episode can be attained by supportive measures. Negative symptomatology includes blunted affect, alogia, avolition, anhedonia and social withdrawal (Andreasen, 1982). In addition, 90 % of patients display cognitive impairments in a variety of cognitive domains. Across patients, the severity of the aforementioned symptom dimensions varies, furthermore, whether schizophrenia is an independent entity compared to similar mental illnesses or a supposed continuum of psychosis-related experiences is subject of lively discussion (Johns and Van Os, 2001, Craddock and Owen, 2010). This led, on the one hand, to the establishment of evidence-based guidelines (Tandon et al., 2013), and, on the other hand, to the definition of "research domain criteria" that cover symptoms rather than circumscribed disorders (Sanislow et al., 2010).

Irrespective of academic debate, patients' quality of life is often decisively impaired. In its Global Burden of Disease Report, the World Health Organization (WHO) reports that acute

schizophrenia is the most severely impairing disorder (Whiteford et al., 2013) and is responsible for a considerable number of disability-adjusted life years (DALYs), especially among people aged 10 to 24 (Gore et al., 2011). The negative effects on social participation are further amplified by self-stigmatization and irrational prejudices against patients and psychiatric treatment (Gaebel et al., 2017). In addition to individual impairments, society incurs annual health costs of €14,000 to €18,000 per patient/per year due to the illness, whereby the indirect treatment costs are a multiple thereof due to incapacity to work and early retirement (Konnopka et al., 2009). Further research suggests that psychotic symptoms only cause a small extent of schizophrenia's long-term negative consequences. Rather, cognitive deficits and negative symptoms lead to a reduction in social participation and the ability to work (Green et al., 2004, Green, 2016). So far, this has been insufficiently considered in the definition of treatment goals and the development of novel therapies.

Concerning the etiopathogenesis of schizophrenia, in addition to genetic predisposition multiple influencing factors are postulated within the framework of a biopsychosocial model (Howes and Murray, 2014). From a neurobiological perspective, there is evidence for imbalance of the mesolimbic dopaminergic system (Howes and Kapur, 2009, Breier et al., 1997), as well as morphological changes in the sense of disturbed structural (Burns et al., 2003) and functional connectivity (Liang et al., 2006) between brain areas (discontinuity hypothesis) (Schmitt et al., 2011). Also, (auto-) immunological processes are thought to play a crucial role (Müller, 2014). In summary, it can be stated that the genetic and developmental vulnerability and resilience of a human being is promoted or inhibited by environmental factors.

1.2 Cognitive impairment in schizophrenia

Cognitive deficits in the order of 1-1.8 standard deviations compared with healthy controls are found in 90 % of patients with schizophrenia (Heaton et al., 2001, Palmer et al., 1997). They include nonsocial cognition like perception, memory, attention, planning ability, processing speed, and social cognition. These deficits persist throughout the course of the disorder and predetermine the psychosocial functioning (Green et al., 2004). Functional deficits in cognitive domains impede the pursuit of interests as well as maintenance of

employment and social relations. Thus, cognitive deficits are of major importance with regard to the long-term outcome of treatment, mortality and quality of life (Kurtz et al., 2012). Since they are detectable before the onset of psychosis (Niendam et al., 2003) and can – albeit to a lesser extent – be found in unaffected relatives (Horan et al., 2008), cognitive impairments are considered a possible endophenotype of schizophrenia (Snitz et al., 2005). Although the degree of cognitive impairments is characteristic of schizophrenia, cognitive deficits are also found in other mental illnesses (MacKenzie et al., 2019). Comparisons of cognitive deficits in schizophrenia to those in dementia (Kazui et al., 2011) and bipolar disorder (Bora and Pantelis, 2015) yield a distinctive pattern and magnitude of cognitive impairments in schizophrenia possibly indicating different underlying mechanisms. This underlines the importance of this symptom complex for early detection of mental illness and points to the possibility of early preventive intervention in schizophrenia.

Working memory takes a central position among cognitive functions. The ability to consciously hold and manipulate information is the basis of conscious sensory information processing. Ergo, working memory is necessary for planned action, reasoning, learning and the formation of memory (Baddeley, 1992b). In several meta-analyses, significant deficits in working memory were identified in patients with schizophrenia. Particularly consistent results are available for spatial working memory deficits (Lee and Park, 2005), which are in the order of Cohen's d = 0.51-1.29 (Forbes et al., 2009).

In recent years, the treatment of cognitive deficits in general and working memory in particular came into focus (Lett et al., 2014). However, pharmacological treatment approaches with second-generation antipsychotic substances showed only minimal improvements in certain cognitive domains and no advantage over older antipsychotic substances in the large-scale, multi-center CATIE study (Keefe et al., 2007). Those minimal improvements contrast with potentially harmful consequences of continuous antipsychotic treatment. In animal experiments a decreasing performance of working memory under antipsychotic medication was observed (Castner et al., 2000), accompanied by a reduction of grey matter (Dorph-Petersen et al., 2005). Initial correlative evidence for similar processes in humans exists as well (Ho et al., 2011).

Another treatment approach targets the modulation of the glutamatergic rather than the dopaminergic system. Neuronal transmission via NMDA receptors is essential for cognitive performance (Wang et al., 2013) and is known to be impaired in schizophrenia (Olney et al., 1999). However, attempts to improve transmission via the substrates glycine and D-cycloserine failed in the CONSIST study (Buchanan et al., 2007). Further neurochemical treatment approaches include modulation of the GABAergic (Buchanan et al., 2011), nicotinergic (Schubert et al., 2006) and monoaminergic systems (Barch and Carter, 2005). Conducted studies yielded mixed results and a recent meta-analysis across 93 studies reports a significant but minimal effect size, Hedges' $g = 0.1$ (Sinkeviciute et al., 2018).

Alternative approaches focus less on neurochemical alterations of the transmitter balance and more on the cognitive abilities themselves. In the knowledge that repeated cognitive effort leads to neuronal plasticity and learning (Colom et al., 2016, Olesen et al., 2004), cognitive training studies have been undertaken. This approach, also called cognitive remediation therapy (CRT), can be carried out as drill and practice training or as metacognitive training. With the former, the patients are trained repeatedly and mostly computer-assisted on one or several cognitive tasks, whereas in metacognitive training, the patients are explicitly taught learning and compensation strategies. The first approach aims at improving lower-level sensory and cognitive function by stimulating neuroplastic processes which are thought to generalize to higher-level cognitive skills (bottom-up). The second, top-down approach assumes that improvements of complex cognitive functions will generalize to other, less complex cognitive functions. Meta-analyses confirm CRT effect sizes in the order of Cohen's $d = 0.4$-0.5, irrespectively of the chosen approach (Wykes et al., 2011).

In addition to behavioral improvements, numerous indications of changes in brain structure and its connectivity through cognitive training were observed. Wykes and colleagues reported an increased activation of frontal regions after working memory training (Wykes et al., 2002), and there is evidence that CRT may slow down the loss of grey matter in early schizophrenia (Eack et al., 2010). In addition to the described functional and morphological changes of the brain, elevated BDNF provides a further indication of a neuroplastic intervention having occurred (Fisher et al., 2009). With the aim of increasing neuroplasticity,

the combination of different neuroplastic interventions, such as CRT, brain stimulation procedures or pharmacological therapy approaches could lead to more pronounced and more sustainable effects (Cramer et al., 2011). Other, initially unspecific interventions, such as sleep, physical activity or the consumption of nicotine, should also be investigated with regard to their neuroplastic properties and integrated into an overall therapeutic concept.

Additionally, the close relationship between negative symptoms and cognitive deficits should be noted. In spite of the ambiguity regarding the direction of the causal relationship, a mutual relationship to social and nonsocial cognition can be assumed. Consequently, CRT improves negative symptoms of patients with schizophrenia with an effect size of Hedges' g = 0.3-0.4 as well (Cella et al., 2017, Linke et al., 2019).

1.3 Dorsolateral prefrontal cortex

The prefrontal cortex (PFC) is an evolutionary young neocortical structure (Fuster, 2015). It is strongly developed in primates and humans and is essential for higher cognitive functions that are considered to be particularly human (Deacon, 1997, Fuster, 2002). These functions are necessary to analyze the information continuously perceived from the environment and to create goal-directed behavior from this flood of information. The orchestration of thoughts and actions in accordance with internal goals (top-down control) is conceptualized under the term "cognitive control" (Miller, 2000).

In order to fulfill this superordinate and integrative function, the PFC projects into various cortical and subcortical structures (Figure 3) and forms a neurophysiological hub. Anatomically, the prefrontal cortex is subdivided into several topographical regions, the dlPFC being discussed in more detail in this dissertation. It consists of parts of the superior and middle frontal gyrus, which corresponds to Brodman areas 46 and 9/46 (Petrides and Pandya, 1999). The dlPFC is associated with cognitive processes such as cognitive control (MacDonald et al., 2000), reasoning, decision making, planning ability, executive functions, working memory (Curtis and D'Esposito, 2003), moral decisions, social cognition and meta-cognition. From this enumeration it becomes clear that the dlPFC is not a highly specialized brain area, but provides the cytoarchitecture and connectivity for different cognitive processes.

The function of the PFC including the dlPFC is altered in schizophrenia. For example, in a variety of cognitive tests based on prefrontal functions, patients with schizophrenia show significant deficits compared to healthy control groups, but also to groups with other mental disorders (Bora and Pantelis, 2015). Structurally, a reduction of the grey matter in the PFC (Fornito et al., 2009) and a change in the integrity of the white matter can be detected using imaging procedures (Lim et al., 1999, Kubicki et al., 2005). With functional imaging, an altered activation signature during cognitive tasks and reduced connectivity to other brain areas in schizophrenia have been replicated multiple times (Meyer-Lindenberg et al., 2005, Zhou et al., 2007). At the neurotransmitter level, there is a deficit in dopamine release in prefrontal and further cortical brain areas during cognitive tasks (Slifstein et al., 2015), which contrasts considerably with dopamine excess in striatal brain structures and illustrates a global imbalance of dopamine (Weinstein et al., 2017). Due to the pathophysiological alteration in the structure and function of the dlPFC in schizophrenia and its importance for cognitive abilities, the dlPFC represents a rational target for neuromodulatory interventions.

1.4 Working memory

Working memory plays a central role for cognitive processes. It describes the ability to keep information in consciousness for a short time and to manipulate it. Working memory as a neuropsychological construct was first introduced by Alan Baddeley (Baddeley, 1992a). He described three subcomponents of working memory: the central executive that controls the focus of attention, the visuospatial sketchpad for manipulating visual impressions, and the phonological loop for storing and retrieving acoustic information. In 2000, Baddeley extended this model to include the episodic buffer, a system capable of integrating different information modalities (Figure 1) (Baddeley, 2000).

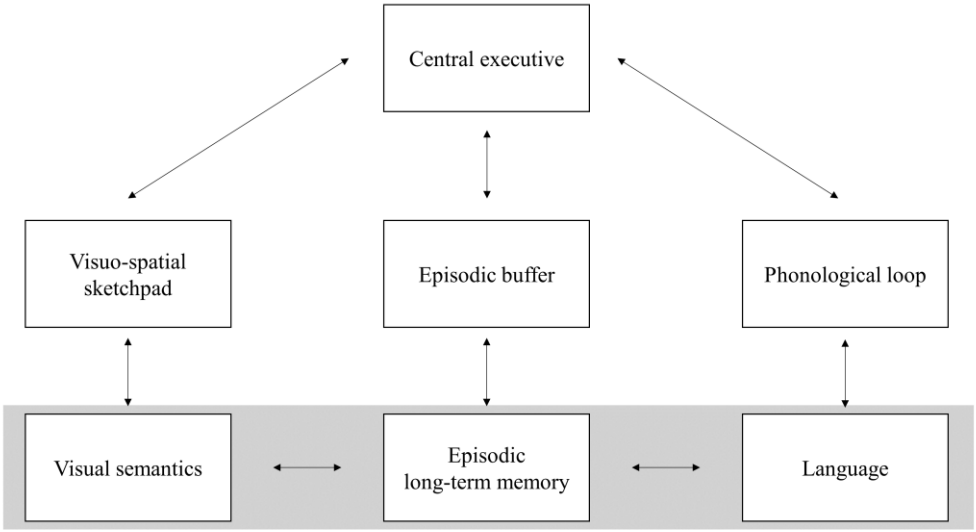

Figure 1: Baddeley's working memory model.
Adapted and modified from Baddeley (2000), Trends in Cognitive Sciences

Working memory is a necessary prerequisite for cognitive operations such as learning or reasoning and plays a decisive role in academic success (Gathercole et al., 2003) and fluid intelligence (Engle et al., 1999). It is assumed that working memory capacity is limited, albeit the possibility of increasing this capacity through training is discussed. A robust increase in working memory performance is found after specific training paradigms, which translates to similar tasks (Peijnenborgh et al., 2016, Schwaighofer et al., 2015). The possibility of transfer to other cognitive domains or an increase in fluid intelligence is in debate (Jaeggi et al., 2008, Melby-Lervåg et al., 2016, Sala and Gobet, 2018). The activation of a fronto-parietal network – a neurophysiological correlate of working memory – can be measured by fMRI. Additional quantitative methods, such as MEG and EEG, show an increased synchronicity of brain activation between these areas. The degree of synchronicity is positively correlated with the amount of information held in working memory (Palva et al., 2010). Causal evidence for the necessity of long-range connectivity for the performance of a working memory task is derived from a landmark study by Robert Reinhart and John Nguyen. They could show that working memory deficits in elderly people emerge from disconnected brain circuits. Through

non-invasive modulation of long-range theta interactions, the information flow between frontal and temporal cortex could be reinstated and working memory deficits were remedied (Reinhart and Nguyen, 2019).

The dorsolateral prefrontal cortex plays the central role in working memory function (Curtis and D'Esposito, 2003). This hypothesis is supported by lesion studies (Müller and Knight, 2006, Pribram et al., 1952) as well as functional imaging techniques (Rottschy et al., 2012), which show activity during short-term storage of working memory content. On the other hand, there are further studies that show no limitation of working memory after lesions of the prefrontal cortex (D'Esposito and Postle, 1999). Therefore, Curtis and Esposito postulated that sensory working memory content is stored in posterior sensory areas, whereas the prefrontal cortex has control over the retrieval process (Curtis and D'Esposito, 2003). There is also cautious evidence for the laterality of the dlPFC. The right dlPFC is assumed to be responsible for spatial information, the left dlPFC for verbal information (Nagel et al., 2013).

1.5 N-back task

The n-back task is an established method for determining the functionality and performance of working memory. There are several variants of this test, which was established by Gevins and Cutillo and is performed on a computer screen (Gevins and Cutillo, 1993). A series of visual stimuli with verbal or spatial information content is presented. The stimuli presented are to be memorized and updated continuously by the subject. The aim is to react, by means of a correct and fast keystroke, to a stimulus that was previously presented *n* stimuli earlier. By changing the parameter *n*, the degree of difficulty of the working memory task can be adjusted. In the included studies, 1-back, 2-back and 3-back levels of difficulty were administered. For each difficulty level, the sensitivity index *d*' was calculated according to the formula: *d*'' = Z(hit rate)-Z(false alarm rate).

In the studies described in this dissertation, n-back tasks with spatial information content (position of a blue square on the screen) and verbal information content (letters) are used. Imaging and stimulation studies showed that the right dlPFC is more involved in spatial information processing, whereas the left dlPFC performs this function for verbal content (Nagel et al., 2013). In addition, parietal areas are activated indicative for the fronto-parietal

network of working memory (Owen et al., 2005). Accordingly, the laterality of the tDCS target structure was selected to match the modality of stimulus presentation in the n-back task.

1.6 Transcranial direct current stimulation

Priori and colleagues (Priori et al., 1998), followed by Nitsche and Paulus (Nitsche and Paulus, 2000), could show that tDCS modulates the excitability of the cortex under the stimulation electrode. The change of excitability depends on the polarity of the stimulation and electrode positioning. Anodal tDCS increases the excitability of the cortex, hereby increasing the probability of occurrence of an action potential, whereas cathodal stimulation has the opposite effect (although it must be noted that this dichotomy is an oversimplification). Motor cortex studies have shown that a single session of 20-30 minute anodal stimulation increases the excitability of the motor cortex for about one hour (Nitsche and Paulus, 2001). Numerous studies have shown that the use of tDCS leads to perfusion changes in local and associated areas (Stagg et al., 2013) as well as changes in brain connectivity (Keeser et al., 2011). The application of tDCS has many degrees of technical freedom. More degrees of complexity are added by the interaction with a constantly active brain (Figure 2). This naturally results in a significant brain state-dependency of tDCS effects (Silvanto et al., 2008), which might contribute to observed non-linear effects of the stimulation (Batsikadze et al., 2013). Effects beyond the stimulation period are of particular interest for the application in patients. It has been shown that the repeated application of tDCS combined with cognitive tasks leads to behavioral and neurophysiological changes which remain detectable for months after the end of stimulation (Ruf et al., 2017, Möller et al., 2017, Au et al., 2016). Long-lasting effects of tDCS can be explained by neuroplastic processes due to changes in protein synthesis as well as intracellular calcium and cAMP levels (Islam et al., 1995, Hattori et al., 1990). The use of tDCS has few side effects (Brunoni et al., 2011) and the repeated use of stimulation did not provide any evidence of structural damage to the brain (Schwippel et al., 2017).

1.7 Effects of tDCS on working memory

1.7.1 Effects of tDCS on working memory in healthy subjects

The modulation of working memory is mostly tested via the use of tDCS on the dlPFC. Various stimulation variants were investigated, including HD-tDCS, anodal tDCS, cathodal tDCS as well as tACS targeting brain oscillations.

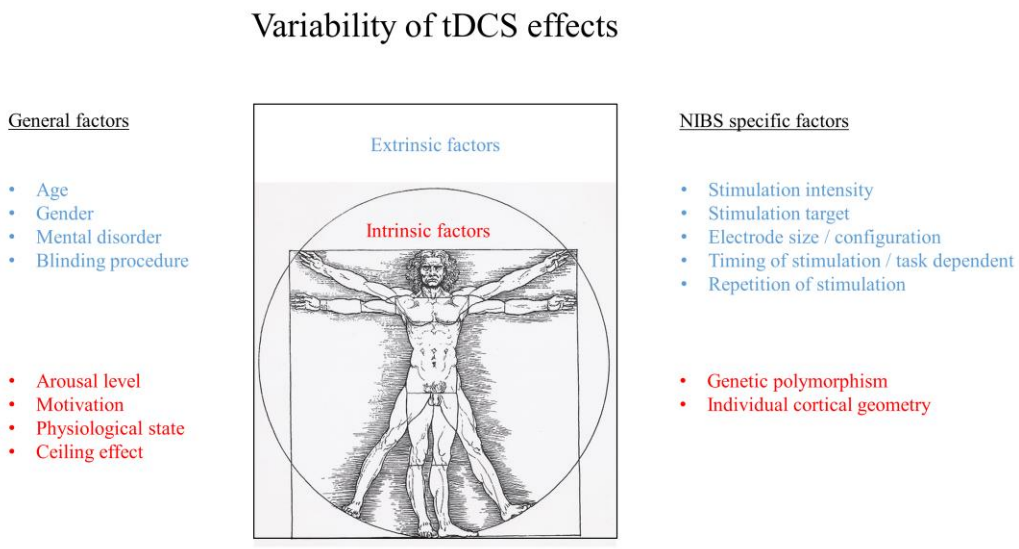

Figure 2: Variability of tDCS effects

Adapted from Polania et al. (2018), Nature Neuroscience

Picture by Hans Bernhard, https://commons.wikimedia.org/wiki/File:Vitruvianischer_Mann.jpg

In healthy subjects, experiments consisting of prefrontal tDCS on cognitive functions (Brunoni and Vanderhasselt, 2014), such as working memory or planning ability, showed behavioral effects during and shortly after application of stimulation. In order to achieve lasting and potentially clinically relevant effects, tDCS is applied over several days or weeks (Brunoni and Vanderhasselt, 2014, Hill et al., 2016). Since tDCS itself, unlike transcranial magnetic stimulation (TMS), does not trigger any action potentials, the effects are decisively determined by the current activity of the cortical neurons. This circumstance enables targeted stimulation by combining tDCS and cognitive activity. Following that hypothesis, first tDCS-supported training paradigms were developed in which tDCS is performed during a cognitive

task over several sessions (Ruf et al., 2017). This approach showed promising results, especially as the cognitive improvements were detectable up to 6 months after application (Au et al., 2016, Katz et al., 2017, Ruf et al., 2017).

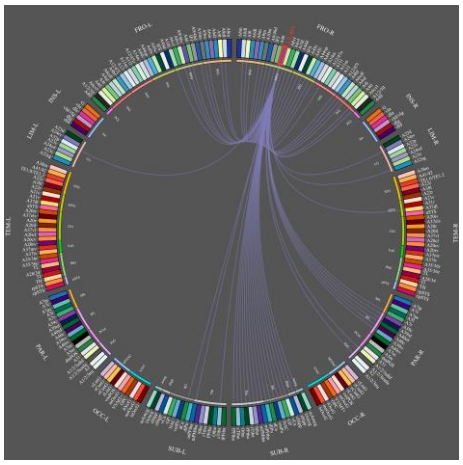

Figure 3: Connectogranm of the right dlPFC
http://atlas.brainnetome.org

1.7.2 Effects of tDCS on working memory in schizophrenia

Starting in 2011, the effect of tDCS on cognition in schizophrenia was investigated. The initial aim was to increase insufficient activity of dlPFC by anodal stimulation. The author of this dissertation identified 20 studies on this topic until September 2019 (Table 1). Only 6/20 studies focused on working memory as the primary outcome. Of these six studies, five studies yielded positive results for the use of anodal stimulation, with contradictory results for the superiority of a specific stimulation intensity. It is also important to differentiate between the single application of tDCS compared to training paradigms. Furthermore, patients perform the working memory task during stimulation (online stimulation) or after the application of stimulation (offline stimulation).

More studies measured a change in working memory in the context of a general study of cognition, for example in the form of the MCCB. In these studies, heterogeneous results are reported. Besides a number of negative findings (Moon et al., 2019, Rassovsky et al., 2018, Gomes et al., 2018, Shiozawa et al., 2016, Rassovsky et al., 2015), several positive findings regarding working memory (Narita et al., 2017, Impey et al., 2017, Nienow et al., 2016,

Padinjareveettil et al., 2015, Smith et al., 2015, Hoy et al., 2014, Schwippel et al., 2018b, Papazova et al., 2018, Orlov et al., 2017), other cognitive parameters (Goder et al., 2013, Vercammen et al., 2011) or negative symptoms (Gomes et al., 2018, Narita et al., 2017) exist.

Regarding neurophysiological changes induced by tDCS, Kate Hoy and colleagues described a significant increase in gamma event-related activity in left dlPFC after 2 mA anodal tDCS of this cortical region. This increase correlated with the behavioral improvement of working memory performance (Hoy et al., 2015). Furthermore, there are hints to the modulation of mismatch negativity (MMN) in conjunction with reaction times during an n-back task (Impey et al., 2017). Similarly, the correct response negativity (CRN) is modulated after 10 tDCS sessions (Moon et al., 2019). The most elegant proof of a connection between tDCS (20 min anodal 1.5 mA tDCS of the medial prefrontal cortex), neurophysiology (theta-oscillations) and cognition (adaptive control) was published by Robert Reinhart and colleagues (Reinhart et al., 2015). They demonstrated that slow oscillations with disturbed synchronicity in the prefrontal cortex are responsible for processing errors in schizophrenia. An intervention with tDCS succeeded in increasing synchronicity of oscillations and improved adaptive control. Thus, the causal connection between cortical dysconnectivity and executive control was experimentally verified.

In summary, there is initial evidence for the beneficial effect of anodal tDCS on the working memory of patients with schizophrenia (Mervis et al., 2017). However, a number of restrictions apply: Successful blinding is not guaranteed in the majority of studies, and working memory was often part of a conglomeration of cognitive parameters rather than primary outcome. Multicenter studies are lacking, as is the investigation of cathodal tDCS or tACS.

1.8 Hypotheses

The studies outlined in this dissertation are among the first steps towards the establishment of a neuromodulatively supported cognitive training paradigm in patients with schizophrenia. With this goal in mind, the conducted studies aim to determine the effective tDCS parameter range regarding current intensity and target region for the enhancement of working memory in schizophrenia. Further information on the experimental design and previous work in this field has been published in the journal Nervenheilkunde by the author of this dissertation (Schwippel et al., 2018a). The following hypotheses were tested in two separate experiments conducted in Tübingen and Munich:

I. Anodal tDCS increases working memory performance in patients with schizophrenia.

II. The effects of anodal tDCS on working memory are intensity specific.

III. Cognitive baseline performance and working memory task difficulty modulate the effect of tDCS.

Table 1: Effect of tDCS and tACS on cognition in schizophrenia

STUDY	N	STUDY DESIGN	COGNITIVE INTERVENTION	TDCS INTERVENTION	TDCS PARAMETER	OUTCOME	RESULTS
Moon et al. 2019 **(MOON ET AL., 2019)**	10	Non-blinded, case series	None	10 sessions/1 week, twice a day	2 mA tDCS with anode between F3+FP1 and cathode between T3+P3	Cognitive tasks: digit span, WCST, CVTL, TMT-B, SWM EEG during flanker task	Significant improvement of WCST, CVLT, TMT-B. No change in SWM and digit span. No significant effect on EEG.
Weickert et al. 2019 **(WEICKERT ET AL., 2019)**	12	Double-blind, RCT, sham, parallel design	Spatial 2-back	20 sessions/4 weeks	Anodal 2 mA tDCS to the right dlPFC, cathode on left temporo-parietal junction, for 20 minutes	Auditory verbal hallucinations (AHRS) and cognition (MCCB)	No effect of tDCS on spatial 2-back or auditory hallucinations. Transfer: 2 mA anodal/cathodal tDCS improved language based working memory after 2 weeks and verbal fluency after 2 and 4 weeks.
Chang et al. 2019 **(CHANG ET AL., 2019)**	60	Double-blind, RCT, sham, parallel design	None	Twice daily/5 days	Anodal 2 mA tDCS to left dlPFC, cathode on left temporo-parietal junction, for 20 minutes	Cognitive Insight and neurocognitive functioning, psychopathology	No effects of tDCS on CGI, PANS positive, PANSS negative, GAF score, SRG-PSP global. Significant effect on PANSS total and PANSS general, on cognitive insight. Only trend towards improvement in Tower of London.
Lindenmayer et al. 2018 **(LINDENMAYER ET AL., 2019)**	28	Double-blind, RCT, sham, parallel design	None	Twice daily/4 weeks	2 mA tDCS with cathode over left temporo-parietal junction and anode over left dlPFC, for 20 minutes	PANSS, MCCB, AHRS	Primary outcome AHRS was significantly more reduced in tDCS group. Working memory was improved in the tDCS group compared with sham.
Jeon et al. 2018 **(JEON ET AL., 2018)**	56	Double-blind, RCT, parallel design	None	10 sessions/2 weeks	Anodal 2 mA tDCS to left dlPFC, cathode over right dlPFC, for 30 minutes	MCCB, WCST, PANSS, CGI, CDSS, 3-month follow up	Significant effect of tDCS on MCCB working memory and composite score.
Schwippel et al. 2018 **(SCHWIPPEL ET AL., 2018B)**	32	Double-blind, RCT, sham, cross-over design	Spatial n-back (1,2,3-back)	Single session	Anodal/sham tDCS to the right dlPFC for 21 min. Experiment I: 1 mA; Experiment II: 2 mA	N-back performance (d')	2 mA anodal tDCS improved working memory performance in the 3-back condition.
Papazova et al. 2018 **(PAPAZOVA ET AL., 2018)**	40	Double-blind, RCT, sham, cross-over design	Verbal n-back (1,2,3-back)	Single session	Anodal/sham tDCS to the left dlPFC for 21 min. Experiment I: 1 mA; Experiment II: 2 mA	N-back performance (d')	Independent of intensity, tDCS improved working memory performance. Further analyses pointed towards improvement with 1 mA only.
Rassovsky et al. 2018 **(RASSOVSKY ET AL., 2018)**	37	Single-blind, RCT cross-over design	None	Single session	2 mA anodal/cathodal/sham tDCS to the left dlPFC for 20 min	BPRS, SANS, social cognition and MCCB	No effect of tDCS on any outcome. Working memory was only improved with sham stimulation.
Gomes et al. 2018 **(GOMES ET AL., 2018)**	24	Double-blind, RCT	None	10 sessions/2 weeks	2 mA anodal/sham tDCS to the left dlPFC	Primary: Working memory score (MCCB) Secondary: PANSS negative score	No effect of tDCS on cognition. Improvement of PANSS negative score after intervention and after 3 month.
Narita et al. 2017 **(NARITA ET AL., 2017)**	28	Non-blinded, case series	None	10 sessions/1 week, twice a day	2 mA anodal tDCS for 20 min to F3	Primary: BACS change after 1 month Secondary: Functional capacity (UPSA Score), PANSS and CDSS	Significant improvement of cognition and functional capacity, CDSS and PANSS scores after 1 month.

Impey et al. 2017 **(IMPEY ET AL., 2017)**	12	Double-blind, RCT cross-over design	None	Single session	2 mA anodal tDCS for 20 min to the left temporal cortex(between C5/C7) or F3	Primary: MMN Secondary: Working memory (1-,2-back task)	Higher accuracy in the 2-back task after F3 tDCS in comparison to sham and C5/C7 tDCS.
Orlov et al. 2017 **(ORLOV ET AL., 2017)**	49	Double-blind, RCT, parallel design	Baseline session, followed by 8 training sessions on day 0, 2, 14, 56	tDCS during training session 2 and 6	2 mA anodal tDCS for 30 min to F3.	Primary: Working memory Secondary: CogState battery	Significant improvement of working memory at the day following tDCS. No effect during stimulation.
Shiozawa et al. 2016 **(SHIOZAWA ET AL., 2016)**	9	Double-blind, RCT, parallel design	Working memory training (n-back) and sequence learning.	10 sessions/ 1 week, during cognitive training	2 mA anodal tDCS for 20 minutes to F3.	Primary: n-back performance	No improvement with tDCS compared to sham stimulation.
Nienow et al. 2016 **(NIENOW ET AL., 2016)**	10	Single-blind, RCT, parallel design	48 sessions of adaptive cognitive training in 16 weeks	28 sessions of tDCS starting in the third week for 20 minutes of training	1 mA anodal stimulation to F3.	Primary: 2-back task Secondary: MCCB composite score	Improvement of working memory with tDCS compared to sham. No transfer to MCCB composite score.
Rassovsky et al. 2015 **(RASSOVSKY ET AL., 2015)**	36	Single-blind, RCT, parallel design	None	Single session	2 mA bilateral tDCS for 20 min to Fp1 and Fp2 (each 1 mA)	Primary: Social Cognition (MSCEIT, FEIT, PONS, TASIT) Secondary: MCCB	Significant improvement of face recognition with stimulation (FEIT). Other tasks with no significant changes.
Padinjareveetil et al. 2015 **(PADINJAREVEETTIL ET AL., 2015)**	2	Case report	20 sessions of cognitive training in 4 weeks	12 sessions of tDCS, 3 sessions/week	2 mA anodal tDCS for 30 min to T3	Primary: MCCB Secondary: Functional capacity (UPSA)	Improvement of working memory, memory and reasoning. Effects were partially stable after 1 month.
Smith et al. 2015 **(SMITH ET AL., 2015)**	33	Double-blind, RCT, parallel design	None	5 sessions of tDCS/~ 9d	2 mA anodal tDCS for 20 min to F3	Primary: MCCB Secondary: PANSS	Anodal tDCS significantly increased the MCCB composite score, subscores of working memory and attention.
Hoy et al. 2014 **(HOY ET AL., 2014)**	18	Double-blind, RCT, cross-over design	None	Single session	1 mA/2 mA anodal or sham tDCS for 20 min to F3.	Primary: N-back performance 0, 20 and 40 min after tDCS	Significant improvement of working memory performance with 2 mA anodaler tDCS after 20 and 40 min.
Goder et al. 2013 **(GODER ET AL., 2013)**	14	Non-blinded, sham controlled, cross-over design	None	Single session. Start of tACS 10 min after start of sleep stage 2.	tACS with 0.75 Hz, between 0 and 300 µA for 20 min. Bilateral electrodes over F3 and F4	Primary: Auditory-Verbal Learning Test Secondary: Procedural learning (mirror tracing), digit span	Improved retention of verbal memory and mood after tACS.
Vercammen et al. 2011 **(VERCAMMEN ET AL., 2011)**	20	Single-blind, RCT, cross-over design	Probabilistic association test	Single session	20 mA anodal tDCS to F3.	Primary: Probabilistic association test	No effect of tDCS on probabilistic associative learning. Hints for the influence of baseline performance in tDCS effects.

Table modified and taken from Schwippel et al. 2018, Nervenheilkunde
AHRS: Auditory Hallucination Rating Scale, **BACS**: Brief Assessment of Cognition, **BPRS**: Brief Psychiatric Rating Scale, **CDSS**: Calgary Depression Scale for Schizophrenia, **CGI**: Clinical Global Impression, **CVTL**: California Verbal Learning Test, **FEIT**: Facial Emotion Identification Test, **GAF**: Global Assessment of Functioning, **MCCB**: MATRICS Consensus Cognitive Battery, **MMN**: Mismatch negativity, **MSCEIT**: Mayer–Salovey–Caruso Emotional Intelligence Test, **N**: Number of subjects, **PANSS**: Positive and Negative Syndrome Scale, **PONS**: Profile of Nonverbal Sensitivity, **SANS**: Scale for the Assessment of Negative Symptoms, **SRG-PSP**: Self-reported version of Social Performance Scale, **SVM**: Spatial Working Memory Test, **TASIT**: The Awareness of Social Inference Test, **TMT**: Trail Making Test, **UPSA**: UCSD Performance-based Skills, **WCST:** Wisconsin Card Sorting Test

2. Results

2.1 Schwippel et al. 2018

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Beneficial effects of anodal transcranial direct current stimulation (tDCS) on spatial working memory in patients with schizophrenia

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Abstract
Schizophrenia is a severe and often detrimental psychiatric disorder. The individual patients' level of functioning is essentially determined by cognitive, particularly working memory (WM), deficits that are critically linked to dysfunctional activity of the dorsolateral prefrontal cortex (dlPFC). Transcranial direct current stimulation (tDCS) can transiently modulate activity of the dlPFC and remote areas and has been shown to improve WM functions. It may therefore provide a new, targeted treatment option.

For this aim, the present study investigated the effect of anodal tDCS of different intensities on spatial WM in patients with schizophrenia. In two experiments, 32 patients performed a spatial *n*-back task with increasing WM load (1-, 2-, and 3-back) at baseline and in two sessions with anodal or sham tDCS (EXP I [$n = 16$]: 1 mA; EXP II [$n = 16$]: 2 mA) to the right dlPFC (cathode: left m. deltoideus). With 1 mA anodal tDCS, no effect on WM performance could be detected. However, 2 mA anodal tDCS increased accuracy (measured by d') of the task with the highest WM load (3-back). This effect was larger in patients with a lower level of general neurocognitive functioning.

These results demonstrate a beneficial effect of 2 mA anodal tDCS on deficient WM accuracy in patients with schizophrenia particularly under challenging conditions and in subjects with

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sham-controlled cross-over studies. After a neurocognitive and psychopathological assessment, the baseline *n*-back task performance was assessed on Monday. Subsequently anodal and sham tDCS sessions were performed on Wednesday and Friday in randomized order. The daytime of the randomized sessions was similar within each patient. Primary outcome was the difference of n-back performance during tDCS and sham stimulation quantified by the baseline adjusted discriminability index d'. The participants received a financial compensation after completion of the last session. The experiment was conducted in accordance to the declaration of Helsinki and was approved by the local ethics committee. All participants gave written informed consent prior to start of the experiment. The trial was registered on clinicaltrials.gov (NCT02823639).

2.2. Patients

32 right-handed patients at the age of 18–60 years with diagnosed schizophrenia (DSM-5) participated in both experiments. The patients were either hospitalized or received outpatient treatment. The medication was kept stable one week before and during the week of experiments with the permission of rescue medication. In experiment I, all patients received antipsychotic medication (experiment I: 2 olanzapine; 3 quetiapine; 2 aripiprazole; 1 ziprasidone; 1 risperidone + quetiapine; 1 risperidone + aripiprazole; 1 risperidone + perphenazine; 1 quetiapine + paliperidone; 1 quetiapine + aripiprazole; 1 quetiapine + perphenazine; 1 haloperidol + aripiprazole; 1 zuclopenthixol + prothipendyl), whereas in experiment II, all but one patient received antipsychotic medication (experiment II: 4 olanzapine; 1 clozapine; 1 aripiprazole; 1 quetiapine; 1 paliperidone; 1 clozapine + haloperidol; 1 aripiprazole + olanzapine; 1 haloperidol + aripiprazole; 1 risperidone + quetiapine; 1 risperidone + quetiapine; 1 aripiprazole + risperidone; 1 aripiprazole + quetiapine; 1 risperidone + quetiapine + aripiprazole). Use of antiepileptic drugs or benzodiazepines > 1 mg lorazepam equivalent was not allowed. Other exclusion criteria included previous seizures, brain implants, cardiac pacemakers, substance dependence with current substance abuse (excluding nicotine) and pregnancy.

2.3. Clinical and cognitive assessment

Prior to the first session, the diagnosis was verified using the M.I.N.I. International Neuropsychiatric Interview in each patient (Sheehan et al., 1998). Handedness was confirmed with the Edinburgh Handedness Questionnaire. The extent of tobacco dependence was measured with Fagerstrom Questionnaire. The Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS) were conducted to quantify psychopathology. Several neurocognitive tests were applied to measure cognitive flexibility (Trail Making Test B, TMT-B), premorbid intelligence (multiple-choice word test, MWT-B), attention and working speed (d2 Test of Attention, d2). The Positive and Negative Affect Schedule (PANAS) was administered before and after each stimulation session. The PANAS and a supplementary adverse effects questionnaire with 6 items was rated with a 5-level Likert scale (1 = no side effect/2 = slight side effect/3 = moderate side effect/4 = considerable side effect/5 = extreme side effect). A summary of demographic data, clinical and cognitive assessments is presented in Tables 1 and 2.

2.4. Transcranial direct current stimulation

Stimulation was performed with a CE-certified DC device (Neuroconn GmbH, Ilmenau, Germany) with 1 mA respectively 2 mA for 21 minutes. The stimulation was started 1 min before the n-back task and was maintained throughout the task. A ramp up and down of 15 s was configured. The anode (35 cm^2), targeting the right dlPFC, was placed over F4 according to the international 10–20 EEG system with the cathode (35 cm^2) placed extracephalic on the contralateral deltoid muscle (Figure 1). The skin was prepared with ethanol and abrasive skin paste to remove dead skin before the electrodes were placed. The extracephalic electrode was fixated with adhesive tape, the anode was secured with a common EEG cap. The order of the tDCS sessions was counterbalanced. Blinding of the experimenter was ensured using the study mode of the DC-device (8 s ramp up, 40 s stimulation, 5 s ramp down). Blinding success and side effects were queried after each stimulation session.

2.5. Spatial *n*-back task

The *n*-back task is a common experimental paradigm to investigate WM. The subjects were asked to monitor a series of stimuli and to respond if a stimulus is presented at the same location than *n* stimuli before, where *n* is a predefined integer (Figure 1). This task encompasses monitoring, updating and manipulating of information. The WM load is adjusted by the value of *n* (Jaeggi et al., 2010).

For this study, a spatial *n*-back task was programmed with PsychoPy Version 1.83.04 (Peirce, 2007). The task encompassed a 1-back, 2-back and 3-back task in ascending order. Each *n*-back difficulty was administered for six minutes with a pause of 60 s in between. All *n*-back tasks comprised 120 + *n* stimuli (3 × 3 cm blue square), which occurred randomly on eight screen positions for 0.5 s. The inter-stimulus interval was set at 2.5 s and 25% of the stimuli were correct targets. The patients were thoroughly instructed to push a specific button on the keyboard as fast as possible, in case a correct target was displayed. No action was demanded, if a false target was presented. The patient's understanding of the task was verified prior to every session with a short paper test. The patients sat in front of a computer screen (distance approx. 40 cm) and were instructed to use their right hand to press the button. An EEG cap was worn during all sessions, while an EEG was recorded in the first session. In the second and third session, the same EEG cap was used to fixate the tDCS electrode on the scalp.

Based on signal detection theory, the discriminability index d' (d-prime) was calculated by using the formula d' = Z(hit rate) − Z(false alarm rate) (Stanislaw and Todorov, 1999). A maximization of correct responses (hits), together

Table 1. Demographic and clinical data.

	Experiment I	Experiment II	*p*
n	16	16	
Female/male	4/12	5/11	.694
Inpatient/outpatient	4/12	3/13	.669
Age (years)	32 ± 7.5	37.3 ± 11.3	.128
Education (years)	14 ± 2.6	15.8 ± 3.6	.124
Fagerstrom	5.9 ± 1.2	2.7 ± 3.2	.002 *
Chlorpromazine equivalents (mg)	669.4 ± 378.4	547.8 ± 237.7	.298
PANSS positive	10.5 ± 4.2	13.8 ± 5.1	.063
PANSS negative	16.6 ± 8.6	14.3 ± 6.8	.407
PANSS general	24.9 ± 7.6	23.3 ± 6	.503
PANSS total	51.9 ± 15.5	51.3 ± 14.8	.92
CDSS	4 ± 4.2	2.6 ± 3.1	.283
TMT-A (s)	30.1 ± 12.7	29.7 ± 10.8	.921
TMT-A (norm)	97.3 ± 22.2	97.3 ± 14.7	.993
TMT-B (s)	77.25 ± 25.5	85.8 ± 51.4	.673
TMT-B (norm)	87.8 ± 12.8	92.4 ± 22.8	.494
D2-GZ	393.3 ± 106.7	400.6 ± 113.6	.855
MWT - B (norm)	103.3 ± 14.6	106 ± 14.7	.608

Data is presented with ± 1 STD. MWT-B and TMT performance was transformed with age adjusted normative data (norm). *t*-test is used for normal distributed interval data, Man-Whitney U test was performed when the assumption of normality was rejected, Fischer's exact test was used for categorical data.

* $p < .05$.

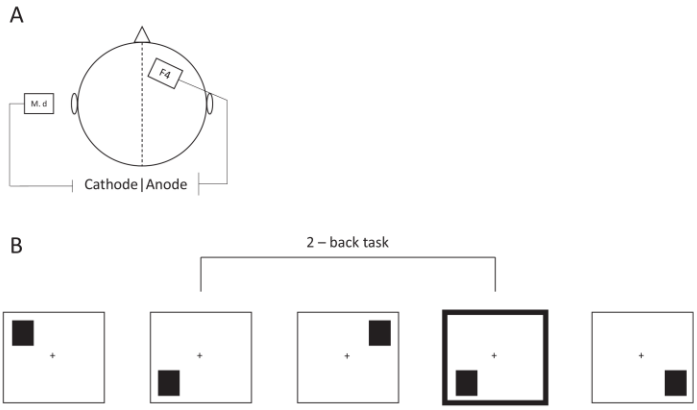

Figure 1. (A) tDCS Electrode placement with anode over F4 and cathode over the deltoid muscle (M.d). (B) Example of a 2-back task. Correct target is labelled by a bold frame.

with a minimization of incorrect responses (false alarms) will lead to a higher d' values, displaying the patient's ability to discriminate between target and non-target stimuli (Haatveit et al., 2010). Adjustment for baseline performance was achieved by dividing the n-back level-specific d' by the corresponding value of the baseline session. A baseline session was included to improve performance stability and to focus the analysis on stimulation-dependent variability by means of an individual baseline adjustment. To assess the effects of tDCS on response speed independent of response accuracy, mean reaction times of all responses (hits and false alarms) were included in the statistical analysis.

2.6. Statistical analysis

The PsychoPy output was transformed with a MATLAB script (MATLAB R2015b, The MathWorks Inc., Natick, MA, USA) and analyzed with IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) and JASP statistical software (JASP Version 0.8.1.2). Statistical outliers ±3

Table 2. Blinding, safety and tDCS effects on mood.

	Anodal stimulation	Sham stimulation	*p*
Experiment I			
Δ PANAS mean positive	−0.13 ± 0.54	0.05 ± 0.52	.256
Δ PANAS mean negative	0.07 ± 0.3	0.09 ± 0.76	.468
Blinding (anodal/sham)	13/3	9/7	.252
Side effects	1.5 ± 0.6	1.2 ± 0.2	.016*
Experiment II			
Δ PANAS mean positive	−0.24 ± 0.51	−0.13 ± 0.29	.414
Δ PANAS mean negative	0.11 ± 0.21	0.19 ± 0.51	.503
Blinding (anodal/sham)	11/5	10/6	.999
Side effects	1.66 ± 0.56	1.44 ± 0.57	.179

Data is presented with ± 1 STD. Δ PANAS is calculated by PANAS (pre) - PANAS (post). *t*-test is used for normal distributed data, Wilcoxon signed-rank test was performed when the assumption of normality was rejected. Fischer's exact test was used for categorical data.

* $p < .05$.

standard deviations from the mean were adjusted to the next extreme value to maintain the relative order of the data points and to minimize their influence (Tabachnick and Fidell, 2013). The level of significance was set 0.05 for all analyses.

Identical statistical analyses were conducted separately for each experiment. First, we examined the effect of tDCS on WM performance in a 2 × 3 repeated measures analysis of covariance (ANCOVA), with *n-back* $level_{1,2,3}$ and $condition_{ANODAL,SHAM}$ as within-subject factors, *baseline adjusted d'* as dependent variable and *mean baseline performance* as covariate. This covariate was introduced to statistically control for the critical effect of the individual baseline performance level, an information that is not included in the dependent variable (baseline adjusted d'). Response times were analyzed using a 2 × 3 repeated measures ANOVA, with *n-back* $level_{1,2,3}$ and $condition_{ANODAL,SHAM}$ as within-subject factors. To test for potential carry-over (order) effects, an additional analysis was performed including the between-subjects factor *treatment order*anodal-sham,sham-anodal. Post-hoc paired *t*-tests were performed in case of significant interactions. Normality was checked with the Shapiro-Wilk test and non-parametric tests were applied if the null-hypothesis was rejected. In case of violation of the assumption of sphericity, the corrected Huynh-Feldt estimates were reported. Partial eta squared (η_p^2) and Cohen's *d* served as measure of effect size. Further exploratory correlations analyses were conducted to investigate the relation between neurocognitive skills, demographic factors and stimulation effectiveness without an adjustment for multiple comparison

3. Results

3.1. Study cohort

The patient samples of both experiments did not differ in terms of demographic, cognitive and psychopathological measurements (Table 1). A Wilcoxon Signed-Ranks Test revealed a significant difference between experiment I and experiment II in the Fagerstrom test for Nicotine Dependence ($Z = 66.5$, $p = .019$). Hence, participants in experiment I were more physically addicted to nicotine than participants in experiment II. All patients completed the experiment according to the protocol. No rescue medication was necessary.

3.2. Analysis of spatial working memory performance (d')

3.2.1. Experiment I: 1 mA

The 2 × 3 repeated measures ANCOVA with $condition_{ANODAL,SHAM}$ and *n-back* $level_{1,2,3}$ as within-subject factors and *mean baseline performance* as covariate did not yield a effects of $condition_{ANODAL,SHAM}$, $F(1,14) = 1.245$, $p = .283$, *n-back* $level_{1,2,3}$ $F(2,28) = 0.133$, $p = .763$ or the interaction $condition_{ANODAL,SHAM}$ *x n-back* $level_{1,2,3}$, $F(2,28) = 0.222$, $p = .702$ (Figure 2). No interaction of $condition_{ANODAL,SHAM}$ x *n-back* $level_{1,2,3}$ *x treatment order*anodal-sham,sham-anodal was found, $F(2,24) = 2.029$, $p = .174$.

3.2.2. Experiment II: 2 mA

The 2 × 3 repeated measures ANCOVA with $condition_{ANODAL,SHAM}$ and *n-back* $level_{1,2,3}$ as within-subject factors and *mean baseline performance* as covariate did not yield a main effect of $condition_{ANODAL,SHAM}$, $F(1,14) = 1.657$, $p = .219$ or *n-back* $level_{1,2,3}$, $F(2,28) = 1.348$, $p = .135$, but a significant interaction of $condition_{ANODAL,SHAM}$ x *n-back* $level_{1,2,3}$, $F(2,28) = 4.946$, $p = .014$, $\eta_p^2 = 0.261$ (Figure 2). Comparison for the 3-back task revealed higher adjusted d' values in the anodal condition than in the sham condition, $t(15) = 2.274$, $p = .038$, $d = 0.568$. In this experiment, an adjustment of outliers was required for one data point. To test its influence, we performed a sensitivity analysis showing similar results after exclusion of the subject ($condition_{ANODAL,SHAM}$ x *n-back* $level_{1,2,3}$, $F(2,26) = 4.793$, $p = .017$). There was no interaction of $condition_{ANODAL,SHAM}$ x *n-back* $level_{1,2,3}$ *x treatment order*anodal-sham,sham-anodal, $F(2,24) = 0.005$, $p = .995$.

In a next step, we investigated whether this effect was driven by changes in hits or false alarms. A Wilcoxon signed-rank test for the 3-back task showed significant less false alarms in the anodal condition ($Mdn = 3.5$) compared to sham ($Mdn = 4$), $Z = 2.055$, $p = .04$, $r = 0.36$. No differences were found for hits ($p = .999$).

3.3. Analysis of response time

3.3.1. Experiment I: 1 mA

A 2 × 3 repeated measures ANOVA with the within-subject factors $condition_{ANODAL,SHAM}$ and *n-back* $level_{1,2,3}$ showed a

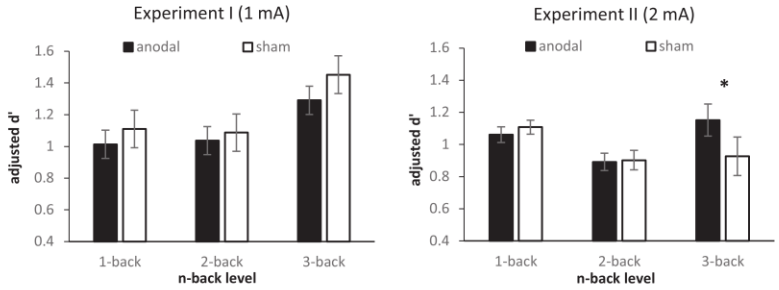

Figure 2. Baseline adjusted d' during anodal and sham stimulation in experiment I (1 mA) and experiment II (2 mA). Error bars represent standard error. * $p < .05$.

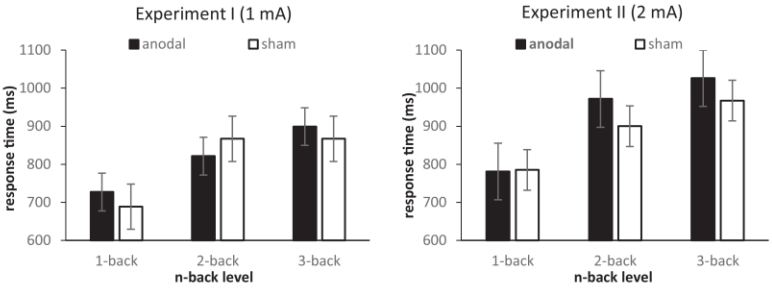

Figure 3. Response times during anodal and sham stimulation in experiment I (1 mA) and experiment II (2 mA). Error bars represent standard error.

main effect of *n-back level* $_{1,2,3}$, $F(2,30) = 10.226$, $p < .001$, $\eta_p^2 = 0.405$, indicating slower response times with increasing WM load (Figure 3). There was no effect of *condition* ($p = .65$) or the interaction of $condition_{ANODAL,SHAM}$ x *n-back* $level_{1,2,3}$ ($p = .243$).

3.3.2. Experiment II: 2 mA

A 2×3 repeated measures ANOVA with the within-subject factors $condition_{ANODAL,SHAM}$ and *n-back level* $_{1,2,3}$ showed a main effect of *condition* $F(1,15) = 5.784$, $p = .03$, $\eta_p^2 = 0.278$, indicating slower response times during anodal stimulation compared to sham (Figure 3). The variable *n-back* $level_{1,2,3}$ showed a significant effect on *response time*, $F(2,30) = 11.027$, $p < .001$, $\eta_p^2 = 0.424$, signifying slower response times with increasing WM load. The interaction of *n-back* $level_{1,2,3}$ *x* $condition_{ANODAL,SHAM}$ was not significant ($p = .26$).

3.4. Contributing factors of stimulation effectiveness

To further explore determinants of tDCS effectiveness, we conducted correlation analyses between the collected neurocognitive and demographic measures and the individual responses to tDCS. The individual tDCS effect was calculated by subtracting baseline adjusted d'_{ANODAL} by baseline adjusted d'_{SHAM}. Complementary to our main results, the correlation analyses showed significant negative correlations between premorbid intelligence (MWT-B), years of education, processing speed (d2-Gz) and tDCS effectiveness (Table 3). A statistical trend was also found for a negative correlation between cognitive flexibility (TMT-B) and tDCS effectiveness. All correlations occurred solely in the 3-back task and were equally directed, suggesting that patients with lower general cognitive abilities benefit more from tDCS, when working at a high cognitive load.

Since both experiments differed significantly in the Fagerstrom score, we investigated the correlation between Fagerstrom score and tDCS effect which rendered non-significant results (Pearson's $r < 0.353$ for all n-back level).

3.5. Influence of tDCS on mood

The Positive and Negative Affect Schedule (PANAS) questionnaire, consisting of 20 items (10 positive, 10 negative) with a five-level Likert scale each, was used to assess the mood of the patients before and after every stimulation session. The mean PANAS positive and negative score was calculated and a delta PANAS positive and negative was derived by subtracting the PANAS score after the stimulation from the PANAS score before the session. In experiment I, a paired *t*-test showed no indication for an

Table 3. Correlations of general cognitive abilities and stimulation effects in experiment II.

		Stimulation effect 1-back	Stimulation effect 2-back	Stimulation effect 3-back	MWT-B (norm)	TMT-B (norm)	d2-GZ
Stimulation effect 1-back	Pearson's r	—					
	p-value	—					
Stimulation effect 2-back	Pearson's r	0.091	—				
	p-value	0.738	—				
Stimulation effect 3-back	Pearson's r	−0.387	−0.348	—			
	p-value	0.139	0.187	—			
MWT-B (norm)	Pearson's r	0.088	0.040	−0.658**	—		
	p-value	0.745	0.883	0.006	—		
TMT-B (norm)	Pearson's r	0.424	0.105	−0.491	0.570*	—	
	p-value	0.102	0.698	0.053	0.021	—	
d2-GZ	Pearson's r	0.042	0.101	−0.522*	0.420	0.641**	—
	p-value	0.877	0.709	0.038	0.106	0.007	—
Education (years)	Pearson's r	0.038	0.048	−0.564*	0.602*	0.506*	0.217
	p-value	0.889	0.859	0.023	0.014	0.045	0.420

Pearson Correlation Coefficient, * $p < .05$, ** $p < .01$; MWT-B and TMT-B performance was transformed with age adjusted normative data. Stimulation effect is calculated by d'(anodal) – d'(sham).

effect of anodal tDCS compared to sham tDCS on positive affect, $t(15) = 1.18$, $p = .256$ or negative affect, $Z = 0.73$, $p = .468$. In experiment II, a paired *t*-test showed no evidence for an effect of anodal tDCS compared to sham tDCS on positive affects, $t(15) = 0.84$, $p = .414$ or negative affects, $t(15) = 0.69$, $p = .503$. In summary, no hint for an effect of tDCS on mood was observed.

3.6. Blinding efficacy

All participants completed a blinding questionnaire after each stimulation session. They were instructed to guess if they received a placebo stimulation or not. A Fischer's exact test was used to compare the occurrence of patient's guesses and the expected distribution. A significant deviation from the hypothesized values was not found in experiment I ($p = .252$) and experiment II ($p = .999$). It can therefore be concluded that the blinding procedure was successful for both experiments (Table 2).

3.7. Tolerability of tDCS

All participants tolerated the tDCS well. One participant quit the experiment due to scheduling difficulties. The adverse effect questionnaire including six items (tingling on electrode side, tingling on head, fatigue, itching, headache, nausea) with a five-level Likert Scale was filled out immediate after every stimulation session by the patient. In experiment I, patients rated the side effect questionnaire significantly higher after anodal stimulation (Mdn = 1.5) compared to sham stimulation (Mdn = 1.17), $Z = 2.4$, $p = .016$. This difference was not observed in experiment II, $Z = 1.34$, $p = .179$. Pooled data of both experiments revealed a significant higher side effect score after anodal stimulation (Mdn = 1.5) compared to sham stimulation (Mdn = 1.17), $Z = 2.55$, $p = .011$ (Table 2). Further analyses with the pooled data, indicated that the significant difference in overall side effects were mainly caused by the items "tingling on head" and "itching" . It has to be mentioned that, although a significant difference between anodal and sham stimulation exists, the degree of severity is rated between "none" (1 on Likert scale) and "slight" (2 on Likert scale). Apart from this, no serious adverse events were reported. Moreover, no exacerbation of psychosis was observed. Therefore, the application of 1 mA and 2 mA tDCS in patients with schizophrenia is save.

4. Discussion

The key finding of this study is that 2 mA anodal tDCS to the right dlPFC can improve n-back performance in patients with schizophrenia. The significant improvement was detected in the task with the highest memory load (3-back). This beneficial effect was negatively correlated with measures of general cognitive ability. Remarkably, a significant slowing of response time was observed with 2 mA anodal tDCS pointing towards a shift in the speed-accuracy tradeoff in favor of accuracy. No effect of 1 mA tDCS on WM performance or response time was found, indicating the necessity of higher current intensities to elicit behavioral effects in patients with schizophrenia.

4.1. The effect of anodal tDCS

Our results substantially add to the preliminary evidence for beneficial effects of anodal tDCS on WM performance in psychiatric patients. The most recent meta-analysis by Hill and colleagues reported a significant improved accuracy and no effect on reaction time for online anodal tDCS in a neuropsychiatric cohort (Hill et al., 2016). Correspondingly, studies focusing on patients with schizophrenia reported improvements of probabilistic association learning dependent on

baseline performance during 2 mA anodal tDCS (Vercammen et al., 2011) and an improvement of WM over time after 2 mA anodal tDCS (Hoy et al., 2014). Further studies implemented these findings in short training paradigms showing increased WM performance during 2 mA (Orlov et al., 2017b), during 1 mA (Nienow et al., 2016) and after 2 mA anodal tDCS (Smith et al., 2015). A recent review on tDCS effects in schizophrenia including online and offline stimulation reported a small effect of anodal tDCS on WM (Mervis et al., 2017). Whether a modulation of cortical excitability during a given task is superior in comparison to modulation prior to a task remains largely unexplored (Oldrati et al., 2018; Stagg et al., 2011), with both interventions yielding promising first results. However, consistent with previous research (Ruf et al., 2017), our focus is the combination of task-specific neuronal activation with excitatory tDCS to shape context-dependent synaptic plasticity and thus support the restoration of malfunctioning brain networks.

In summary, our results are in line with previous reports and strengthen the evidence for beneficial effects of online anodal tDCS on WM in schizophrenia. Since tDCS effects are often variable (Horvath et al., 2016) and non-linear (Batsikadze et al., 2013a), the subsequent discussion will focus on factors influencing tDCS effectiveness in our study.

4.2. Task-dependent effects of tDCS

The beneficial tDCS effect on d' was specifically observed during the n-back level with the highest cognitive load (3-back). This is in accordance with previous findings showing that activity of the targeted network (Ruf et al., 2017; Zwissler et al., 2014) and cognitive demands of task performance (Ehlis et al., 2016; Gill et al., 2015; Pope et al., 2015) can essentially determine the efficacy of tDCS. Most likely, the concurrent cortical activation is decisive since tDCS itself does not directly induce action potentials but modulates membrane potentials and thus particularly ongoing activity (Bikson and Rahman, 2013; Silvanto and Pascual-Leone, 2008). Referring to our experiment, the visuospatial n-back task consistently activates the right dlPFC (Fried et al., 2014; Nagel et al., 2013). Here, an increasing task difficulty by means of increasing cognitive load, is associated with broader distribution of activation and recruitment of additional cortical areas (Carlson et al., 1998; Harvey et al., 2005). Interestingly, a non-linear relation between cognitive load and dlPFC activation is observed along with dlPFC deactivation after the individual capacity is exceeded (Callicott et al., 1999). Thus, the tDCS intervention encounters a different brain state during the performance of the 3-back task, compared to the task with less cognitive load. Consistently, previous studies in healthy subjects showed that tDCS and TMS effects are related to memory load (Barr et al., 2013; Jones and Berryhill, 2012; Pope et al., 2015).

In patients with schizophrenia showing neuroanatomical alterations like reduced volume of the dlPFC (Cannon et al., 2002) and disturbances in functional connectivity (Bittner et al., 2015), the interplay between brain stimulation and brain state becomes even more complex. Likewise, imaging studies show a wider spatial distribution of activation within the dlPFC during a WM task (Holt et al., 1999) and a variable pattern of prefrontal hyper- and hypoactivation (Glahn et al., 2005; Potkin et al., 2009; Whitfield-Gabrieli et al., 2009). Specifically, a left shift of task-related dlPFC activation has been suggested (Manoach, 2002). In this framework, patients with schizophrenia show an increase of dlPFC activation with a relatively low WM load and an early decrease with higher load. This modified pattern of cortical recruitment might contribute to the observed load-dependent effects of tDCS and the variability in previous results. Therefore, our data supports the notion that dysfunctional prefrontal hypoactivity during a challenging cognitive task might be a reasonable target for supportive anodal stimulation.

4.3. Influence of individual cognitive ability

Besides the critical role of task difficulty, we found that lower general cognitive abilities are associated with higher stimulation effectiveness. Especially patients with comparatively low premorbid intelligence (MWT-B), less sustained attention (d2), and cognitive flexibility (TMT-B) as well as subjects with fewer years of education, benefitted more from stimulation during the 3-back task. Hence, cognitive load and basic cognitive abilities interact in providing optimal responsiveness for tDCS. This interaction might be responsible for high interindividual variability (Katz et al., 2017). Accordingly, previous studies have shown a critical, albeit variable, influence of cognitive abilities on tDCS effectiveness (Berryhill and Jones, 2012; Tseng et al., 2012). Thus, tDCS effects on WM are likely based on a non-linear interaction between task difficulty and the individual level of cognitive functioning as reflected in baseline task performance (Learmonth et al., 2015; Ruf et al., 2017; Tseng et al., 2012; Vercammen et al., 2011) and general neurocognitive abilities. Additional factors like age, gender or genetic makeup most probably also effect the modulatory properties of tDCS (Krause and Cohen Kadosh, 2014; Wiegand et al., 2016), but are beyond the scope of this study.

4.4. Intensity-dependent effects of tDCS

There is an ongoing discussion about the necessity of higher current strengths in neuropsychiatric patients. Our results show behavioral effects with the use of 2 mA tDCS but not with 1 mA and are thus in compliance with the existing meta-analytic evidence (Hill et al., 2016).

Studies on the human motor cortex suggest that 2 mA anodal tDCS can significantly increase motor evoked potential (MEP) amplitudes up to 90 minutes after stimulation (Batsikadze et al., 2013b). Comparisons of current intensities on motor learning showed a steeper learning curve with 1.5 mA compared to 1 mA (Cuypers et al., 2013). These findings were extended to cognitive functions by Boggio and colleagues, who showed an increased WM performance in patients with Parkinson's disease with 2 mA anodal tDCS, but not with 1 mA anodal tDCS or sham stimulation (Boggio et al., 2006). Further studies with patients suffering from spinal cord injury (Murray et al., 2015) or schizophrenia (Hoy et al., 2014) support the notion, that higher current intensities might be necessary to elicit behavioral effects. This might be due to the concurrent medication intake

(Brunoni et al., 2013) or related to impaired neuroplasticity of the disorder itself (Hasan et al., 2011). However, a simple linear relationship between intensity and effect is not likely and the optimal stimulation intensity will be dependent on complex interactions between multiple intra- and inter-individual factors and stimulation parameters.

4.5. Response time

Parallel to the effect on 3-back accuracy, a significant slowing of response time was detected only in the 2 mA condition. This finding contrasts with a previous meta-analysis reporting faster response times with anodal stimulation (Brunoni and Vanderhasselt, 2014). However, most of the included tDCS studies were conducted in healthy participants and a more recent meta-analysis reported no effects of anodal tDCS on reaction time in a neuropsychiatric cohort (Hill et al., 2016). Particularly, the only trial involving patients with schizophrenia did not find an effect on response speed in a 2-back task (Hoy et al., 2014). In our study, participants were instructed to give correct responses on the different n-back levels, as quick as possible. This hierarchical task assignment might have supported a tDCS-induced shift of the speed-accuracy trade off in favor of accuracy, at least with effective 2 mA tDCS. Accordingly, d' improvement was particularly conveyed by the reduction of false alarms thus suggesting that 2 mA tDCS strengthens prefrontal control mechanisms reflected by the avoidance of quick false alarms for the benefit of slower hits in the most challenging condition.

4.6. Cognitive control

The concept of cognitive control describes the ability to coordinate thoughts and actions in relation to internal goals (Koechlin et al., 2003). This capability to overrule habitual reactions is essential for higher cognitive functions like planning ability or executive functions and produces meaningful behavior. In patients with schizophrenia, deficits in WM are attributed to an impairment of cognitive control (Eich et al., 2014). In these patients, the inhibition of task irrelevant stimuli is most likely compromised due to a diminished top-down control (Perlstein et al., 2001). Working memory and cognitive control share the dlPFC as key region and disturbances of dlPFC function are related to impairments in both measures in schizophrenia (Fornito et al., 2011; MacDonald III et al., 2005; Snitz et al., 2006). Therefore, improvement of WM accuracy by concomitant tDCS based on the inhibition of responses to distractors is in line with previous findings on the amelioration of cognitive control by tDCS in healthy subjects (Metuki et al., 2012; Vanderhasselt et al., 2013) and in subjects with depression (Wolkenstein and Plewnia, 2013). However, in our study, the increase of cognitive control was apparently achieved at the expense of a slowing in response time. This observation further underlines the complexity of interactions between task characteristics, the individual brain and the multitude of stimulation parameters and points beyond a simple concept of cognitive enhancement by anodal tDCS. Nevertheless, our data demonstrates that a targeted use of tDCS can help to improve a relevant behavioral deficits in patients with schizophrenia (Enticott et al., 2008) and thus may eventually enlarge the armamentarium for the treatment of schizophrenia.

4.7. Limitations

Some limitations to our study have to be considered: First, our predefined study sample was rather small (2 x $n = 16$). However, the resulting medium to large effect size confirmed our initial estimate and the sample size is comparable to previous studies. This allowed for a rather homogenous sample by excluding schizoaffective disorder, left handedness and any medication changes one week prior and during the experimental week. Second, tobacco dependency has been shown to influence neuroplasticity and tDCS effects in healthy subjects and in patients with schizophrenia (Grundey et al., 2012; Strube et al., 2015). It cannot be ruled out, that a higher number of smokers in experiment I prevented tDCS effects in this sample (Brunelin et al., 2015). However, the Fagerstrom score did not correlate with stimulation effectiveness in both experiments. Third, while the effects of other stimulation parameters would have also been worth investigating, we have focused on 1 and 2 mA anodal tDCS to the right dlPFC during a spatial *n*-back task to provide reliable data that are useful for future clinical trials. Fourth, although we ensured a wash-out period of 48 h between the experimental sessions, we cannot rule out carry-over effects of the stimulation. However, including treatment order as between-subjects factor did not provide evidence for this assumption. Finally, the reported correlation analyses would not survive corrections for multiple testing and have to be considered exploratory.

5. Conclusions

The beneficial effects of tDCS on WM performance, its conditions and clinical potential is still under debate, particularly in patients with schizophrenia. With this study, we have demonstrated that WM accuracy can be ameliorated by concomitant 2 mA tDCS. This effect was particularly visible during the most challenging 3-back task and most pronounced in subjects with lower cognitive abilities. Therefore, these results substantially add to the knowledge on parameters and conditions of an effective WM enhancement by tDCS in patients with schizophrenia. Most importantly, these findings will enable for a data-driven development of future translational studies testing the clinical efficacy of stimulation-enhanced cognitive training in schizophrenia.

Conflict of interest

W.S. received paid speakership by Mag&More. A.H. has received a paid speakership from Desitin, Otsuka, Janssen-Cilag and Lundbeck. He was member of an advisory board of Roche and is member of a Janssen-Cilag advisory board. All other authors declare that they have no conflicts of interest.

Contributors

C.P. and A.H. designed the study and wrote the protocol. T.S. conducted the experiments. T.S. and C.P. performed the statistical analysis and wrote the first draft of the manuscript. All authors were involved in reviewing and editing the manuscript. The final manuscript was approved by all authors

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References

Au, J., Katz, B., Buschkuehl, M., Bunarjo, K., Senger, T., Zabel, C., Jaeggi, S.M., Jonides, J., 2016. Enhancing working memory training with transcranial direct current stimulation. J Cogn Neurosci 28, 1419–1432.

Barch, D.M., Sheline, Y.I., Csernansky, J.G., Snyder, A.Z., 2003. Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. Biol Psychiat 53, 376–384.

Barr, M.S., Farzan, F., Rajji, T.K., Voineskos, A.N., Blumberger, D.M., Arenovich, T., Fitzgerald, P.B., Daskalakis, Z.J., 2013. Can repetitive magnetic stimulation improve cognition in schizophrenia? Pilot data from a randomized controlled trial. Biol. Psychiat. 73, 510–517.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.F., Nitsche, M., 2013a. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J. Physiol. 591, 1987–2000.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.F., Nitsche, M.A., 2013b. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J. Physiol. 591, 1987–2000.

Benwell, C.S.Y., Learmonth, G., Miniussi, C., Harvey, M., Thut, G., 2015. Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias. Cortex 69, 152–165.

Berryhill, M.E., Jones, K.T., 2012. tDCS selectively improves working memory in older adults with more education. Neurosci. Lett. 521, 148–151.

Bikson, M., Rahman, A., 2013. Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. Front. Hum. Neurosci. 7, 688.

Bittner, R.A., Linden, D.E.J., Roebroeck, A., Hartling, F., Rotarska-Jagiela, A., Maurer, K., Goebel, R., Singer, W., Haenschel, C., 2015. The when and where of working memory dysfunction in early-onset schizophrenia-a functional magnetic resonance imaging study. Cereb. Cortex 25, 2494–2506.

Boggio, P.S., Ferrucci, R., Rigonatti, S.P., Covre, P., Nitsche, M., Pascual-Leone, A., Fregni, F., 2006. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J. Neurol. Sci. 249, 31–38.

Brunelin, J., Hasan, A., Haesebaert, F., Nitsche, M.A., Poulet, E., 2015. Nicotine Smoking prevents the effects of frontotemporal transcranial direct current stimulation (tDCS) in hallucinating patients with schizophrenia. Brain Stimul. 8, 1225–1227.

Brunoni, A.R., Ferrucci, R., Bortolomasi, M., Scelzo, E., Boggio, P.S., Fregni, F., Dell'Osso, B., Giacopuzzi, M., Altamura, A.C., Priori, A., 2013. Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: Findings from a naturalistic study. Eur. Psychiat. 28, 356–361.

Brunoni, A.R., Vanderhasselt, M.A., 2014. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn. 86, 1–9.

Callicott, J.H., Mattay, V.S., Bertolino, A., Finn, K., Coppola, R., Frank, J.A., Goldberg, T.E., Weinberger, D.R., 1999. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb. Cortex 9, 20–26.

Cannon, T.D., Thompson, P.M., van Erp, T.G.M., Toga, A.W., Poutanen, V.P., Huttunen, M., Lonnqvist, J., Standerskjold-Nordenstam, C.G., Narr, K.L., Khaledy, M., Zoumalan, C.I., Dail, R., Kaprio, J., 2002. Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. Proc. Natl. Acad. Sci. USA 99, 3228–3233.

Carlson, S., Martinkauppi, S., Rämä, P., Salli, E., Korvenoja, A., Aronen, H.J., 1998. Distribution of cortical activation during visuospatial n-back tasks as revealed by functional magnetic resonance imaging. Cereb. Cortex 8, 743–752.

Chong, H.Y., Teoh, S.L., Wu, D.B.C., Kotirum, S., Chiou, C.F., Chaiyakunapruk, N., 2016. Global economic burden of schizophrenia: a systematic review. Neuropsych. Dis. Treat. 12, 357–373.

Cuypers, K., Leenus, D.J., van den Berg, F.E., Nitsche, M.A., Thijs, H., Wenderoth, N., Meesen, R.L., 2013. Is motor learning mediated by tDCS intensity? PLoS One 8, e67344.

D'Esposito, M., Postle, B.R., 2015. The cognitive neuroscience of working memory. Annu. Rev. Psychol. 66, 115–142.

Dedoncker, J., Brunoni, A.R., Baeken, C., Vanderhasselt, M.A., 2016. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimul. 9, 501–517.

Ehlis, A.C., Haeussinger, F.B., Gastel, A., Fallgatter, A.J., Plewnia, C., 2016. Task-dependent and polarity-specific effects of prefrontal transcranial direct current stimulation on cortical activation during word fluency. Neuroimage 140, 134–140.

Eich, T.S., Nee, D.E., Insel, C., Malapani, C., Smith, E.E., 2014. Neural correlates of impaired cognitive control over working memory in schizophrenia. Biol. Psychiat. 76, 146–153.

Enticott, P.G., Ogloff, J.R., Bradshaw, J.L., 2008. Response inhibition and impulsivity in schizophrenia. Psychiat. Res. 157, 251–254.

Fornito, A., Yoon, J., Zalesky, A., Bullmore, E.T., Carter, C.S., 2011. General and specific functional connectivity disturbances in first-episode schizophrenia during cognitive control performance. Biol. Psychiat. 70, 64–72.

Fried, P.J., Rushmore, R.J., Moss, M.B., Valero-Cabre, A., Pascual-Leone, A., 2014. Causal evidence supporting functional dissociation of verbal and spatial working memory in the human dorsolateral prefrontal cortex. Eur. J. Neurosci. 39, 1973–1981.

Fusar-Poli, P., Deste, G., Smieskova, R., Barlati, S., Yung, A.R., Howes, O., Stieglitz, R.D., Vita, A., McGuire, P., Borgwardt, S., 2012. Cognitive functioning in prodromal psychosis a meta-analysis. Arch. Gen. Psychiat. 69, 562–571.

Gill, J., Shah-Basak, P.P., Hamilton, R., 2015. It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function. Brain Stimul. 8, 253–259.

Glahn, D.C., Ragland, J.D., Abramoff, A., Barrett, J., Laird, A.R., Bearden, C.E., Velligan, D.I., 2005. Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. Hum. Brain Mapp. 25, 60–69.

Green, M.F., Horan, W.P., Lee, J., 2015. Social cognition in schizophrenia. Nat. Rev. Neurosci. 16, 620–631.

Grundey, J., Thirugnanasambandam, N., Kaminsky, K., Drees, A., Skwirba, A.C., Lang, N., Paulus, W., Nitsche, M.A., 2012. Neuroplasticity in cigarette smokers is altered under withdrawal and partially restituted by nicotine exposition. J. Neurosci. 32, 4156–4162.

Haatveit, B.C., Sundet, K., Hugdahl, K., Ueland, T., Melle, I., Andreassen, O.A., 2010. The validity of d prime as a working memory index: results from the "Bergen n-back task". J. Clin. Exp. Neuropsyc. 32, 871–880.

Harvey, P.-O., Fossati, P., Pochon, J.-B., Levy, R., LeBastard, G., Lehéricy, S., Allilaire, J.-F., Dubois, B., 2005. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. Neuroimage 26, 860–869.

Hasan, A., Nitsche, M.A., Rein, B., Schneider-Axmann, T., Guse, B., Gruber, O., Falkai, P., Wobrock, T., 2011. Dysfunctional long-term potentiation-like plasticity in schizophrenia revealed by transcranial direct current stimulation. Behav. Brain Res. 224, 15–22.

Hill, A.T., Fitzgerald, P.B., Hoy, K.E., 2016. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimul. 9, 197–208.

Holt, J., Van Horn, J., Meyer-Lindenberg, A., 1999. Multiple sources of signal abnormality underlying prefrontal hypofunction and increased variability in the sites of activation within BA 9/46 in individual medication free schizophrenic patients. Soc. Neurosci. 14, 18.

Horvath, J.C., Vogrin, S.J., Carter, O., Cook, M.J., Forte, J.D., 2016. Effects of a common transcranial direct current stimulation (tDCS) protocol on motor evoked potentials found to be highly variable within individuals over 9 testing sessions. Exp. Brain Res. 234, 2629–2642.

Hoy, K.E., Arnold, S.L., Emonson, M.R.L., Daskalakis, Z.J., Fitzgerald, P.B., 2014. An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. Schizophr. Res. 155, 96–100.

Hoy, K.E., Bailey, N.W., Arnold, S.L., Fitzgerald, P.B., 2015. The effect of transcranial Direct Current Stimulation on gamma activity and working memory in schizophrenia. Psychiat. Res. 228, 191–196.

Hughes, C., Kumari, V., Soni, W., Das, M., Binneman, B., Drozd, S., O'Neil, S., Mathew, V., Sharma, T., 2003. Longitudinal study of symptoms and cognitive function in chronic schizophrenia. Schizophr. Res. 59, 137–146.

Jaeggi, S.M., Buschkuehl, M., Perrig, W.J., Meier, B., 2010. The concurrent validity of the N-back task as a working memory measure. Memory 18, 394–412.

Jones, K.T., Berryhill, M.E., 2012. Parietal contributions to visual working memory depend on task difficulty. Front Psychiat. 3, 81.

Katz, B., Au, J., Buschkuehl, M., Abagis, T., Zabel, C., Jaeggi, S.M., Jonides, J., 2017. Individual differences and long-term consequences of tDCS-augmented cognitive training. J Cogn Neurosci 1–11.

Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., Brunelin, J., Moller, H.J., Reiser, M., Padberg, F., 2011. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J. Neurosci. 31, 15284–15293.

Koechlin, E., Ody, C., Kouneiher, F., 2003. The architecture of cognitive control in the human prefrontal cortex. Science 302, 1181–1185.

Krause, B., Cohen Kadosh, R., 2014. Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. Front Syst. Neurosci. 8, 25.

Learmonth, G., Thut, G., Benwell, C.S.Y., Harvey, M., 2015. The implications of state-dependent tDCS effects in aging: Behavioural response is determined by baseline performance. Neuropsychologia 74, 108–119.

Leifker, F.R., Bowie, C.R., Harvey, P.D., 2009. Determinants of everyday outcomes in schizophrenia: the influences of cognitive impairment, functional capacity, and symptoms. Schizophr Res 115, 82–87.

Li, X., Xiao, Y.H., Zhao, Q., Leung, A.W.W., Cheung, E.F.C., Chan, R.C.K., 2015. The neuroplastic effect of working memory training in healthy volunteers and patients with schizophrenia: Implications for cognitive rehabilitation. Neuropsychologia 75, 149–162.

MacDonald III, A.W., Carter, C.S., Kerns, J.G., Ursu, S., Barch, D.M., Holmes, A.J., Stenger, V.A., Cohen, J.D., 2005. Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. Am. J. Psychiat. 162, 475–484.

Manoach, D.S., 2002. Prefrontal cortex dysfunction during working memory performance in schizophrenia: Reconciling discrepant findings. Biol. Psychiat. 51, 104s -104s.

Mervis, J.E., Capizzi, R.J., Boroda, E., MacDonald 3rd, A.W., 2017. Transcranial direct current stimulation over the dorsolateral prefrontal cortex in schizophrenia: a quantitative review of cognitive outcomes. Front Hum. Neurosci. 11, 44.

Metuki, N., Sela, T., Lavidor, M., 2012. Enhancing cognitive control components of insight problems solving by anodal tDCS of the left dorsolateral prefrontal cortex. Brain Stimul. 5, 110–115.

Murray, L.M., Edwards, D.J., Ruffini, G., Labar, D., Stampas, A., Pascual-Leone, A., Cortes, M., 2015. Intensity dependent effects of transcranial direct current stimulation on corticospinal excitability in chronic spinal cord injury. Arch. Phys. Med. Rehab. 96, S114–S121.

Nagel, B.J., Herting, M.M., Maxwell, E.C., Bruno, R., Fair, D., 2013. Hemispheric lateralization of verbal and spatial working memory during adolescence. Brain Cogn. 82, 58–68.

Nienow, T.M., Lim, K.O., MacDonald, A.W., 2016. TDCS produces incremental gain when combined with working memory training in patients with schizophrenia: a proof of concept pilot study. Schizophr. Res. 172, 218–219.

Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. Lond. 527, 633–639.

Nitsche, M.A., Paulus, W., 2001. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57, 1899–1901.

Oldrati, V., Colombo, B., Antonietti, A., 2018. Combination of a short cognitive training and tDCS to enhance visuospatial skills: a comparison between online and offline neuromodulation. Brain Res. 1678, 32–39.

Orlov, N.D., O'Daly, O., Tracy, D.K., Daniju, Y., Hodsoll, J., Valdearenas, L., Rothwell, J., Shergill, S.S., 2017a. Stimulating thought: a functional MRI study of transcranial direct current stimulation in schizophrenia. Brain 140, 2490–2497.

Orlov, N.D., Tracy, D.K., Joyce, D., Patel, S., Rodzinka-Pasko, J., Dolan, H., Hodsoll, J., Collier, T., Rothwell, J., Shergill, S.S., 2017b. Stimulating cognition in schizophrenia: A controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning. Brain Stimul. 10, 560–566.

Peirce, J.W., 2007. PsychoPy – Psychophysics software in Python. J. Neurosci. Meth. 162, 8–13.

Perlstein, W.M., Carter, C.S., Noll, D.C., Cohen, J.D., 2001. Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. Am. J. Psychiat. 158, 1105–1113.

Pope, P.A., Brenton, J.W., Miall, R.C., 2015. Task-specific facilitation of cognition by anodal transcranial direct current stimulation of the prefrontal cortex. Cereb. Cortex 25, 4551–4558.

Potkin, S.G., Turner, J.A., Brown, G.G., McCarthy, G., Greve, D.N., Glover, G.H., Manoach, D.S., Belger, A., Diaz, M., Wible, C.G., Ford, J.M., Mathalon, D.H., Gollub, R., Lauriello, J., O'Leary, D., van Erp, T.G.M., Toga, A.W., Preda, A., Lim, K.O., Fbirn, 2009. Working memory and DLPFC inefficiency in schizophrenia: The FBIRN study. Schizophrenia Bull. 35, 19–31.

Reinhart, R.M., Zhu, J., Park, S., Woodman, G.F., 2015. Synchronizing theta oscillations with direct-current stimulation strengthens adaptive control in the human brain. Proc. Natl. Acad. Sciences 112, 9448–9453.

Ruf, S.P., Fallgatter, A.J., Plewnia, C., 2017. Augmentation of working memory training by transcranial direct current stimulation (tDCS). Sci. Rep. 7, 876.

Schneider, M., Walter, H., Moessnang, C., Schafer, A., Erk, S., Erk, S., Romund, L., Garbusow, M., Dixson, L., Heinz, A., Romanczuk-Seiferth, N., Meyer-Lindenberg, A., Tost, H., 2017. Altered DLPFC-hippocampus connectivity during working memory: independent replication and disorder specificity of a putative genetic risk phenotype for schizophrenia. Schizophrenia Bull. 43, 1114–1122.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiat. 59 (Suppl 20), 22–33 quiz 34-57.

Silvanto, J., Pascual-Leone, A., 2008. State-dependency of transcranial magnetic stimulation. Brain Topogr. 21, 1–10.

Smith, R.C., Boules, S., Mattiuz, S., Youssef, M., Tobe, R.H., Sershen, H., Lajtha, A., Nolan, K., Amiaz, R., Davis, J.M., 2015. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr. Res. 168, 260–266.

Snitz, B.E., Macdonald 3rd, A.W., Carter, C.S., 2006. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr. Bull. 32, 179–194.

Stagg, C., Jayaram, G., Pastor, D., Kincses, Z., Matthews, P., Johansen-Berg, H., 2011. Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. Neuropsychologia 49, 800–804.

Stagg, C.J., Lin, R.L., Mezue, M., Segerdahl, A., Kong, Y.Z., Xie, J.Y., Tracey, I., 2013. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. J. Neurosci. 33, 11425–11431.

Stanislaw, H., Todorov, N., 1999. Calculation of signal detection theory measures. Behav. Res. Meth. Ins. C 31, 137–149.

Strassnig, M.T., Raykov, T., O'Gorman, C., Bowie, C.R., Sabbag, S., Durand, D., Patterson, T.L., Pinkham, A., Penn, D.L., Harvey, P.D., 2015. Determinants of different aspects of everyday outcome in schizophrenia: the roles of negative symptoms, cognition, and functional capacity. Schizophr. Res. 165, 76–82.

Strube, W., Bunse, T., Nitsche, M.A., Wobrock, T., Aborowa, R., Misewitsch, K., Herrmann, M., Falkai, P., Hasan, A., 2015. Smoking restores impaired LTD-like plasticity in schizophrenia: a transcranial direct current stimulation study. Neuropsychopharmacology 40, 822–830.

Subramaniam, K., Luks, T.L., Garrett, C., Chung, C., Fisher, M., Nagarajan, S., Vinogradov, S., 2014. Intensive cognitive training in schizophrenia enhances working memory and associated prefrontal cortical efficiency in a manner that drives long-term functional gains. Neuroimage 99, 281–292.

Tabachnick, B.G., Fidell, L.S., 2013. Using Multivariate Statistics, sixth ed. Pearson Education, Boston.

Tseng, P., Hsu, T.Y., Chang, C.F., Tzeng, O.J.L., Hung, D.L., Muggleton, N.G., Walsh, V., Liang, W.K., Cheng, S.K., Juan, C.H., 2012. Unleashing potential: transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. J. Neurosci. 32, 10554–10561.

Vanderhasselt, M.-A., De Raedt, R., Brunoni, A.R., Campanhã, C., Baeken, C., Remue, J., Boggio, P.S., 2013. tDCS over the left prefrontal cortex enhances cognitive control for positive affective stimuli. PLoS One 8, e62219.

Vercammen, A., Rushby, J.A., Loo, C., Short, B., Weickert, C.S., Weickert, T., 2011. Transcranial direct current stimulation (Tdcs) influences probabilistic association learning in people with schizophrenia. Schizophrenia Bull. 37, 231–232.

Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J.D.E., Seidman, L.J., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives persons with schizophrenia. Proc. Natl. Acad. Sci. USA 106, 4572 -4572.

Wiegand, A., Nieratschker, V., Plewnia, C., 2016. Genetic modulation of transcranial direct current stimulation effects on cognition. Front Hum. Neurosci. 10, 651.

Wolkenstein, L., Plewnia, C., 2013. Amelioration of cognitive control in depression by transcranial direct current stimulation. Biol. Psychiat. 73, 646–651.

Zwissler, B., Sperber, C., Aigeldinger, S., Schindler, S., Kissler, J., Plewnia, C., 2014. Shaping memory accuracy by left prefrontal transcranial direct current stimulation. J. Neurosci. 34, 4022–4026.

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Improving working memory in schizophrenia: Effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC

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ABSTRACT

Deficits in various cognitive processes, such as working memory, are characteristic for schizophrenia, lowering patients' functioning and quality of life. Recent research suggests that transcranial direct stimulation (tDCS) applied to the dorsolateral prefrontal cortex (DLPFC) may be a potential therapeutic intervention for cognitive deficits in schizophrenia. Here, we examined the effects of online tDCS to the DLPFC on working memory (WM) performance in 40 schizophrenia patients in two separate experiments with a double blind, sham-controlled, cross-over design. Patients underwent single sessions of active and sham tDCS in a randomized order. Stimulation parameters were anode F3, cathode right deltoid muscle, 21 min tDCS duration, 1 mA tDCS in Experiment 1 ($N = 20$) and 2 mA tDCS in Experiment 2 ($N = 20$). Primary outcome was the change in WM performance as measured by a verbal n-back paradigm (1- to 3-back). Irrespective of the stimulation intensity, data analysis showed a significant higher WM accuracy during active tDCS than during sham tDCS ($p = 0.019$), but no main effect of stimulation intensity ($p = 0.392$). Subsequent separate analyses revealed a significantly improved WM performance only during 1 mA ($p = 0.048$). TDCS facilitated WM functioning in schizophrenia, with an advantage of 1 mA over 2 mA. Our results support the notion that tDCS may be a potential treatment for cognitive deficits in schizophrenia and emphasize the need for future research on the specific stimulation parameters.

1. Introduction

Working memory (WM) is crucial for human behavior and plays a key role for academic (Alloway and Alloway, 2010; Barch and Ceaser, 2012) and professional success (Higgins et al., 2007). In order to effectively manage everyday life it is essential to quickly process and store information, to coordinate and regulate cognitive functions, and to control and direct attention. WM deficits are characteristic for schizophrenia, lowering patients' employment opportunities, social functioning and quality of life, and contributing to the tremendous burden of the disorder (Barch and Ceaser, 2012; Bowie and Harvey, 2006; Lee and Park, 2005). Moreover, attempts to treat WM impairment with psychopharmacology or cognitive training have just moderate success (Carbon and Correll, 2014; Lett et al., 2014). Given the importance of this symptom domain and the lack of convincing therapeutic strategies, novel treatment options need to be developed (Hasan et al., 2016).

Anatomically and functionally, WM is associated with the dorsolateral prefrontal cortex (DLPFC) and its remote areas (Barch and Ceaser, 2012; Curtis and D'Esposito, 2003). Due to its high level of structural and functional connectivity (Curtis and D'Esposito, 2003), DLPFC plays a key role in information processing and cognitive control (e.g. Barbey et al., 2013; Miller, 2000) and is crucial not only for executive functions (Niendam et al., 2012) such as WM (Esposito et al., 1995), but also for higher psychological processes such as decision making (Colombo et al., 2016; Heekeren et al., 2006; Krawczyk, 2002) and moral judgement (Jeurissen et al., 2014). Accordingly, in schizophrenia, cognitive deficits have been often linked to structural and functional abnormalities in the prefrontal cortex (Barch and Ceaser, 2012; Minzenberg et al., 2009), especially in the DLPFC (Perlstein et al., 2001; Potkin et al., 2009). Moreover, WM impairment associated with a reduced DLPFC activation and altered DLPFC-Hippocampus connectivity seems to be specific for schizophrenia (Barch et al., 2003; Schneider et al., 2017). Thus, recent research has focused on the DLPFC as a main region of interest for treatment of WM impairment (e.g. Arnsten et al., 2017; Lett et al., 2014).

A promising intervention could be transcranial direct stimulation (tDCS), which, applied to the (DLPFC), has been shown to enhance WM (Hill et al., 2016; Mervis et al., 2017). TDCS is a non-invasive

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brain stimulation technique that alters cortical excitability through application of a weak electrical current on the scalp via anode and cathode, either increasing or reducing neuronal activity, depending on electrode placement, current intensity, and duration of stimulation (for details see, Nitsche et al., 2008). Anodal tDCS (a-tDCS) applied to the left DLPFC could boost cognitive processing in healthy participants (Fregni et al., 2005; Hill et al., 2016) as well as in patients with Parkinson's disease (Boggio et al., 2006) and major depression (Oliveira et al., 2013). A recent meta-analysis pooled the results of 19 studies with both healthy and clinical samples and showed an improvement in WM functioning only in working speed and not in accuracy (Brunoni and Vanderhasselt, 2014). Splitting analyses for healthy and neuropsychiatric cohorts demonstrates, however, that a-tDCS to the DLPFC in clinical samples increased accuracy, but not reaction times in cognitive performance with subtle advantages of online tDCS application (Dedoncker et al., 2016; Hill et al., 2016). First research with schizophrenia patients yielded positive results as well. For instance, a single tDCS application could affect patients' WM on both behavioral and neurophysiological levels, prompting an increase not only in performance accuracy, but also in gamma event-related synchronisation of the left DLPFC (Hoy et al., 2014; Hoy et al., 2015). Interestingly, this effect was present only following stimulation at 2 mA but not at 1 mA (Hoy et al., 2014). Even more promising results can be deducted from the combination of brain stimulation and cognitive training (Orlov et al., 2017).

Despite first evidence for the positive effects of anodal tDCS on cognitive functions, the empirical data for the impact of online tDCS on WM functions in schizophrenia is still scarce. In addition, specific tDCS parameters for the best treatment outcome, such as intensity, need still to be determined. In the present sham-controlled study, we compared for the first time the effects of an online 1 mA or 2 mA a-tDCS on a WM task with different cognitive loads. We conducted two subsequent experiments with schizophrenia patients, undergoing either a 1 mA or a 2 mA a-tDCS, and a sham session. We stimulated the left DLPFC, a region considered to be the most suitable target to enhance verbal WM (Ruf et al., 2017). Differently to previous research, we did not examine performance at only one difficulty level, but increased cognitive load in the course of three test blocks. Investigating the impact of tDCS in relation of varying task complexity is essential, since imaging studies observed a non-linear DLPFC response to a parametric raise in cognitive load (inverted-U-hypothesis, Manoach, 2003), i.e. DLPFC activation drops during highest cognitive loads. Recent research suggests a flattening of this inverted U-relationship (Van Snellenberg et al., 2016) and an inefficiency of DLPFC function in schizophrenia, which may result in hyper- or hypoactivation depending on task difficulty (Potkin et al., 2009). In line with prior research, we expected more accurate and faster task responses during active tDCS, with an advantage of the 2 mA dose. Moreover, we assumed that increase in cognitive load will lead to poorer task performance that would significant interact with brain stimulation.

2. Materials and methods

Forty-three ($N = 43$) schizophrenia patients were recruited from the Department of Psychiatry and Psychotherapy, Klinikum der Universität München. However, three of them (two in Experiment 1 and one in Experiment 2) withdrew their informed consent due to personal reasons (for CONSORT chart, see Supplementary Fig. S1). The final sample consisted of forty schizophrenia patients ($N = 40$, see Supplementary material). Patients' diagnoses were made by consulted psychiatrists and confirmed by the Mini-International Neuropsychiatry Interview (M.I.N.I., Sheehan et al., 1998). All patients received a financial compensation for their participation. The study conformed to the standards of the Declaration of Helsinki and its later amendments and was approved by the local ethics committee of the Ludwig-Maximilians-University Munich. All participants were fully informed about the procedures and gave written informed consent. The study was part of a large research project and registered under https://clinicaltrials.gov/ct2/show/NCT02823639. Neurological illness (e.g. Parkinson's disease, Multiple Sclerosis), serious medical conditions (e.g. oncological or rheumatic diseases) and pregnancy were exclusion criteria. In both experiments, we tested twenty patients. The samples showed no statistical difference in gender, age, smoking behavior (Heatherton et al., 1991) and Edinburgh handedness inventory (Oldfield, 1971). Descriptive characteristics of the study sample are shown in Table 1.

2.1. Procedure

Both experiments had an identical double-blind cross-over design, consisting of a pre-stimulation baseline, an active and a sham tDCS session. Each of these sessions was conducted on different days and both tDCS sessions were separated by at least three working days, as suggested by previous research (Nitsche et al., 2008). The baseline started with the M.I.N.I. (Sheehan et al., 1998) and a background questionnaire on demographics, medical history, medication, handedness (Oldfield, 1971) and smoking behavior (Heatherton et al., 1991). Furthermore, we assessed symptoms severity using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) and the Calgary Depression Scale for Schizophrenia (CDSS, Addington et al., 1990). Then, we measured crystalline intelligence with the Multiple-Choice Vocabulary Intelligence (Mehrfachwahl-Wortschatz-Intelligenztest, MWT-B, Lehrl et al., 1995), processing speed and cognitive flexibility with the Trail Making Test A and B (TMT-A, TMT-B, Tombaugh, 2004), and attention with the d2 Test (Brickenkamp et al., 2010). The pre-stimulation baseline concluded with a training of the complete n-back task to reduce the impact of initial learning on our experimental design (active vs. sham tDCS). The next two experimental conditions were at least 24 h after the baseline and proceeded identically: the patients received either active or sham tDCS in a random order while performing a WM task. Randomization list was created with Random.org (https://www.random.org/lists/).

2.2. Transcranial direct current stimulation

TDCS was applied by an Eldith DC-stimulator (neuroCare Group Munich, Germany) with 35 cm^2 saline soaked (NaCl 0.9%) sponge electrodes. For DLPFC stimulation, we placed the anode over F3 (EEG 10–20 system) and the reference electrode on the right deltoid muscle to reduce the risk for unspecific stimulation of other cortical areas (Plewnia et al., 2015). Impedance was controlled by the device and by the investigator throughout the complete experiment and NaCl was added if necessary to keep the impedance below ~10 kΩ. In the active tDCS sessions, patients received either 1 mA (Experiment 1) or 2 mA (Experiment 2) for 21 min, with a ramp up and ramp down of the current for 15 s. Sham tDCS was performed with the manufacturer's built-in sham mode (Palm et al., 2013) and blinding of patients and investigators was ensured by using the manufactures' stimulation codes. Integrity of blinding was assessed after each session with patients and investigators judging, if the received tDCS was active or sham. We measured tolerability of tDCS during and after stimulation with the Comfort Rating Questionnaire (CRQ, Palm et al., 2016).

2.3. Working memory task

We examined the effect of brain stimulation on WM with a verbal n-back paradigm programmed using PsychoPy (Version 1.83.01, Peirce, 2009). On a standard computer screen a letter from sets of 8 letters, randomly selected out of the alphabet (A to Z), appeared every 2.5 s in a pseudo-randomized order for 500 ms. When the current letter was the same as the letter showed one (1-back), two (2-back) or three (3-back) trials before, patients had to press the space button as quickly as possible. The task consisted of three experimental blocks with 30 targets: 1-back (121 trials), 2-back (122 trials) and 3-back (123 trials).

Table 1
Demographic, clinical and neuropsychological characteristics.
Statistics represent the comparison of the 1 mA and the 2 mA group. Abbreviations: CPZ: chlorpromazine equivalents; PANSS: Positive and Negative Syndrome Scale; CDSS: Calgary Depression Scale for Schizophrenia; MWT-B: Mehrfachwahl-Wortschatz-Intelligenztest; TMT: Trail Making Test; *M*: mean; *SD*: standard deviation; *df*: degree of freedom. χ^2: Chi square test; *F*: F statistic.

	All ($N = 40$)	1 mA ($N = 20$)	2 mA ($N = 20$)	χ^2 (df)	p
Sex (male: female)	31: 9	15: 5	16: 4	0.13 (1)	0.723
Hand preference (right: left)	35: 5	18 : 2	17: 3	0.23 (1)	0.633
Smoker (yes: no)	22: 18	12: 8	10: 10	0.40 (1)	0.525
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	F (df_1, df_2)	p
Demographics					
Age	37.13 (10.63)	36.60 (10.63)	37.65 (10.78)	0.10 (1, 38)	0.758
School Years	11.21 (2.28)	11.17 (2.48)	11.25 (2.15)	0.12 (1, 36)	0.912
Fagerstrom Nicotine Dependence	2.53 (2.94)	2.55 (2.93)	2.50 (3.04)	<0.01 (1, 38)	0.958
CPZ	479.15 (420.26)	498.00 (458.26)	460.30 (389.60)	0.08 (1, 38)	0.781
Age of onset (in years)	27.48 (7.85)	28.40 (9.00)	26.55 (6.60)	0.55 (1,38)	0.463
Duration of illness (in years)	9.15 (7.62)	7.15 (6.86)	11.15 (7.98)	2.89 (1, 38)	0.097
Severity of illness					
PANSS Total Score	56.53 (13.21)	52.65 (7.76)	60.40 (16.33)	3.68 (1, 38)	0.063
PANSS Positive symptoms	14.23 (4.13)	13.00 (2.68)	15.45 (4.97)	3.77 (1, 38)	0.060
PANSS Negative symptoms	13.88 (4.42)	12.85 (3.07)	14.90 (5.34)	2.22 (1, 38)	0.145
PANSS General symptoms	28.43 (6.67)	26.80 (3.92)	30.05 (8.39)	2.46 (1, 38)	0.125
CDSS	3.53 (3.48)	3.30 (2.94)	3.75 (4.01)	0.16 (1, 38)	0.688
Neuropsychological Tests					
MWT-B	26.54 (5.69)	26.00 (6.67)	27.05 (4.71)	0.33 (1, 38)	0.572
TMT-A (s)	34.80 (17.84)	30.81 (11.43)	38.78 (22.12)	2.05 (1, 38)	0.161
TMT-B (s)	84.80 (39.24)	79.10 (31.31)	90.22 (45.69)	0.78 (1, 37)	0.383
d2: attention score	152.80 (58.07)	162.05 (61.34)	143.55 (54.57)	1.02 (1, 38)	0.320

Blocks appeared in successive order to gradually increase cognitive load. Applying the Signal Detection Theory (Green and Swets, 1966; Macmillan and Creelman, 1991), we estimated hit rate, false alarm rate, discriminability index (d prime) and response criterion c (for detailed calculations see, Haatveit et al., 2010; Stanislaw and Todorov, 1999). *Hit rate* describes the probability of correctly recognising signals, whereas *false alarm* rate depicts the probability of mistakenly recognising noise stimuli as signals. Thus, the distance between them, *d prime*, reflects how good the patients discriminate between targets and irrelevant stimuli. The tendency to respond with signal or noise regardless of the stimulus is quantified as *c*. Here, a small c value represents a more liberal response criterion, whereas a high c value - a more conservative one. For the present n-back task, d prime and mean reaction times for each cognitive load served as main measures of WM. Due to missing data, we run analysis for reaction times and criterion c with sample of $n = 19$ in Experiment 1 and $n = 19$ in Experiment 2 at baseline, and $n = 19$ in Experiment 1 for the tDCS sessions.

2.4. Statistical analysis

We conducted all statistical analysis at significance level of $\alpha = 0.05$ using SPSS 24 (IBM Inc.) for Windows. First, we examined effects of tDCS on task performance in two separate 2 (sham vs. tDCS) × 3 (cognitive load) within-subject RM-ANOVAs for Experiment 1 and for Experiment 2. Next, we compared the effects of different tDCS intensities by analyzing data from both experiments together in a 2 (stimulation intensity) × 2 (sham vs. tDCS) × 3 (cognitive load) mixed-design RM-ANOVA. Demographic and clinical differences between experimental samples were assessed using ANOVAs and χ^2-tests. In case of violation of the assumption of sphericity (Mauchly test of sphericity, $p < .05$), the corrected Greenhouse-Geisser estimates were reported. Partial eta square (η_p^2) served as a measure of effect size.

3. Results

3.1. Demographics and clinical data

Samples did not differ in their clinical data and cognitive performance at baseline (Table 1). Patients had moderate positive and negative symptoms according to PANSS, no relevant depressive symptoms according to CDSS, but showed impairments in working speed, attention and cognitive flexibility according to TMT-A/B and d2 test. At baseline, samples did not differ in their n-back performance as well, as measured by d prime ($F_{(1, 38)} = 0.01$, $p = .940$), reaction times ($F_{(1, 36)} = 0.08$, $p = .784$) and c ($F_{(1, 36)} = 0.18$, $p = .674$). Raw values of patients' n-back performance during baseline, active and sham tDCS are presented in the Supplementary material.

3.2. Discriminability index d prime

In Experiment 1, the RM-ANOVA showed that patients' discriminability during sham tDCS was lower than during active 1 mA tDCS ($p =$ 0 .048, $\eta_p^2 = 0.19$, observed power = 0.52). During active 2 mA tDCS, however, d prime improved numerically, but this pattern did not reach significance ($p = 0.145$, $\eta_p^2 = 0.11$). In both experiments, increasing cognitive load resulted in lower discriminability ($p_{Exp1} <$0 .001, $\eta_p^2 =$ 0.83, and $p_{Exp2} <$ .001, $\eta_p^2 = 0.84$), but did not interact with experimental condition ($p_{Exp1} = 0.826$ and $p_{Exp2} = .667$). As expected, the subsequent mixed model RM-ANOVA revealed significant effects for cognitive load ($p <$ .001, $\eta_p^2 = 0.84$,) and greater d prime values during tDCS than during sham ($p = 0.019$, $\eta_p^2 = 0.14$, observed power = 0.67, Fig. 1). Contrary to our hypothesis, the Condition × Load interaction did not reach significance ($p = 0.760$). Stimulation intensity had neither a main ($p = 0.392$, $\eta_p^2 = 0.02$) nor interaction effects on d prime. For details, see Table 2 and Supplementary Table S1. Order of tDCS sessions as well as smoking did not have any main effect on d prime values (F_{order} (1, 36) = 0.66, $p_{order} = 0.421$; $F_{smoking}$ (1, 36) = 0.19, $p_{smoking} = 0.664$) nor any influence on the significant effects of tDCS on d prime (F_{order} (1, 36) = 6.78, $p_{order} = 0.013$; $F_{smoking}$ (1, 36) = 5.93, $p_{smoking} = 0.020$).

3.3. Reaction time

Contrary to our hypothesis, there were no significant main or interaction effects of tDCS on reaction times (RM-ANOVA, see Table 2 and Supplementary Table S1). In contrast, cognitive load had a statistical impact on performance speed, indicating a slower response during 2- and 3-back (Fig. 1.)

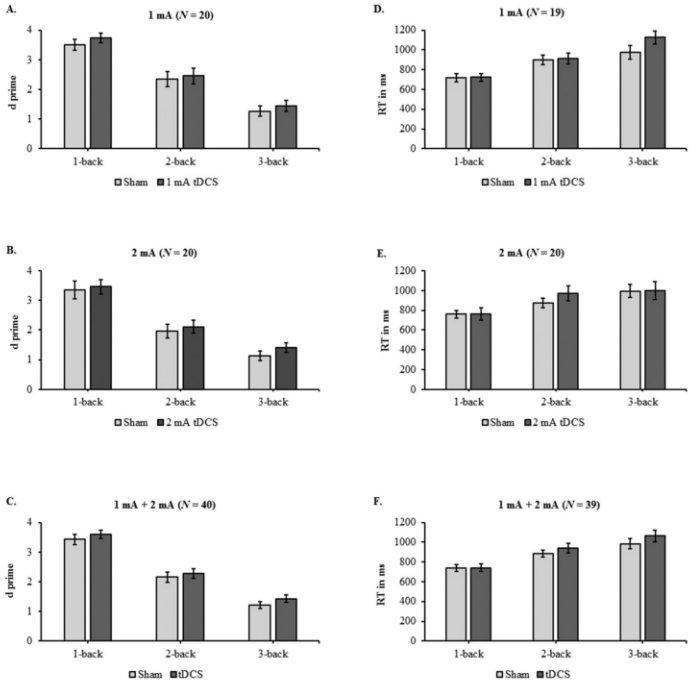

Fig. 1. WM performance during active and sham tDCS across cognitive loads (1-, 2- and 3-back) and experimental groups. Mean d prime values in the (A) 1 mA group, (B) 2 mA group and (C) in both groups. Mean reaction times in the (D) 1 mA group (E) 2 mA group and (F) in both groups. Bars indicate standard errors of mean (SEM).

Table 2
Effects of mixed-design RM-ANOVAs.
RM-ANOVAs with factors 'stimulation intensity', 'experimental condition' (tDCS vs. sham) and 'cognitive load' on d prime, reaction time and criterion c across experimental conditions; Abbreviations: *F*: F statistic; *df*: degrees of freedom; *p*: *p*-value.

	1 mA			2 mA			1 mA + 2 mA		
	F	(df_1, df_2)	*p*	*F*	(df_1, df_2)	*p*	*F*	(df_1, df_2)	*p*
D prime									
Condition (tDCS vs. sham)	4.48	(1, 19)	0.048*	2.31	(1, 19)	0.145	6.05	(1, 38)	0.019*
Load	92.52	(2, 38)	<0.001***	100.54	(1.51, 28.70)	<0.001***	191.63	(2, 76)	<0.001***
Condition × load	0.19	(2, 38)	0.826	0.41	(2, 38)	0.667	0.28	(2, 76)	0.760
Intensity	–	–	–	–	–	–	0.75	(1, 38)	0.392
Condition × intensity	–	–	–	–	–	–	< 0.01	(1, 38)	0.975
Load × intensity	–	–	–	–	–	–	0.75	(2, 76)	0.478
Condition × Load × intensity	–	–	–	–	–	–	0.31	(2, 76)	0.734
Reaction time									
Condition (tDCS vs. sham)	1.87	(1, 18)	0.189	0.75	(1, 19)	0.398	2.29	(1, 37)	0.139
Load	25.24	(1.32, 23.69)	<0.001***	13.89	(1.37, 26.08)	<0.001***	37.95	(1.40, 51.65)	<0.001***
Condition × load	3.45	(1.23, 22.10)	0.069	1.41	(2, 38)	0.256	1.24	(1.43, 52.92)	0.288
Intensity	–	–	–	–	–	–	0.05	(1, 37)	0.829
Condition × intensity	–	–	–	–	–	–	0.03	(1, 37)	0.873
Load × stimulation	–	–	–	–	–	–	1.10	(1.40, 51.65)	0.321
Condition × load × intensity	–	–	–	–	–	–	3.25	(1.43, 52.92)	0.062
Criterion c									
Condition (tDCS vs. sham)	1.83	(1, 18)	0.193	0.09	(1, 19)	0.766	0.64	(1, 37)	0.429
Load	18.72	(1.44, 25.92)	<0.001***	26.31	(1.42, 27.05)	<0.001***	44.15	(1.43, 53.01)	<0.001***
Condition × load	0.32	(2, 36)	0.726	0.79	(2, 38)	0.461	0.88	(2, 74)	0.420
Intensity	–	–	–	–	–	–	4.42	(1, 37)	0.042*
Condition × intensity	–	–	–	–	–	–	1.45	(1, 37)	0.236
Load × intensity	–	–	–	–	–	–	0.04	(1.43, 53.01)	0.914
Condition × load × intensity	–	–	–	–	–	–	0.23	(2, 74)	0.798

* $p < 0.05$.
*** $p < 0.001$.

3.4. Criterion c

Analysis for both experiments separately and together in a mixed-design RM-ANOVA showed similar patterns of results for criterion c (see Table 2 and Fig. 1). Overall, there was no significant effect of active tDCS. N-back level, however, increased the c score ($p<0.001$), indicating that patient responded more conservatively with the increasing cognitive load (for mean c values, see Supplementary Table S1). There were no interaction effects. Furthermore, there was significant overall difference between experimental groups, showing that patients in Experiment 2 had overall higher c values than patients in Experiment 1 ($p = 0.042$, $\eta_p^2 = 0.11$).

3.5. Hit rate

Data analysis showed similar pattern of results for hit rate as for d prime. In Experiment 1, hit rate was significantly higher during active tDCS compared to sham ($p = 0.038$, $\eta_p^2 = 0.21$, observed power = 0.56). In Experiment 2, however, there was no significant change in hit rate during 2 mA stimulation ($p = 0.341$, $\eta_p^2 = 0.05$). The subsequent mixed model RM-ANOVA revealed higher hit rate values during tDCS than during sham ($p = 0.034$, $\eta_p^2 = 0.11$, observed power = 0.57). Stimulation intensity had neither a main ($p = 0.204$) nor an interaction effect on hit rate. For details, see Supplementary Tables S2 and S3.

3.6. False alarm rate

Analysis for both experiments separately and together in a mixed-design RM-ANOVA showed similar result patterns for false alarm rates. Overall, there was no significant effect of experimental condition and of tDCS in particular. As expected, cognitive load led to a significant increase in false alarms ($p < .001$). Stimulation intensity, however, had no effect. For details, see Supplementary Tables S2 and S3.

3.7. TDCS tolerability

Overall, no relevant adverse events occurred and tDCS was well tolerated. There were no group differences in the perceived overall comfort scores with $F_{(1,38)} = 1.63$, $p = 0.210$. Furthermore, tDCS had a similar impact on comfort scores as sham, $F_{(1,38)} = 0.03$, $p = 0.856$. However, paired *t*-test analysis for each stimulation intensity revealed that in Experiment 2 CRQ scores during 2 mA stimulation were significantly higher than during sham, $t_{(19)} = 2.19$, $p = 0.041$, indicating a higher level of discomfort during the active stimulation. In contrast, in Experiment 1, perceived comfort during 1 mA tDCS did not differ from the perceived comfort during sham, $t_{(19)} = -0.10$, $p = 0.920$.

3.8. Integrity of blinding

Unexpectedly, the majority of patients (70%) correctly recognized the session with active tDCS. Separate analysis for stimulation intensity showed that 1 mA tDCS could be correctly identified by 60% of the patients, and 2 mA tDCS by 80%. Chi-square goodness of fit tests comparing the occurrence of "correct recognized/incorrect recognized" active tDCS with the hypothesized occurrence 50/50 showed that significant deviation from the expected values in Experiment 2 ($\chi^2(1) = 7.20$, $p = 0.007$), but not in Experiment 1 ($\chi^2(1) = 0.80$, $p = 0.371$). In contrast, the correct recognition of sham stimulation by patients did not differ from the hypothesized values ($\chi^2_{EXP1}(1) = 0.00$, $p = 1.00$; $\chi^2_{EXP2}(1) = 1.80$, $p = 0.180$). Sham stimulation was recognized by 50% of the patients in Experiment 1 and by 65% in Experiment 2. Comparative analysis showed that there were no differences between both stimulation groups in the correct recognition of active ($\chi^2(1) = 1.91$, $p = 0.168$), and sham tDCS ($\chi^2(1) = 0.92$, $p = 0.337$).

4. Discussion

To our knowledge, this is the first study that systematically compared the effects of two different online tDCS intensities applied to the left DLPFC on simultaneous WM performance in schizophrenia patients across three cognitive loads. Specifically, we analyzed response accuracy and reaction times on a verbal 1-, 2- and 3-back task during a sham and an active 1 mA or 2 mA a-tDCS session. In line with our hypotheses, active online tDCS enhanced WM significantly, i.e. during tDCS patients were able to recognize relevant stimuli more correctly than during sham stimulation. However, this improvement did not extend to working speed or decision criterion. Remarkably, we could not observe the previously reported advantage of the higher current (Hoy et al., 2014; Hoy et al., 2015), implying that tDCS effects on cognition, especially when cognitive tests and tDCS are applied at the same time, could be less dose dependent as presumed. Last, against our assumptions, there was no significant interaction between tDCS and cognitive load.

Our findings are consistent with previous studies demonstrating that tDCS to the DLPFC could prompt more accurate WM functioning in schizophrenia patients, as measured by d prime, but not affect processing speed (Hoy et al., 2014). The lack of significant change in reaction times indicates that the observed increase in d prime could not be explained by a speed-accuracy tradeoff. Subsequent analysis showed no changes in false alarm rates, but a significant improvement of hit rates, leading to higher d prime values. Moreover, higher d prime scores did not reflect in altered criterion c values and therefore could not be caused by an adjustment of task performance strategies. Thus, tDCS may mainly target patients' ability to distinguish between relevant and irrelevant information, which have been shown to be impaired in schizophrenia (Huang et al., 2013; Li et al., 2002; Nuechterlein et al., 2015).

Against prior research demonstrating a significant advantage of higher tDCS intensity (Boggio et al., 2006; Hoy et al., 2014; Hoy et al., 2015), we did not find any statistical differences in WM performance during 1 mA and 2 mA. In fact, subsequent separate analysis showed that the effect of 1 mA was more pronounced, leading to a significant better task performance compared to the sham condition. On the other hand, during 2 mA tDCS we observed a similar numeric increase of d prime that did not reach significance. These findings might be due to differences in study designs. While previous research investigated the effects of 1 mA and 2 mA tDCS on WM *after* stimulation (Boggio et al., 2006; Hoy et al., 2014; Hoy et al., 2015), we analyzed them *during* stimulation. The analysis of tDCS tolerability and blinding integrity showed that 2 mA caused patients a slightly greater discomfort and was more noticeable than 1 mA. Hence, it is possible that the higher current dose had a more distracting effect during task conduction and led to the smaller WM improvement. Thus, we suggest that 2 mA may be more effective when applied offline. Alternatively, the lack of effect of 2 mA tDCS could be explained with patients' more conservative approach to the task in Experiment 2 compared to patients in Experiment 1 as shown by the analysis on the decision criterion c. These findings emphasize the need for future research with large samples to explore online and offline effects of different tDCS intensities in order to find the protocol with the most promising results. From a physiological perspective, tDCS motor-cortex studies indicate a non-linear intensity-dependent effect of tDCS favoring lower tDCS intensities (Batsikadze et al., 2013; Jamil et al., 2017) and such effect could partly explain the observed differences between both stimulation intensities.

As expected, higher task difficulty decreased WM performance across all experimental conditions. However, there was no interaction between cognitive load and brain stimulation, resulting in similar patterns of increase in accuracy in 1-, 2- and 3-back during tDCS. This effect could be partly explained by individual differences in neuropsychological functioning. The severity of cognitive deficits in schizophrenia is considered to be heterogeneous (Weickert et al., 2000) and influenced by

factors like education and general intelligence (Goldstein and Shemansky, 1995). Such heterogeneity was evident in our sample as well with d prime SDs varying between 0.46 and 1.32, where maximum possible d prime value was 4.67 (see Supplementary Table S1). A personalized cognitive task, such as the adaptive n-back, would take into account the performance variance and thus be more suitable for the exploration of the WM - cognitive load relationship in schizophrenia. Since increasing task complexity does not necessarily lead to a greater activation of the DLPFC, prior research adopted the notion that this interaction is non-linear (Manoach, 2003). Moreover, a dysfunction in DLPFC in relation to cognitive load has been previously described in schizophrenia patients (Potkin et al., 2009). Taking these findings into account, further research on this topic is crucial for the thorough understanding of the neural mechanisms underlying WM and how they are impaired in schizophrenia. Combining neuroimaging techniques like EEG and MRI with behavioral data and non-invasive brain stimulation could shed more light on this important topic.

In our study, we observed that a single online-tDCS session applied to the left DLFPC during task execution facilitates WM in schizophrenia patients. This finding is consistent with previous research showing WM improvement in schizophrenia patients after repeated stimulation with 2 mA tDCS (Smith et al., 2015). First work combining cognitive training with tDCS demonstrated results that are even more promising. Those studies indicate that both 1 mA (Ruf et al., 2017) and 2 mA (Orlov et al., 2017) anodal stimulation to the left DLPFC could boost learning curves during WM training. Furthermore, positive effects could be transferred to a non-trained task and be observed even after 9 months in healthy controls (Ruf et al., 2017) and after 6 weeks in schizophrenia patients (Orlov et al., 2017), but there were no direct comparisons of the add-on impact of tDCS in regard of specific tDCS parameters. Notably, similar to our results, no significant WM improvement in schizophrenia patients occurred during the first 2 mA tDCS session, implying that positive effects of brain stimulation are evident only after a consolidation period (Orlov et al., 2017). However, our results suggest that the consolidation period during 1 mA may be slightly shorter than during 2 mA. These findings underline the need for future research on the specific parameters of tDCS in the context of a long-term treatment for cognitive impairment.

Despite having a larger sample than previous publications, our sample size may have been too small to detect a significant effect for 2 mA. Moreover, larger sample sizes would allow to explore possibly moderating factors like sex (Meiron and Lavidor, 2013), smoking behavior (Strube et al., 2015; Wing et al., 2011), motivation and intelligence (Jaeggi et al., 2014). Furthermore, the unavoidable pre-specification of tDCS and training parameters limits the generalizability of our results (Ruf et al., 2017). In addition, despite applying the widely used blinding techniques, we still observed a breakage of blinding, especially during 2 mA. Although surprising, our findings are in line with previous work, demonstrating that blinding of participants and investigators regarding 2 mA tDCS might be challenging (O'Connell et al., 2012). Thus, double-blindness can only be assumed for our 1 mA experiment. We suggest that future research should address effectivity of blinding techniques across stimulation intensities and stress the need to always report blinding integrity data. Finally, we used a single-session design to exploit the effects of tDCS on WM. We cannot rule out that repetitive application of tDCS (Hasan et al., 2016) may have resulted in different outcomes. Moreover, we investigated the effects of tDCS only during the stimulation application. Further research should examine long-term after-effects of online tDCS beyond the period of stimulation. Advantages of our study are the randomized and controlled study design with different tDCS intensities and cognitive load, the well-characterized and clinical stable schizophrenia sample and the independence of both subsamples.

In conclusion, tDCS emerges to be an effective and tolerable method for the treatment of cognitive deficits in schizophrenia. However, further research on the specific tDCS parameters as well on the demographic and clinical factors that might affect cognitive performance is much needed.

Contributors

I.P. was responsible for literature search, data collection and analysis, and wrote the final draft of the manuscript. A.H. was responsible for study design, data analysis and manuscript editing. W.S., C.P. and T.S. were responsible for study design and for contributing to data analysis and results interpretation. B.B. and B.H. were responsible for data collection and participated in the data analysis. F.P. and U.P. contributed to literature searching and manuscript editing. P.F. and A.F. contributed to the funding of this research project. *All authors contributed to and have approved the final manuscript.*

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Conflict of interest

I.P, B.B, B.H, C.P. and T.S. report no conflict of interest. W.S. received paid speakership by Mag&More. P.F. was honorary speaker for Janssen-Cilag, Astra-Zeneca, Eli Lilly, Bristol Myers- Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth, and Essex. During the last 5 years, but not presently, he was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck. F.P. has received speaker's honorarium from Mag&More GmbH and the neuroCare Group as well as support with equipment from neuroConn GmbH, Ilmenau, Germany, Mag&More GmbH and Brainsway Inc., Jerusalem, Israel. U.P. received speaker's honorarium from NeuroCare Group and has a private practice with NeuroCare Group. A.F. reports no conflicts of interests related to the content of the report. A.H. has received a paid speakership from Desitin, Otsuka, Janssen-Cilag and Lundbeck. He was member of an advisory board of Roche and is member of a Janssen-Cilag advisory board.

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This work is part of the MD theses of B.B and B.H.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.06.032.

References

Addington, D., Addington, J., Schissel, B., 1990. A depression rating scale for schizophrenics. Schizophr. Res. 3 (4), 247–251.
Alloway, T.P., Alloway, R.G., 2010. Investigating the predictive roles of working memory and IQ in academic attainment. J. Exp. Child Psychol. 106 (1), 20–29.
Arnsten, A.F.T., Girgis, R.R., Gray, D.L., Mailman, R.B., 2017. Novel dopamine therapeutics for cognitive deficits in schizophrenia. Biol. Psychiatry 81 (1), 67–77.
Barbey, A.K., Colom, R., Grafman, J., 2013. Dorsolateral prefrontal contributions to human intelligence. Neuropsychologia 51 (7), 1361–1369.
Barch, D.M., Ceaser, A., 2012. Cognition in schizophrenia: core psychological and neural mechanisms. Trends Cogn. Sci. 16 (1), 27–34.
Barch, D.M., Sheline, Y.I., Csernansky, J.G., Snyder, A.Z., 2003. Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. Biol. Psychiatry 53 (5), 376–384.
Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.F., Nitsche, M.A., 2013. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J. Physiol. 591 (7), 1987–2000.
Boggio, P.S., Ferrucci, R., Rigonatti, S.P., Covre, P., Nitsche, M., Pascual-Leone, A., Fregni, F., 2006. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J. Neurol. Sci. 249 (1), 31–38.
Bowie, C.R., Harvey, P.D., 2006. Cognitive deficits and functional outcome in schizophrenia. Neuropsychiatr. Dis. Treat. 2 (4), 531–536.
Brickenkamp, R., Schmidt-Atzert, L., Liepmann, D., 2010. Test d2-Revision: Aufmerksamkeits-und Konzentrationstest. Hogrefe, Göttingen.
Brunoni, A.R., Vanderhasselt, M.A., 2014. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn. 86, 1–9.
Carbon, M., Correll, C.U., 2014. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. CNS Spectr. 19 (S1), 35–53.
Colombo, B., Balzarotti, S., Mazzucchelli, N., 2016. The influence of the dorsolateral prefrontal cortex on attentional behavior and decision making. A t-DCS study on emotionally vs. functionally designed objects. Brain Cogn. 104, 7–14.
Curtis, C.E., D'Esposito, M., 2003. Persistent activity in the prefrontal cortex during working memory. Trends Cogn. Sci. 7 (9), 415–423.
Dedoncker, J., Brunoni, A.R., Baeken, C., Vanderhasselt, M.A., 2016. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimul. 9 (4), 501–517.

Esposito, M.D., Detre, J.A., Alsop, D.C., Shin, R.K., 1995. The neural basis of the central executive system of working memory. Nature 378 (6554), 279.
Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M.A., Rigonatti, S.P., Silva, M.T., Paulus, W., Pascual-Leone, A., 2005. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp. Brain Res. 166 (1), 23–30.
Goldstein, G., Shemansky, W.J., 1995. Influences on cognitive heterogeneity in schizophrenia. Schizophr. Res. 18 (1), 59–69.
Green, D.M., Swets, J.A., 1966. Signal Detection Theory and Psychophysics. Wiley, New York.
Haatveit, B.C., Sundet, K., Hugdahl, K., Ueland, T., Melle, I., Andreassen, O.A., 2010. The validity of d prime as a working memory index: results from the "Bergen n-back task". J. Clin. Exp. Neuropsychol. 32 (8), 871–880.
Hasan, A., Strube, W., Palm, U., Wobrock, T., 2016. Repetitive noninvasive brain stimulation to modulate cognitive functions in schizophrenia: a systematic review of primary and secondary outcomes. Schizophr. Bull. 42 (1), 95–109.
Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., Fagerstrom, K.O., 1991. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br. J. Addict. 86 (9), 1119–1127.
Heekeren, H.R., Marrett, S., Ruff, D.A., Bandettini, P.A., Ungerleider, L.G., 2006. Involvement of human left dorsolateral prefrontal cortex in perceptual decision making is independent of response modality. Proc. Natl. Acad. Sci. U. S. A. 103 (26), 10023–10028.
Higgins, D.M., Peterson, J.B., Pihl, R.O., Lee, A.G., 2007. Prefrontal cognitive ability, intelligence, Big Five personality, and the prediction of advanced academic and workplace performance. J. Pers. Soc. Psychol. 93 (2), 298–319.
Hill, A.T., Fitzgerald, P.B., Hoy, K.E., 2016. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimul. 9 (2), 197–208.
Hoy, K.E., Arnold, S.L., Emonson, M.R., Daskalakis, Z.J., Fitzgerald, P.B., 2014. An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. Schizophr. Res. 155 (1–3), 96–100.
Hoy, K.E., Bailey, N.W., Arnold, S.L., Fitzgerald, P.B., 2015. The effect of transcranial Direct Current Stimulation on gamma activity and working memory in schizophrenia. Psychiatry Res. 228 (2), 191–196.
Huang, C.L.-C., Hsiao, S., Hwu, H.-G., Howng, S.-L., 2013. Are there differential deficits in facial emotion recognition between paranoid and non-paranoid schizophrenia? A signal detection analysis. Psychiatry Res. 209 (3), 424–430.
Jaeggi, S.M., Buschkuehl, M., Shah, P., Jonides, J., 2014. The role of individual differences in cognitive training and transfer. Mem. Cogn. 42 (3), 464–480.
Jamil, A., Batsikadze, G., Kuo, H.I., Labruna, L., Hasan, A., Paulus, W., Nitsche, M.A., 2017. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J. Physiol. 595 (4), 1273–1288.
Jeurissen, D., Sack, A.T., Roebroeck, A., Russ, B.E., Pascual-Leone, A., 2014. TMS affects moral judgment, showing the role of DLPFC and TPJ in cognitive and emotional processing. Front. Neurosci. 8, 18.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Krawczyk, D.C., 2002. Contributions of the prefrontal cortex to the neural basis of human decision making. Neurosci. Biobehav. Rev. 26 (6), 631–664.
Lee, J., Park, S., 2005. Working memory impairments in schizophrenia: a meta-analysis. J. Abnorm. Psychol. 114 (4), 599.
Lehrl, S., Triebig, G., Fischer, B., 1995. Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta Neurol. Scand. 91 (5), 335–345.
Lett, T.A., Voineskos, A.N., Kennedy, J.L., Levine, B., Daskalakis, Z.J., 2014. Treating working memory deficits in schizophrenia: a review of the neurobiology. Biol. Psychiatry 75 (5), 361–370.
Li, C.-S.R., Chen, M.-c., Yang, Y.-y., Chen, M.-c., Tsay, P.-K., 2002. Altered performance of schizophrenia patients in an auditory detection and discrimination task: exploring the 'self-monitoring' model of hallucination. Schizophr. Res. 55 (1), 115–128.
Macmillan, N.A., Creelman, C.D., 1991. Detection Theory: A User's Guide. CUP Archive.
Manoach, D.S., 2003. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr. Res. 60 (2), 285–298.
Meiron, O., Lavidor, M., 2013. Unilateral prefrontal direct current stimulation effects are modulated by working memory load and gender. Brain Stimul. 6 (3), 440–447.
Mervis, J.E., Capizzi, R.J., Boroda, E., MacDonald 3rd, A.W., 2017. Transcranial direct current stimulation over the dorsolateral prefrontal cortex in schizophrenia: a quantitative review of cognitive outcomes. Front. Hum. Neurosci. 11, 44.
Miller, E.K., 2000. The prefontral cortex and cognitive control. Nat. Rev. Neurosci. 1 (1), 59–65.
Minzenberg, M.J., Laird, A.R., Thelen, S., Carter, C.S., Glahn, D.C., 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch. Gen. Psychiatry 66 (8), 811–822.
Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., Carter, C.S., 2012. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cogn. Affect. Behav. Neurosci. 12 (2), 241–268.
Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F., Pascual-Leone, A., 2008. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 1 (3), 206–223.
Nuechterlein, K.H., Green, M.F., Calkins, M.E., Greenwood, T.A., Gur, R.E., Gur, R.C., Lazzeroni, L.C., Light, G.A., Radant, A.D., Seidman, L.J., Siever, L.J., Silverman, J.M., Sprock, J., Stone, W.S., Sugar, C.A., Swerdlow, N.R., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Braff, D.L., 2015. Attention/vigilance in schizophrenia: performance results from a large multi-site study of the Consortium on the Genetics of Schizophrenia (COGS). Schizophr. Res. 163 (1), 38–46.
O'Connell, N.E., Cossar, J., Marston, L., Wand, B.M., Bunce, D., Moseley, G.L., De Souza, L.H., 2012. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2 mA. PLoS One 7 (10), e47514.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113.
Oliveira, J.F., Zanao, T.A., Valiengo, L., Lotufo, P.A., Bensenor, I.M., Fregni, F., Brunoni, A.R., 2013. Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder. Neurosci. Lett. 537, 60–64.
Orlov, N.D., Tracy, D.K., Joyce, D., Patel, S., Rodzinka-Pasko, J., Dolan, H., Hodsoll, J., Collier, T., Rothwell, J., Shergill, S.S., 2017. Stimulating cognition in schizophrenia: a controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning. Brain Stimul. 10 (3), 560–566.
Palm, U., Reisinger, E., Keeser, D., Kuo, M.F., Pogarell, O., Leicht, G., Mulert, C., Nitsche, M.A., Padberg, F., 2013. Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. Brain Stimul. 6 (4), 690–695.
Palm, U., Keeser, D., Hasan, A., Kupka, M.J., Blautzik, J., Sarubin, N., Kaymakanova, F., Unger, I., Falkai, P., Meindl, T., Ertl-Wagner, B., Padberg, F., 2016. Prefrontal transcranial direct current stimulation for treatment of schizophrenia with predominant negative symptoms: a double-blind, sham-controlled proof-of-concept study. Schizophr. Bull. 42 (5), 1253–1261.
Peirce, J., 2009. Generating stimuli for neuroscience using PsychoPy. Front. Neuroinform. 2 (10).
Perlstein, W.M., Carter, C.S., Noll, D.C., Cohen, J.D., 2001. Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. Am. J. Psychiatry 158 (7), 1105–1113.
Plewnia, C., Schroeder, P.A., Wolkenstein, L., 2015. Targeting the biased brain: non-invasive brain stimulation to ameliorate cognitive control. Lancet Psychiatry 2 (4), 351–356.
Potkin, S.G., Turner, J.A., Brown, G.G., McCarthy, G., Greve, D.N., Glover, G.H., Manoach, D.S., Belger, A., Diaz, M., Wible, C.G., Ford, J.M., Mathalon, D.H., Gollub, R., Lauriello, J., O'Leary, D., van Erp, T.G., Toga, A.W., Preda, A., Lim, K.O., Fbirn, 2009. Working memory and DLPFC inefficiency in schizophrenia: the FBIRN study. Schizophr. Bull. 35 (1), 19–31.
Ruf, S.P., Fallgatter, A.J., Plewnia, C., 2017. Augmentation of working memory training by transcranial direct current stimulation (tDCS). Sci. Rep. 7 (1), 876.
Schneider, M., Walter, H., Moessnang, C., Schafer, A., Erk, S., Mohnke, S., Romund, L., Garbusow, M., Dixson, L., Heinz, A., Romanczuk-Seiferth, N., Meyer-Lindenberg, A., Tost, H., 2017. Altered DLPFC-hippocampus connectivity during working memory: independent replication and disorder specificity of a putative genetic risk phenotype for schizophrenia. Schizophr. Bull. 43 (5), 1114–1122.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl 20), 22–33 (quiz 34–57).
Smith, R.C., Boules, S., Mattiuz, S., Youssef, M., Tobe, R.H., Sershen, H., Lajtha, A., Nolan, K., Amiaz, R., Davis, J.M., 2015. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr. Res. 168 (1–2), 260–266.
Stanislaw, H., Todorov, N., 1999. Calculation of signal detection theory measures. Behav. Res. Methods Instrum. Comput. 31 (1), 137–149.
Strube, W., Bunse, T., Nitsche, M.A., Wobrock, T., Aborowa, R., Misewitsch, K., Herrmann, M., Falkai, P., Hasan, A., 2015. Smoking restores impaired LTD-like plasticity in schizophrenia: a transcranial direct current stimulation study. Neuropsychopharmacology 40 (4), 822–830.
Tombaugh, T., 2004. Trail Making Test A and B: normative data stratified by age and education. Arch. Clin. Neuropsychol. 19 (2), 203–214.
Van Snellenberg, J.X., Girgis, R.R., Horga, G., van de Giessen, E., Slifstein, M., Ojeil, N., Weinstein, J.J., Moore, H., Lieberman, J.A., Shohamy, D., Smith, E.E., Abi-Dargham, A., 2016. Mechanisms of working memory impairment in schizophrenia. Biol. Psychiatry 80 (8), 617–626.
Weickert, T.W., Goldberg, T.E., Gold, J.M., Bigelow, L.B., Egan, M.F., Weinberger, D.R., 2000. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Arch. Gen. Psychiatry 57 (9), 907–913.
Wing, V.C., Bacher, I., Sacco, K.A., George, T.P., 2011. Neuropsychological performance in patients with schizophrenia and controls as a function of cigarette smoking status. Psychiatry Res. 188 (3), 320–326.

3. Discussion of publications

3.1 Schwippel et al. 2018

Schwippel and colleagues investigated the effects of 1 mA and 2 mA anodal tDCS to the right dlPFC von spatial working memory in patients with schizophrenia. The published study could show that 2 mA anodal tDCS of the right dlPFC can improve spatial working memory in the n-back task (Schwippel et al., 2018b). The improvement was detectable at the highest difficulty level of the n-back task (3-back) and correlated negatively with several scales of cognitive baseline performance. This effect was not found for the experimental group receiving 1 mA anodal stimulation. Another indication of intensity specificity is the effect of tDCS on response times. Here, only 2 mA anodal tDCS slowed response times in the n-back task. This points to a modulation of the speed-accuracy trade-off towards accuracy enabling the patients to press the keyboard more deliberately during stimulation with 2 mA, thus expanding time of working memory recollection. The observed effect could be additionally mediated by the hierarchical instruction to press the keyboard as "correctly and fast" as possible.

Regarding limitations, the small number of participants must be considered. Even if the number is comparable with similar studies, the number of 16 subjects for each intensity must be classified as low. The within-subject design, however, reduces the interindividual variability. Potential carry-over effects are plausible in a within-subject design. These detrimental effects have been adequately countered by a transitional period of 48 hours between repeated measurements. In addition, the study populations for experiment I (1 mA) and experiment II (2 mA) differed in their Fagerstrom test scores. The difference in physical tobacco dependence is relevant because it has been shown that nicotine modulates neuroplasticity in healthy subjects and patients with schizophrenia (Strube et al., 2015). Therefore, an influence of smoking status on the observed effects of different stimulation intensities cannot be excluded, although correlation analyses between Fagerstrom test score and tDCS effectiveness did not yield significant results. From a statistical point of view, results from the explorative analyses of the publication need to be explicitly regarded as

preliminary and need further experimental confirmation. This is especially true, since exploratory results were not corrected for multiple comparisons.

In summary, the study by Schwippel et al. reported beneficial, intensity-specific and task-dependent effects of anodal tDCS on working memory in patients with schizophrenia.

3.2 Papazova et al. 2018

Papazova and colleagues investigated the effect of 1 and 2 mA tDCS to the left dlPFC on verbal working memory in patients with schizophrenia (Papazova et al., 2018). They found an increased accuracy during the application of anodal tDCS which was independent of current intensity. Post hoc, a significant effect for 1 mA anodal tDCS on working memory performance was detected. Response times were not influenced by the stimulation.

In contrast to Schwippel and colleagues (Schwippel et al., 2018b), neither the superiority of a higher current intensity nor a change in response times was observed. Therefore, the effect on performance cannot be caused by a shift in speed-accuracy trade-off. The results are consistent with another tDCS study in patients with schizophrenia which reported no improvement in response times in addition to increased performance (Hoy et al., 2014). Hence, tDCS could specifically affect the ability to differentiate important from unimportant stimuli, an ability known to be reduced in schizophrenia (Nuechterlein et al., 2015).

A limitation of the study is the inclusion of left and right-handed participants, which leads to increased heterogeneity and ignores possible implications regarding laterality of brain functions. For example, previous studies have demonstrated reduced working memory performance in left-handers, which was especially pronounced in left-handers with right hemispheric speech areas (Powell et al., 2012). This is particularly relevant since the study by Papazova et al. was based on the hypothesis of left lateralized verbal working memory. However, a twin study could show that this assignment can be overruled in left-handed people (Lux et al., 2008). This means that Papazova et al. potentially modulated a brain area (left dlPFC) in left-handed participants which is responsible for spatial and not, as intended, for verbal information. The aforementioned hypothesis could represent the decisive difference in comparison to the study by Schwippel et al. and explain the lack of dose-

response relationship. An additional limitation is due to the fact that merely Experiment I (1 mA) can be assumed to be successfully blinded. In experiment II (2 mA), a majority of 80 % of the patients recognized the verum stimulation.

4. General discussion

4.1 Neuroplastic interventions in schizophrenia

Neuroplasticity describes the ability of the brain to change its own structure and function in response to environmental experiences. There is evidence for the presence of an activity-dependent form of neuroplasticity in response to environmental stimuli. This has implications for brain development, memory and learning as well as for brain disorders or brain damage. Neuroplasticity occurs at the cellular level inter alia through synaptic plasticity (Whitlock et al., 2006). This specific form of neuroplasticity describes the activity-dependent modulation of synaptic connectivity. This modulation can manifest itself in the range of a few milliseconds or a few minutes to hours. The latter, known as long-term depression (LTD) and long-term potentiation (LTP), is NMDA-dependent and results in increased or decreased transmission between two or more neurons (Bliss and Collingridge, 1993).

It has been shown that neuroplasticity is altered in schizophrenia (McCullumsmith, 2015). However, it remains controversial how central this finding is in the pathophysiology and etiology of the disorder. Nevertheless, evidence exists that altered neuroplasticity contributes to abnormal distributed activity and altered functional connectivity and in this sense to dysconnectivity (Friston and Frith, 1995). This pathophysiological process can take place via abnormal regulation of NMDA-dependent plasticity by unregulated neurotransmitters such as dopamine or acetylcholine (Stephan et al., 2009). The influence of NMDA receptors is impressively documented by the intake of ketamine, an NMDA receptor antagonist, which can lead to a psychotic state (Newcomer et al., 1999). Due to the dysfunction of NMDA receptors, hyperglutamatergic and hypoglutamatergic states may occur in schizophrenia. The relationship between NMDA receptor dysfunction and negative symptoms as well as cognitive dysfunction is well documented (Neill et al., 2010, Malhotra et al., 1997). In summary, the dysconnectivity hypothesis and the glutamate hypothesis might share altered neuroplasticity as an overarching malfunction (Moghaddam and Javitt, 2012).

Hence, modulation of neuroplasticity through environmental stimuli like psychotherapy or cognitive training or by direct neuromodulatory interventions might address this central dysfunction. With regard to the potential neuroplastic effects of non-invasive brain stimulation, a recent study investigated the relationship between excitability and plasticity. Kozyrev and colleagues were able to show in animal experiments that rTMS generates a transient brain state with increased excitability and variability, which represents a time window for neuroplasticity (Kozyrev et al., 2018). In this time window, a functional reorganization of the visual cortex could be induced by visual stimuli. In conclusion, the authors describe a brain state transiently destabilized by TMS that sensitizes the cortex for sensory input. In contrast to the direct induction of a plasticity window by TMS, non-depolarizing tDCS is often coupled with a stimulus. This stimulus may consist of a further neuromodulatory intervention, as in metaplastic priming by tDCS (Hurley and Machado, 2017), or of an environmental stimulus. Thus, tDCS can be understood rather as a modulator than as an inductor of synaptic plasticity (Kronberg et al., 2017). This dependence on endogenous synaptic plasticity is further highlighted by the absence of long-term tDCS effects after blockade of NMDA receptors (Liebetanz et al., 2002).

The possibility of opening a window of synaptic plasticity by means of tDCS, thus modulating endogenous synaptic plasticity, displays an opportunity to enhance therapeutic interventions in schizophrenia. Specific and individualized therapeutic interventions can repeatedly take place in this time frame. Here, tDCS itself is not the therapeutic intervention but a door opener for psychotherapy or cognitive remediation, which both rely on plasticity to alter neuronal connectivity and hereby behavior. Still, the optimal administration of tDCS to each patient remains a challenge. The investigation of predictors of tDCS response and a method to monitor neuroplastic effects during stimulation are essential to titrate tDCS parameters for each individual in order to ensure a maintained plasticity window. Further personalization is essential for the selection of a fitting therapeutic intervention utilizing the newly gained neuroplasticity. Additionally, the interdependence of neuroplasticity-inducing tDCS and other therapeutic interventions making use of neuroplasticity needs to be monitored. Unaddressed so far are the time immediately after intervention and the following

sleep cycle, which are critical to further strengthen synaptic connections and newly adopted behavior.

4.2 tDCS parameter

4.2.1 tDCS: Intensity

Computer models predict an electric field of less than 1 V/m in the cortex, inducing modulation of the membrane potential of pyramidal cells, which is considered the primary mechanism of tDCS action. It is plausible to assume that an increase in intensity leads to an increase in electric field power and increasing modulation of the membrane potential. Whether a subsequent increase in behavioral effects is to be expected with higher intensities is in debate. Animal experiments and experiments performed on brain slices support this hypothesis, although higher current intensities were used compared to human application. However, this theory presupposes stable environmental conditions that cannot be achieved in the living brain. The magnification of the electric field also leads to unspecific stimulation of a widely branched cortical network and subcortical structures. This phenomenon is also caused by the use of large-area (35 cm^2) stimulation electrodes in human subjects. Furthermore, the total dose of applied energy in the physical sense not only depends on the intensity, but also on the duration of application, electrode configuration and neuroanatomy, which equally influence the effects of tDCS.

Currently, current strengths between 0.5 and 4 mA are used in humans. With increasing current intensity, the test person feels a stronger tingling sensation due to skin resistance, which can compromise the blinding procedure and indirectly influence the measured effect via placebo and nocebo effects. Investigations have shown a safe blinding for 1 mA, whereas contradictory results are available for 2 mA with regard to successful blinding (Palm et al., 2013, O'connell et al., 2012, Wallace et al., 2016). For the use of 3 and 4 mA, few investigations exist so far. However, initial data indicate a low side effect rate and the possibility of adequate blinding (Reckow et al., 2018, Borges et al., 2017).

The dose-response relationship of tDCS is primarily investigated by TMS induced MEP of the primary motor cortex. First studies showed higher MEP after application of 2 mA compared to 1 mA tDCS after 20 minutes of anodal tDCS in healthy volunteers (Nitsche and

Paulus, 2000). Recent studies experimentally altering duration, intensity and brain state indicate a more complicated mechanism and question the postulated linear relationship between intensity and MEP amplitude (Ho et al., 2016). In addition, MEP studies are based on electrophysiological measurements after tDCS application and the results can hardly be transferred to non-motor areas.

Furthermore, the prediction of behavioral and thus clinical effects of tDCS in patients with schizophrenia is complicated. Here, plasticity-inducing tDCS meets an altered neurophysiology caused by the disorder itself (Stephan et al., 2009, McCullumsmith et al., 2004). This complex interaction is further complicated by frequent pharmacological treatments (Agarwal et al., 2016). Only a few studies directly compared the effectiveness of different tDCS current intensities in patients with schizophrenia. There is also a large variance in cognitive tests and electrode configurations used, which further reduces comparability. Previous studies have produced contradictory results, i.e. both the superiority of 2 mA (Schwippel et al., 2018b, Hoy et al., 2014) and non-superiority of a high intensity (Papazova et al., 2018). However, the majority of published studies on tDCS and schizophrenia exclusively used 2 mA (e.g. (Gomes et al., 2018, Rassovsky et al., 2018), see table 1). The generalizability of these findings for patients with schizophrenia is equally limited by the fact that currents above 2 mA were not tested. In addition, distinctive current intensities may be required to influence different symptoms and their anatomical target structures. It should also be noted that, from a methodological point of view, a finding of a significant effect of one amperage compared to a non-significant effect of another amperage does not indicate a dose-response relationship.

In summary, the linear relationship between intensity and behavioral effects is questionable for the reasons described above (Esmaeilpour et al., 2018, Batsikadze et al., 2013). Esmaeilpour and colleagues postulate a "complex state-dependent non-monotonic dose response" of tDCS (Esmaeilpour et al., 2018). Since tDCS modulates current brain activity, it is conceivable that the interaction of current intensity and endogenous brain activity is of major importance for brain plasticity and behavior.

4.2.2 tDCS: Duration

The energy that tDCS delivers to the brain is a function of current intensity, area of the stimulation electrode, resistance and time. The time factor includes the stimulation duration of a single application as well as the repetitive application of tDCS in several sessions. From a physical point of view, an extension of the stimulation duration increases the energy applied by tDCS. As already discussed in 4.2.1, increasing the energy by modulating the current intensity with constant time does not necessarily lead to an improvement of efficacy or to neuroplastic effects at all. In fact, there is evidence that a narrow corridor of optimal electrical energy hitting the neurons exists. Above and below this energy level, no or even contradictory effects of tDCS are to be expected (Lisman, 2001, Stagg et al., 2018). It should be noted that the desired neuroplastic effects are triggered electrically by voltage changes of calcium receptors and thus a change of the membrane potential as well as by neurochemical processes, e.g. mediated by GABA. The initiation of these different neuroplastic processes occurs with a time delay, so that the tDCS, which remains constant over time, meets a brain in different neuroplastic states. In light of this premise, the optimal dimension of time to maximize neuroplasticity should exist while stable current intensity is presumed.

Already the first publication by Nitsche and Paulus illustrated intensity-dependent (1 mA more effective than 0.8 mA) and time-dependent (5 min more effective than 4 min tDCS) effects of tDCS (Nitsche and Paulus, 2000, Bastani and Jaberzadeh, 2012). Subsequent studies optimized intensity and stimulation duration with the aim of increasing MEP after motor cortex stimulation. Stimulation durations of 9-13 minutes and 1 mA anodal tDCS were able to increase excitability of the motor cortex up to 90 minutes after completion of tDCS (Nitsche and Paulus, 2001, Nitsche et al., 2008). In later studies, stimulation duration was increased to 20 minutes in patient collectives after stroke (Hummel et al., 2005) and with frontal application of tDCS (Ohn et al., 2008). Studies on the effects of significantly longer tDCS sessions on motor cortex plasticity and working memory are rare (Hill et al., 2016), but the study by Batsikadze and colleagues showed that an extension of the stimulation duration, at least for cathodal tDCS, does not lead to an increase of neuroplasticity (Batsikadze et al., 2013). This paradigm shift, which questioned the linear correlation of

stimulation duration and neuroplastic effects, was complemented by Gamboa and colleagues. In a study utilizing theta-burst stimulation, doubling of the stimulation time led to an inversion of effect direction, ergo the prolonged excitatory stimulation had an inhibitory effect (Gamboa et al., 2010). First pilot studies directly compared the excitatory properties of different stimulation durations for tDCS. Here, 20 minutes of anodal 1 mA or 2 mA tDCS increased short-interval intracortical inhibition (SICI) and decreased intracortical facilitation (ICF) whereas 30 minutes of stimulation did not alter cortical excitability (Vignaud et al., 2018). In an analysis of seven studies and 89 subjects, Ho and colleagues also showed that 2 mA is not superior to 1 mA stimulation in terms of cortical excitability (Ho et al., 2016). In addition, they reported increased motor excitability through repetitive tDCS application. A first meta-analytical examination of the excitability of the motor cortex yielded a mean effect size (SMD = 0.52) of 13 minutes for anodal tDCS compared to a lower effect size (SMD = 0.26) after 10 minutes of stimulation. It should be noted that only six studies were included in this analysis, the stimulation durations were not directly compared experimentally and only single session stimulation was applied (Bastani and Jaberzadeh, 2012).

For neurocognitive parameters and prefrontal tDCS no inversion of effect with increasing stimulation duration has been published so far. However, a large number of negative study results exist, which could partly be due to a suboptimal stimulation duration. The effect of repetitive tDCS stimulation was meta-analytically investigated in a patient group with schizophrenia. The authors could show that twice daily application of tDCS and the number of >10 stimulation sessions was significantly superior to sham treatment (Kim et al., 2018). The analysis included 7 studies with 242 patients, targeting auditory verbal hallucinations, as well as 9 studies with 313 patients, addressing positive and negative symptoms in schizophrenia.

In summary, it can be stated that both stimulation duration and stimulation intensity have a non-linear influence on cortical excitability of the motor cortex. This finding is complicated by a hardly quantifiable influence of the individual brain state on the effects of tDCS. These interindividual differences of brain state could lead to negative study results (Tremblay et al., 2016). This is particularly true if targeting prefrontal brain structures and cognitive

parameters. Here, the aim of creating a stable and comparable brain state across individuals is far more difficult to achieve, since the instruction to relax the muscles is easier to follow than instructions potentially targeting prefrontal brain functions.

4.2.3 tDCS: Polarity

The simplified statement that anodal stimulation increases excitability and cathodal stimulation decreases excitability is not fully valid. Rather, the degree of excitability is influenced by intensity, duration, brain state and polarity. The anatomical translation into non-motor areas and the polarity-specific effects of tDCS on cognitive functions further complicate the prediction of effects. This is especially true, since the excitability of frontal brain areas is difficult to quantify, and higher cognitive functions result from the recruitment of a branched neuronal network.

With regard to the motor cortex, the AeCi effect (anodal-excitation / cathodal-inhibition) was postulated after the first studies by Nitsche and Paulus (Nitsche and Paulus, 2000, Nitsche et al., 2003) and animal experiments (Wachter et al., 2011). This postulate was supported by polarity-specific findings regarding cortical neurotransmitters (Stagg et al., 2009) and motor learning processes (Stagg et al., 2011). This effect was meta-analytically confirmed in 10 out of 15 investigated studies (Jacobson et al., 2012), whereby the analysis was dated from 2012 and only included homogeneous studies published before 2010. New studies on the motor cortex cast doubt on this dichotomy. One study with functional magnetic resonance imaging showed a modulation of functional connectivity after 10 min 1 mA cathodal tDCS, but not after anodal or sham stimulation (Amadi et al., 2014). A recently published study investigating paired associative stimulation (PAS) induced plasticity showed the induction of plasticity independent of polarity (Faber et al., 2017).

The investigation of cognitive processes with tDCS is difficult due to the use of inconsistent cognitive tests. Some studies confirmed the AeCI effect, whereas the majority were able to reproduce only part of it. The direct comparison between anodal and cathodal tDCS is rare. A meta-analysis published in 2016 comprising 61 studies with subjects and neuropsychiatric patients showed that a single session of anodal tDCS improved speed (subjects) and accuracy (patients) in cognitive tasks, which did not apply to cathodal stimulation (Dedoncker et al.,

2016). Interestingly, some studies reported an improvement in cognitive performance in conjunction with cathodal stimulation (Monti et al., 2008). Two hypotheses are conceivable to explain these findings. Either cathodal tDCS had an excitatory effect or inhibitory processes may lead to an improvement of certain cognitive functions (Schroeder and Plewnia, 2017). With regard to the first hypothesis, it has been shown that an extension of cathodal stimulation duration leads to an increase in cortical excitability (Batsikadze et al., 2013), which could be due to a peak effect of the calcium influence (Lugon et al., 2015). With regard to the second hypothesis, it is important to note that neuropsychiatric disorders can be associated with the over-activation of distinct brain areas. For example, inhibitory cathodal tDCS is used in the treatment of auditory verbal hallucinations to alleviate activation of the temporo-parietal cortex (Brunelin et al., 2012). Other non-invasive brain stimulation procedures, such as theta-burst stimulation, also adopt inhibitory stimulation paradigms for the treatment of depression and tinnitus (Schwippel et al., 2019). Further mechanisms explaining the effectiveness of cathodal stimulation are a possible improvement of the signal-to-noise ratio in the brain (Zwissler et al., 2014), a priming function of cathodal stimulation (Christova et al., 2015) and the reduction of distractive network activity (Schroeder et al., 2016).

4.2.4 tDCS: Brain state-dependency

Another factor influencing the tDCS effect is the state of the brain. The brain state is manifested in current neurochemical constellations, oscillations and the use of functional networks. This initial brain state encountered by tDCS is therefore dependent on the brain activity before the start of stimulation. This effect, conceptualized as metaplasticity, has far-reaching consequences for the effectiveness of stimulation and could explain part of the heterogeneity of stimulation effects. However, even more temporally distant factors influencing brain activity are illustrated in figure 4.

Speaking of task-shaped neuronal activity, the influence of individual cognitive abilities is conceivable and has been repeatedly associated with stimulation effects. Here, the efficacy of network activation differs as a function of task difficulty and individual cognitive ability (Manoach, 2003). This leads to differential tDCS effects like the ceiling effect, since subjects

already performing very well in a cognitive task have little room for improvement by tDCS. Their neuronal networks are already sufficiently shaped to perform the task well. On the other hand, several studies indicate that subjects and especially patients with initially lower task performance benefit disproportionately from the stimulation (Schwippel et al., 2018b). Following these thoughts, tDCS does not necessarily encounter brains harmonized by a defined cognitive task, but rather individual activity patterns of the subjects, which can diverge further with increasing task difficulty. Since the performance in cognitive tasks is often related to general intelligence, one would expect a relevant impact of this factor as well. Fittingly, previous studies have shown a variable influence of general cognitive functions on tDCS effectiveness (Katz et al., 2017, Berryhill and Jones, 2012) and a non-linear interaction between initial task performance and task difficulty (Learmonth et al., 2015, Tseng et al., 2012). The variance of the brain states might even be increased in patients with schizophrenia. This is due to considerable interindividual differences in the severity of symptoms, underlying pathophysiology, cognitive abilities and medication. This is of particular importance with regard to tDCS effects, since tDCS itself does not trigger any action potentials. Additional studies on healthy volunteers support that notion and showed that tDCS and TMS effects depend on the level of difficulty of the memory task (Pope et al., 2015, Jones and Berryhill, 2012). A study in patients with schizophrenia showed an expansion of cortical activity (Holt et al., 1999) and a variable picture of hyperactive and hypoactive prefrontal areas during a working memory task. Here, patients with schizophrenia already show a high activity of the dlPFC at a low working memory load (which is subjectively high), which decreases fast when the working memory load increases (Manoach, 2003). This specific pattern of cortical recruitment (inverted U-curve) could explain the observed task-dependent effects in patients with schizophrenia.

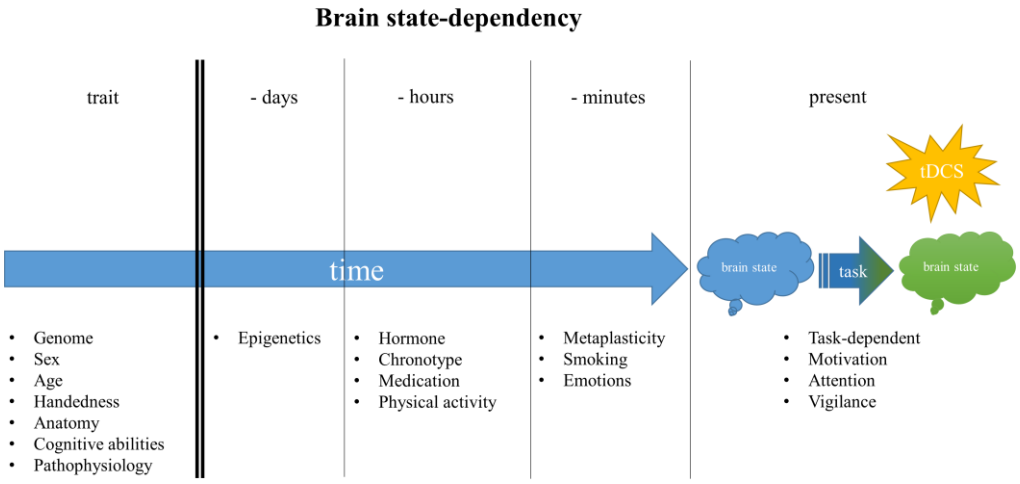

Figure 4: Brain state-dependency

4.3 Future of tDCS treatment in schizophrenia

The treatment of schizophrenia remains a challenge for patients and practitioners alike in the 21st century. In addition to the antidopaminergic mechanism of action of antipsychotics, the pharmacological arsenal of psychiatrists remains empty with regard to therapy-refractory productive symptoms or negative and cognitive symptoms. Pharmaceutical approaches targeting the glutamatergic or gabaergic signal transduction pathway remain experimental. Additionally, significant side effects of pharmacological agents negatively influence quality of life and potentially the lifespan. Psychotherapeutic treatments have become established and effective. Yet, psychotherapy requires a certain stability of productive symptoms, and a minimum of cognitive capability. Innovative approaches combine psychotherapeutic content with computer programs, such as the AVATAR program (Craig et al., 2018). However, psychotherapeutic interventions remain relatively expensive and, due to their limited availability, a privilege for a selected group of patients. In general, a new therapeutic option should be evaluated by following prerequisites:

(1) Safety / side-effect profile
(2) Effectiveness
(3) Applicability / Availability

(4) Cost-benefit ratio

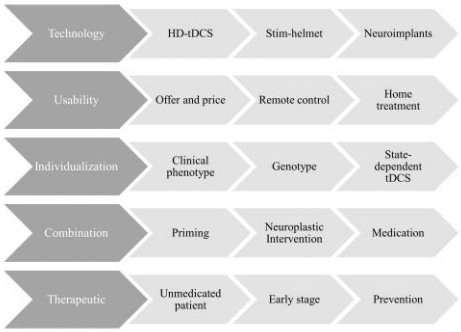

Figure 5: Future of tDCS therapy in neuropsychiatric patients

Regarding non-invasive neuromodulatory procedures (tDCS, TMS), patient safety is in principle ensured – even though there is no systematic investigation of the long-term effect of repeated stimulation treatments. Since tDCS is easy to apply and, especially considering long-term use, inexpensive, there is a good cost-benefit ratio. This would allow a broad use with patients. Then, treatment would not depend on monetary possibilities or the place of residence. The effectiveness of tDCS in improving cognitive deficits and other symptom dimensions is the focus of this dissertation and is currently investigated in a number of multicenter studies. As tDCS is a neuroplastic intervention, it is reasonable to integrate other neuroplastic stimuli in an increasingly personalized treatment plan. Possible candidates are nutrition, aerobic sports, sleep and cognitive stimuli. Figure 5 illustrates further areas of improvement with regard to technology, therapeutic intervention and other aspects of future tDCS treatments.

5. Conclusion

The present dissertation presents the application of tDCS for the treatment of cognitive deficits in patients with schizophrenia in two publications. The studies systematically investigate the effect of different stimulation intensities on verbal and spatial working memory in schizophrenia. The investigations are based on preliminary work in healthy volunteers (Ruf et al., 2017).

In the experiment by Schwippel and colleagues, improvement of spatial working memory was demonstrated with 2 mA tDCS (Schwippel et al., 2018b). There is first evidence that the stimulation effect is influenced by general cognitive abilities of the patients and by task difficulty. The stimulation effect is manifested in the improvement of the error rate, in

combination with a slowing of response time, which is suggestive for a speed-accuracy trade-off.

With regard to verbal working memory, Papazova and colleagues showed a beneficial effect of tDCS on working memory performance (Papazova et al., 2018). Interestingly, no effect of intensity was observed, although tDCS with lower intensity (1 mA) proved to be more effective. A slowing of the response time was only numerically present.

In summary, tDCS can improve working memory performance in schizophrenia, although the optimal stimulation parameters and predictors of effectiveness remain the subject of future research.

6. Summary in German language

Die vorliegende Dissertation untersucht die Anwendung von tDCS zur Behandlung von kognitiven Defiziten bei Menschen mit Schizophrenie in mehreren Experimenten.

Im Experiment von Schwippel und Kollegen wurde die Verbesserung des räumlichen Arbeitsgedächtnisses mit 2 mA tDCS nachgewiesen. Es zeigten sich erste Hinweise darauf, dass die Stimulationswirkung von den allgemeinen kognitiven Fähigkeiten der Patienten und von der Schwierigkeit der Aufgabe beeinflusst wird. Der Stimulationseffekt zeigte sich in der Verbesserung der Fehlerrate in Kombination mit einer Verlangsamung der Reaktionszeit, was für eine Anpassung der Balance zwischen Geschwindigkeit und Genauigkeit spricht.

In Bezug auf das verbale Arbeitsgedächtnis wiesen Papazova und Kollegen einen positiven Einfluss von tDCS auf die Arbeitsgedächtnisleistung von Menschen mit Schizophrenie nach. Interessanterweise wurde kein Intensitätseffekt beobachtet, obwohl sich in der post hoc Analyse tDCS in der niedrigeren Intensität (1 mA) als effektiver erwies. Eine Verlangsamung der Reaktionszeit war lediglich numerisch nachweisbar.

Zusammenfassend lässt sich konstatieren, dass tDCS die Arbeitsgedächtnisleistung von Menschen mit Schizophrenie verbessern kann. Die optimalen Stimulationsparameter und weitere Prädiktoren für die Wirksamkeit der Stimulation sind Gegenstand der zukünftigen Forschung.

7. Bibliography

AGARWAL, S. M., BOSE, A., SHIVAKUMAR, V., NARAYANASWAMY, J. C., CHHABRA, H., KALMADY, S. V., VARAMBALLY, S., NITSCHE, M. A., VENKATASUBRAMANIAN, G. & GANGADHAR, B. N. 2016. Impact of antipsychotic medication on transcranial direct current stimulation (tDCS) effects in schizophrenia patients. *Psychiatry research,* 235**,** 97-103.

AMADI, U., ILIE, A., JOHANSEN-BERG, H. & STAGG, C. J. 2014. Polarity-specific effects of motor transcranial direct current stimulation on fMRI resting state networks. *Neuroimage,* 88**,** 155-161.

ANDREASEN, N. C. 1982. Negative symptoms in schizophrenia: definition and reliability. *Archives of general psychiatry,* 39**,** 784-788.

AU, J., KATZ, B., BUSCHKUEHL, M., BUNARJO, K., SENGER, T., ZABEL, C., JAEGGI, S. M. & JONIDES, J. 2016. Enhancing working memory training with transcranial direct current stimulation. *Journal of cognitive neuroscience,* 28**,** 1419-1432.

BADDELEY, A. 1992a. Working memory. *Science,* 255**,** 556-559.

BADDELEY, A. 1992b. Working memory: The interface between memory and cognition. *Journal of cognitive neuroscience,* 4**,** 281-288.

BADDELEY, A. 2000. The episodic buffer: a new component of working memory? *Trends in cognitive sciences,* 4**,** 417-423.

BARCH, D. M. & CARTER, C. S. 2005. Amphetamine improves cognitive function in medicated individuals with schizophrenia and in healthy volunteers. *Schizophrenia research,* 77**,** 43-58.

BASTANI, A. & JABERZADEH, S. 2012. Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. *Clinical neurophysiology,* 123**,** 644-657.

BATSIKADZE, G., MOLIADZE, V., PAULUS, W., KUO, M. F. & NITSCHE, M. 2013. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of physiology,* 591**,** 1987-2000.

BERRYHILL, M. E. & JONES, K. T. 2012. tDCS selectively improves working memory in older adults with more education. *Neuroscience letters,* 521**,** 148-151.

BLISS, T. V. P. & COLLINGRIDGE, G. L. 1993. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature,* 361**,** 31.

BORA, E. & PANTELIS, C. 2015. Meta-analysis of cognitive impairment in first-episode bipolar disorder: comparison with first-episode schizophrenia and healthy controls. *Schizophrenia bulletin,* 41**,** 1095-1104.

BORGES, H., KHADKA, N., BOATENG, A., PANERI, B., NASSIS, E., SHIN, Y., CHOI, H., KIM, S., LEE, K. & BIKSON, M. 2017. Tolerability of up to 4 mA tDCS using adaptive stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation,* 10**,** e31-e32.

BREIER, A., SU, T.-P., SAUNDERS, R., CARSON, R., KOLACHANA, B., DE BARTOLOMEIS, A., WEINBERGER, D., WEISENFELD, N., MALHOTRA, A. & ECKELMAN, W. 1997. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proceedings of the National Academy of Sciences,* 94**,** 2569-2574.

BRUNELIN, J., MONDINO, M., GASSAB, L., HAESEBAERT, F., GAHA, L., SUAUD-CHAGNY, M.-F., SAOUD, M., MECHRI, A. & POULET, E. 2012. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *American Journal of Psychiatry,* 169**,** 719-724.

BRUNONI, A. R., AMADERA, J., BERBEL, B., VOLZ, M. S., RIZZERIO, B. G. & FREGNI, F. 2011. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology,* 14**,** 1133-1145.

BRUNONI, A. R. & VANDERHASSELT, M. A. 2014. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain and Cognition,* 86**,** 1-9.

BUCHANAN, R. W., JAVITT, D. C., MARDER, S. R., SCHOOLER, N. R., GOLD, J. M., MCMAHON, R. P., HERESCO-LEVY, U. & CARPENTER, W. T. 2007. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. *American Journal of Psychiatry,* 164**,** 1593-1602.

BUCHANAN, R. W., KEEFE, R. S. E., LIEBERMAN, J. A., BARCH, D. M., CSERNANSKY, J. G., GOFF, D. C., GOLD, J. M., GREEN, M. F., JARSKOG, L. F. & JAVITT, D. C. 2011. A randomized clinical trial of MK-0777 for the treatment of cognitive impairments in people with schizophrenia. *Biological psychiatry,* 69**,** 442-449.

BURNS, J., JOB, D., BASTIN, M., WHALLEY, H., MACGILLIVRAY, T., JOHNSTONE, E. & LAWRIE, S. M. 2003. Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study. *The British Journal of Psychiatry,* 182**,** 439-443.

CASTNER, S. A., WILLIAMS, G. V. & GOLDMAN-RAKIC, P. S. 2000. Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. *Science,* 287**,** 2020-2022.

CELLA, M., PRETI, A., EDWARDS, C., DOW, T. & WYKES, T. 2017. Cognitive remediation for negative symptoms of schizophrenia: a network meta-analysis. *Clinical psychology review,* 52**,** 43-51.

CHANG, C.-C., KAO, Y.-C., CHAO, C.-Y. & CHANG, H.-A. 2019. Enhancement of cognitive insight and higher-order neurocognitive function by fronto-temporal transcranial direct current stimulation (tDCS) in patients with schizophrenia. *Schizophrenia research,* 208**,** 430-438.

CHRISTOVA, M., RAFOLT, D. & GALLASCH, E. 2015. Cumulative effects of anodal and priming cathodal tDCS on pegboard test performance and motor cortical excitability. *Behavioural brain research,* 287**,** 27-33.

COLOM, R., MARTÍNEZ, K., BURGALETA, M., ROMÁN, F. J., GARCÍA-GARCÍA, D., GUNTER, J. L., HUA, X., JAEGGI, S. M. & THOMPSON, P. M. 2016. Gray matter volumetric changes with a challenging adaptive cognitive training program based on the dual n-back task. *Personality and Individual Differences,* 98**,** 127-132.

CRADDOCK, N. & OWEN, M. J. 2010. The Kraepelinian dichotomy–going, going… but still not gone. *The British Journal of Psychiatry,* 196**,** 92-95.

CRAIG, T. K., RUS-CALAFELL, M., WARD, T., LEFF, J. P., HUCKVALE, M., HOWARTH, E., EMSLEY, R. & GARETY, P. A. 2018. AVATAR therapy for auditory verbal hallucinations in people with psychosis: a single-blind, randomised controlled trial. *The Lancet Psychiatry,* 5**,** 31-40.

CRAMER, S. C., SUR, M., DOBKIN, B. H., O'BRIEN, C., SANGER, T. D., TROJANOWSKI, J. Q., RUMSEY, J. M., HICKS, R., CAMERON, J. & CHEN, D. 2011. Harnessing neuroplasticity for clinical applications. *Brain,* 134**,** 1591-1609.

CURTIS, C. E. & D'ESPOSITO, M. 2003. Persistent activity in the prefrontal cortex during working memory. *Trends in cognitive sciences,* 7**,** 415-423.

D'ESPOSITO, M. & POSTLE, B. R. 1999. The dependence of span and delayed-response performance on prefrontal cortex. *Neuropsychologia,* 37**,** 1303-1315.

DEACON, T. 1997. The symbolic species. New York: Norton.
DEDONCKER, J., BRUNONI, A. R., BAEKEN, C. & VANDERHASSELT, M.-A. 2016. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. *Brain Stimulation,* 9**,** 501-517.
DORPH-PETERSEN, K.-A., PIERRI, J. N., PEREL, J. M., SUN, Z., SAMPSON, A. R. & LEWIS, D. A. 2005. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology,* 30**,** 1649.
EACK, S. M., HOGARTY, G. E., CHO, R. Y., PRASAD, K. M. R., GREENWALD, D. P., HOGARTY, S. S. & KESHAVAN, M. S. 2010. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. *Archives of general psychiatry,* 67**,** 674-682.
ENGLE, R. W., TUHOLSKI, S. W., LAUGHLIN, J. E. & CONWAY, A. R. 1999. Working memory, short-term memory, and general fluid intelligence: a latent-variable approach. *Journal of experimental psychology: General,* 128**,** 309.
ESMAEILPOUR, Z., MARANGOLO, P., HAMPSTEAD, B. M., BESTMANN, S., GALLETTA, E., KNOTKOVA, H. & BIKSON, M. 2018. Incomplete evidence that increasing current intensity of tDCS boosts outcomes. *Brain stimulation,* 11**,** 310-321.
FABER, H., OPITZ, A., MÜLLER-DAHLHAUS, F. & ZIEMANN, U. 2017. Polarity-independent effects of tDCS on paired associative stimulation-induced plasticity. *Brain stimulation,* 10**,** 1061-1069.
FISHER, M., HOLLAND, C., SUBRAMANIAM, K. & VINOGRADOV, S. 2009. Neuroplasticity-based cognitive training in schizophrenia: an interim report on the effects 6 months later. *Schizophrenia bulletin,* 36**,** 869-879.
FORBES, N. F., CARRICK, L. A., MCINTOSH, A. M. & LAWRIE, S. M. 2009. Working memory in schizophrenia: a meta-analysis. *Psychological medicine,* 39**,** 889-905.
FORNITO, A., YÜCEL, M., PATTI, J., WOOD, S. & PANTELIS, C. 2009. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. *J Schizophrenia research,* 108**,** 104-113.
FRISTON, K. J. & FRITH, C. D. 1995. Schizophrenia: a disconnection syndrome. *Clin Neurosci,* 3**,** 89-97.
FUSTER, J. 2015. *The prefrontal cortex,* Academic Press.
FUSTER, J. M. 2002. Frontal lobe and cognitive development. *J Neurocytol,* 31**,** 373-85.
GAEBEL, W., RÖSSLER, W. & SARTORIUS, N. 2017. *The Stigma of Mental Illness-End of the Story?,* Springer.
GAMBOA, O. L., ANTAL, A., MOLIADZE, V. & PAULUS, W. 2010. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. *Experimental brain research,* 204**,** 181-187.
GATHERCOLE, S. E., BROWN, L. & PICKERING, S. J. 2003. Working memory assessments at school entry as longitudinal predictors of National Curriculum attainment levels. *Educational Child Psychology,* 20**,** 109-122.
GEVINS, A. & CUTILLO, B. 1993. Spatiotemporal dynamics of component processes in human working memory. *Electroencephalography and clinical Neurophysiology,* 87**,** 128-143.
GODER, R., BAIER, P. C., BEITH, B., BAECKER, C., SEECK-HIRSCHNER, M., JUNGHANNS, K. & MARSHALL, L. 2013. Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia. *Schizophrenia Research,* 144**,** 153-154.

GOMES, J., TREVIZOL, A., DUCOS, D., GADELHA, A., ORTIZ, B., FONSECA, A., AKIBA, H., AZEVEDO, C., GUIMARAES, L. & SHIOZAWA, P. 2018. Effects of transcranial direct current stimulation on working memory and negative symptoms in schizophrenia: a phase II randomized sham-controlled trial. *Schizophrenia Research: Cognition,* 12**,** 20-28.

GORE, F. M., BLOEM, P. J., PATTON, G. C., FERGUSON, J., JOSEPH, V., COFFEY, C., SAWYER, S. M. & MATHERS, C. D. 2011. Global burden of disease in young people aged 10–24 years: a systematic analysis. *The Lancet,* 377**,** 2093-2102.

GREEN, M. F. 2016. Impact of cognitive and social cognitive impairment on functional outcomes in patients with schizophrenia. *J Clin Psychiatry,* 77 Suppl 2**,** 8-11.

GREEN, M. F., KERN, R. S. & HEATON, R. K. 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia research,* 72**,** 41-51.

HÄFNER, H., MAURER, K. & AN DER HEIDEN, W. 2013. ABC Schizophrenia study: an overview of results since 1996. *Social psychiatry and psychiatric epidemiology,* 48**,** 1021-1031.

HATTORI, Y., MORIWAKI, A. & HORI, Y. 1990. Biphasic effects of polarizing current on adenosine-sensitive generation of cyclic AMP in rat cerebral cortex. *Neuroscience letters,* 116**,** 320-324.

HEATON, R. K., GLADSJO, J. A., PALMER, B. W., KUCK, J., MARCOTTE, T. D. & JESTE, D. V. 2001. Stability and course of neuropsychological deficits in schizophrenia. *Archives of general psychiatry,* 58**,** 24-32.

HILL, A. T., FITZGERALD, P. B. & HOY, K. E. 2016. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. *Brain stimulation,* 9**,** 197-208.

HO, B.-C., ANDREASEN, N. C., ZIEBELL, S., PIERSON, R. & MAGNOTTA, V. 2011. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Archives of general psychiatry,* 68**,** 128-137.

HO, K.-A., TAYLOR, J. L., CHEW, T., GÁLVEZ, V., ALONZO, A., BAI, S., DOKOS, S. & LOO, C. K. 2016. The effect of transcranial direct current stimulation (tDCS) electrode size and current intensity on motor cortical excitability: evidence from single and repeated sessions. *Brain stimulation,* 9**,** 1-7.

HOLT, J., VAN HORN, J. & MEYER-LINDENBERG, A. 1999. Multiple sources of signal abnormality underlying prefrontal hypofunction and increased variability in the sites of activation within BA 9/46 in individual medication free schizophrenic patients. *Society for Neuroscience,* 14**,** 18.

HORAN, W. P., BRAFF, D. L., NUECHTERLEIN, K. H., SUGAR, C. A., CADENHEAD, K. S., CALKINS, M. E., DOBIE, D. J., FREEDMAN, R., GREENWOOD, T. A. & GUR, R. E. 2008. Verbal working memory impairments in individuals with schizophrenia and their first-degree relatives: findings from the Consortium on the Genetics of Schizophrenia. *Schizophrenia research,* 103**,** 218-228.

HOWES, O. D. & KAPUR, S. 2009. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophrenia bulletin,* 35**,** 549-562.

HOWES, O. D. & MURRAY, R. M. 2014. Schizophrenia: an integrated sociodevelopmental-cognitive model. *The Lancet,* 383**,** 1677-1687.

HOY, K. E., ARNOLD, S. L., EMONSON, M. R. L., DASKALAKIS, Z. J. & FITZGERALD, P. B. 2014. An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. *Schizophrenia Research,* 155**,** 96-100.

HOY, K. E., BAILEY, N. W., ARNOLD, S. L. & FITZGERALD, P. B. 2015. The effect of transcranial Direct Current Stimulation on gamma activity and working memory in schizophrenia. *Psychiatry Research,* 228**,** 191-196.

HUMMEL, F., CELNIK, P., GIRAUX, P., FLOEL, A., WU, W.-H., GERLOFF, C. & COHEN, L. G. 2005. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain,* 128**,** 490-499.

HURLEY, R. & MACHADO, L. 2017. Using tDCS priming to improve brain function: Can metaplasticity provide the key to boosting outcomes? *Neuroscience & Biobehavioral Reviews,* 83**,** 155-159.

IMPEY, D., BADDELEY, A., NELSON, R., LABELLE, A. & KNOTT, V. 2017. Effects of transcranial direct current stimulation on the auditory mismatch negativity response and working memory performance in schizophrenia: a pilot study. *Journal of Neural Transmission,* 124**,** 1489-1501.

ISLAM, N., AFTABUDDIN, M., MORIWAKI, A., HATTORI, Y. & HORI, Y. 1995. Increase in the calcium level following anodal polarization in the rat brain. *Brain research,* 684**,** 206-208.

JACOBSON, L., KOSLOWSKY, M. & LAVIDOR, M. 2012. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Experimental brain research,* 216**,** 1-10.

JAEGGI, S. M., BUSCHKUEHL, M., JONIDES, J. & PERRIG, W. J. 2008. Improving fluid intelligence with training on working memory. *Proceedings of the National Academy of Sciences,* 105**,** 6829-6833.

JEON, D.-W., JUNG, D.-U., KIM, S.-J., SHIM, J.-C., MOON, J.-J., SEO, Y.-S., JUNG, S.-S., SEO, B.-J., KIM, J.-E. & OH, M. 2018. Adjunct transcranial direct current stimulation improves cognitive function in patients with schizophrenia: A double-blind 12-week study. *Schizophrenia research,* 197**,** 378-385.

JOHNS, L. C. & VAN OS, J. 2001. The continuity of psychotic experiences in the general population. *Clinical psychology review,* 21**,** 1125-1141.

JONES, K. T. & BERRYHILL, M. 2012. Parietal contributions to visual working memory depend on task difficulty. *Frontiers in psychiatry,* 3**,** 81.

KATZ, B., AU, J., BUSCHKUEHL, M., ABAGIS, T., ZABEL, C., JAEGGI, S. M. & JONIDES, J. 2017. Individual differences and long-term consequences of tDCS-augmented cognitive training. *Journal of cognitive neuroscience,* 29**,** 1498-1508.

KAZUI, H., YOSHIDA, T., TAKAYA, M., SUGIYAMA, H., YAMAMOTO, D., KITO, Y., WADA, T., NOMURA, K., YASUDA, Y. & YAMAMORI, H. 2011. Different characteristics of cognitive impairment in elderly schizophrenia and Alzheimer's disease in the mild cognitive impairment stage. *Dementia and geriatric cognitive disorders extra,* 1**,** 20-30.

KEEFE, R. S. E., BILDER, R. M., DAVIS, S. M., HARVEY, P. D., PALMER, B. W., GOLD, J. M., MELTZER, H. Y., GREEN, M. F., CAPUANO, G. & STROUP, T. S. 2007. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Archives of general psychiatry,* 64**,** 633-647.

KEESER, D., MEINDL, T., BOR, J., PALM, U., POGARELL, O., MULERT, C., BRUNELIN, J., MÖLLER, H.-J., REISER, M. & PADBERG, F. 2011. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. *Journal of Neuroscience,* 31**,** 15284-15293.

KIM, J., IWATA, Y., PLITMAN, E., CARAVAGGIO, F., CHUNG, J. K., SHAH, P., BLUMBERGER, D. M., POLLOCK, B. G., REMINGTON, G. & GRAFF-GUERRERO, A. 2018. A meta-analysis of transcranial direct current stimulation for schizophrenia:"Is more better?". *Journal of Psychiatric Research*.

KONNOPKA, A., KLINGBERG, S., WITTORF, A. & KÖNIG, H.-H. 2009. The cost of schizophrenia in Germany: a systematic review of the literature. *Psychiatrische Praxis,* 36**,** 211-218.

KOZYREV, V., STAADT, R., EYSEL, U. T. & JANCKE, D. 2018. TMS-induced neuronal plasticity enables targeted remodeling of visual cortical maps. *Proceedings of the National Academy of Sciences,* 115**,** 6476-6481.

KRONBERG, G., BRIDI, M., ABEL, T., BIKSON, M. & PARRA, L. C. 2017. Direct current stimulation modulates LTP and LTD: activity dependence and dendritic effects. *Brain stimulation,* 10**,** 51-58.

KUBICKI, M., PARK, H., WESTIN, C. F., NESTOR, P. G., MULKERN, R. V., MAIER, S. E., NIZNIKIEWICZ, M., CONNOR, E. E., LEVITT, J. J., FRUMIN, M., KIKINIS, R., JOLESZ, F. A., MCCARLEY, R. W. & SHENTON, M. E. 2005. DTI and MTR abnormalities in schizophrenia: analysis of white matter integrity. *Neuroimage,* 26**,** 1109-18.

KURTZ, M. M., BRONFELD, M. & ROSE, J. 2012. Cognitive and social cognitive predictors of change in objective versus subjective quality-of-life in rehabilitation for schizophrenia. *Psychiatry research,* 200**,** 102-107.

KYZIRIDIS, T. C. 2005. Notes on the history of schizophrenia. *German Journal of Psychiatry,* 8**,** 42-48.

LEARMONTH, G., THUT, G., BENWELL, C. S. Y. & HARVEY, M. 2015. The implications of state-dependent tDCS effects in aging: behavioural response is determined by baseline performance. *Neuropsychologia,* 74**,** 108-119.

LEE, J. & PARK, S. 2005. Working memory impairments in schizophrenia: a meta-analysis. *Journal of abnormal psychology,* 114**,** 599.

LETT, T. A., VOINESKOS, A. N., KENNEDY, J. L., LEVINE, B. & DASKALAKIS, Z. J. 2014. Treating Working Memory Deficits in Schizophrenia: A Review of the Neurobiology. *Biological Psychiatry,* 75**,** 361-370.

LIANG, M., ZHOU, Y., JIANG, T., LIU, Z., TIAN, L., LIU, H. & HAO, Y. 2006. Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging. *Neuroreport,* 17**,** 209-213.

LIEBETANZ, D., NITSCHE, M. A., TERGAU, F. & PAULUS, W. 2002. Pharmacological approach to synaptic and membrane mechanisms of DC-induced neuroplasticity in man. *Brain,* 125**,** 2238-2247.

LIM, K. O., HEDEHUS, M., MOSELEY, M., DE CRESPIGNY, A., SULLIVAN, E. V. & PFEFFERBAUM, A. 1999. Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Arch Gen Psychiatry,* 56**,** 367-74.

LINDENMAYER, J. P., KULSA, M. K. C., SULTANA, T., KAUR, A., YANG, R., LJURI, I., PARKER, B. & KHAN, A. 2019. Transcranial direct-current stimulation in ultra-treatment-resistant schizophrenia. *Brain stimulation,* 12**,** 54-61.

LINKE, M., JANKOWSKI, K. S., WICHNIAK, A., JAREMA, M. & WYKES, T. 2019. Effects of cognitive remediation therapy versus other interventions on cognitive functioning in schizophrenia inpatients. *Neuropsychological rehabilitation,* 29**,** 477-488.

LISMAN, J. E. 2001. Three Ca2+ levels affect plasticity differently: the LTP zone, the LTD zone and no man's land. *The Journal of physiology,* 532**,** 285-285.

LUGON, M. D. M. V., BATSIKADZE, G., FRESNOZA, S., GRUNDEY, J., KUO, M.-F., PAULUS, W., NAKAMURA-PALACIOS, E. M. & NITSCHE, M. A. 2015. Mechanisms of nicotinic modulation of glutamatergic neuroplasticity in humans. *Cerebral Cortex,* 27**,** 544-553.

LUX, S., KELLER, S., MACKAY, C., EBERS, G., MARSHALL, J. C., CHERKAS, L., REZAIE, R., ROBERTS, N., FINK, G. R. & GURD, J. M. 2008. Crossed cerebral lateralization for verbal and visuo-spatial function in a pair of handedness discordant monozygotic twins: MRI and fMRI brain imaging. *Journal of anatomy,* 212**,** 235-248.

MACDONALD, A. W., COHEN, J. D., STENGER, V. A. & CARTER, C. S. 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science,* 288**,** 1835-1838.

MACKENZIE, L. E., UHER, R. & PAVLOVA, B. 2019. Cognitive performance in first-degree relatives of individuals with vs without major depressive disorder: a meta-analysis. *JAMA psychiatry,* 76**,** 297-305.

MALHOTRA, A. K., PINALS, D. A., ADLER, C. M., ELMAN, I., CLIFTON, A., PICKAR, D. & BREIER, A. 1997. Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. *Neuropsychopharmacology,* 17**,** 141.

MANOACH, D. S. 2003. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophrenia research,* 60**,** 285-298.

MCCULLUMSMITH, R. E. 2015. Evidence for schizophrenia as a disorder of neuroplasticity. Am Psychiatric Assoc.

MCCULLUMSMITH, R. E., CLINTON, S. M. & MEADOR-WOODRUFF, J. H. 2004. Schizophrenia as a disorder of neuroplasticity. *International review of neurobiology***,** 19-47.

MCGRATH, J., SAHA, S., CHANT, D. & WELHAM, J. 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic reviews,* 30**,** 67-76.

MELBY-LERVÅG, M., REDICK, T. S. & HULME, C. 2016. Working memory training does not improve performance on measures of intelligence or other measures of "far transfer" evidence from a meta-analytic review. *Perspectives on Psychological Science,* 11**,** 512-534.

MELTZER, H. Y. 1997. Treatment-resistant schizophrenia-the role of clozapine. *Current medical research and opinion,* 14**,** 1-20.

MERVIS, J. E., CAPIZZI, R. J., BORODA, E. & MACDONALD III, A. W. 2017. Transcranial direct current stimulation over the dorsolateral prefrontal cortex in schizophrenia: a quantitative review of cognitive outcomes. *Frontiers in human neuroscience,* 11**,** 44.

MEYER-LINDENBERG, A. S., OLSEN, R. K., KOHN, P. D., BROWN, T., EGAN, M. F., WEINBERGER, D. R. & BERMAN, K. F. 2005. Regionally specific disturbance of dorsolateral prefrontal–hippocampal functional connectivity in schizophrenia. *Archives of general psychiatry,* 62**,** 379-386.

MILLER, E. K. 2000. The prefontral cortex and cognitive control. *Nature reviews neuroscience,* 1**,** 59.

MOGHADDAM, B. & JAVITT, D. 2012. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology,* 37**,** 4.

MÖLLER, A., NEMMI, F., KARLSSON, K. & KLINGBERG, T. 2017. Transcranial electric stimulation can impair gains during working memory training and affects the resting state connectivity. *Frontiers in human neuroscience,* 11**,** 364.

MONTI, A., COGIAMANIAN, F., MARCEGLIA, S., FERRUCCI, R., MAMELI, F., MRAKIC-SPOSTA, S., VERGARI, M., ZAGO, S. & PRIORI, A. 2008. Improved naming after transcranial direct current stimulation in aphasia. *Journal of Neurology, Neurosurgery & Psychiatry,* 79**,** 451-453.

MOON, S.-Y., KIM, M., HWANG, W. J., LEE, T. Y. & KWON, J. S. 2019. A pilot study investigating the effect of transcranial direct current stimulation on the electrophysiological correlates of working memory in patients with schizophrenia. *Psychiatry Research: Neuroimaging,* 284**,** 9-12.

MÜLLER, N. 2014. Immunology of schizophrenia. *Neuroimmunomodulation,* 21**,** 109-116.

MÜLLER, N. & KNIGHT, R. 2006. The functional neuroanatomy of working memory: contributions of human brain lesion studies. *Neuroscience,* 139**,** 51-58.

NAGEL, B. J., HERTING, M. M., MAXWELL, E. C., BRUNO, R. & FAIR, D. 2013. Hemispheric lateralization of verbal and spatial working memory during adolescence. *Brain and cognition,* 82**,** 58-68.

NARITA, Z., INAGAWA, T., SUEYOSHI, K., LIN, C. & SUMIYOSHI, T. 2017. Possible facilitative effects of repeated anodal transcranial direct current stimulation on functional outcome 1 month later in schizophrenia: an open trial. *Frontiers in psychiatry,* 8**,** 184.

NEILL, J. C., BARNES, S., COOK, S., GRAYSON, B., IDRIS, N. F., MCLEAN, S. L., SNIGDHA, S., RAJAGOPAL, L. & HARTE, M. K. 2010. Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDA receptor antagonism. *Pharmacology & therapeutics,* 128**,** 419-432.

NEWCOMER, J. W., FARBER, N. B., JEVTOVIC-TODOROVIC, V., SELKE, G., MELSON, A. K., HERSHEY, T., CRAFT, S. & OLNEY, J. W. 1999. Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology,* 20**,** 106.

NIENDAM, T. A., BEARDEN, C. E., ROSSO, I. M., SANCHEZ, L. E., HADLEY, T., NUECHTERLEIN, K. H. & CANNON, T. D. 2003. A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *American Journal of Psychiatry,* 160**,** 2060-2062.

NIENOW, T. M., LIM, K. O. & MACDONALD, A. W. 2016. TDCS produces incremental gain when combined with working memory training in patients with schizophrenia: A proof of concept pilot study. *Schizophrenia Research,* 172**,** 218-219.

NITSCHE, M. A., COHEN, L. G., WASSERMANN, E. M., PRIORI, A., LANG, N., ANTAL, A., PAULUS, W., HUMMEL, F., BOGGIO, P. S. & FREGNI, F. 2008. Transcranial direct current stimulation: state of the art 2008. *Brain stimulation,* 1**,** 206-223.

NITSCHE, M. A., NITSCHE, M. S., KLEIN, C. C., TERGAU, F., ROTHWELL, J. C. & PAULUS, W. 2003. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clinical Neurophysiology,* 114**,** 600-604.

NITSCHE, M. A. & PAULUS, W. 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of physiology,* 527**,** 633-639.

NITSCHE, M. A. & PAULUS, W. 2001. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology,* 57**,** 1899-1901.

NUECHTERLEIN, K. H., GREEN, M. F., CALKINS, M. E., GREENWOOD, T. A., GUR, R. E., GUR, R. C., LAZZERONI, L. C., LIGHT, G. A., RADANT, A. D. & SEIDMAN, L. J. 2015. Attention/vigilance in schizophrenia: performance results from a large multi-site study of the Consortium on the Genetics of Schizophrenia (COGS). *Schizophrenia research,* 163**,** 38-46.

O'CONNELL, N. E., COSSAR, J., MARSTON, L., WAND, B. M., BUNCE, D., MOSELEY, G. L. & DE SOUZA, L. H. 2012. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2mA. *PloS one,* 7**,** e47514.

OHN, S. H., PARK, C.-I., YOO, W.-K., KO, M.-H., CHOI, K. P., KIM, G.-M., LEE, Y. T. & KIM, Y.-H. 2008. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. *Neuroreport,* 19**,** 43-47.

OLESEN, P. J., WESTERBERG, H. & KLINGBERG, T. 2004. Increased prefrontal and parietal activity after training of working memory. *Nature neuroscience,* 7**,** 75.

OLNEY, J. W., NEWCOMER, J. W. & FARBER, N. B. 1999. NMDA receptor hypofunction model of schizophrenia. *Journal of psychiatric research,* 33**,** 523-533.

ORLOV, N. D., TRACY, D. K., JOYCE, D., PATEL, S., RODZINKA-PASKO, J., DOLAN, H., HODSOLL, J., COLLIER, T., ROTHWELL, J. & SHERGILL, S. S. 2017. Stimulating

cognition in schizophrenia: a controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning. *Brain stimulation,* 10**,** 560-566.

OWEN, A. M., MCMILLAN, K. M., LAIRD, A. R. & BULLMORE, E. 2005. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human brain mapping,* 25**,** 46-59.

PADINJAREVEETTIL, A. M. T., ROGERS, J., LOO, C. & MARTIN, D. 2015. Transcranial Direct Current Stimulation to Enhance Cognitive Remediation in Schizophrenia. *Brain Stimulation,* 8**,** 307-309.

PALM, U., REISINGER, E., KEESER, D., KUO, M.-F., POGARELL, O., LEICHT, G., MULERT, C., NITSCHE, M. A. & PADBERG, F. 2013. Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. *Brain stimulation,* 6**,** 690-695.

PALMER, B. W., HEATON, R. K., PAULSEN, J. S., KUCK, J., BRAFF, D., HARRIS, M. J., ZISOOK, S. & JESTE, D. V. 1997. Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology,* 11**,** 437.

PALVA, J. M., MONTO, S., KULASHEKHAR, S. & PALVA, S. 2010. Neuronal synchrony reveals working memory networks and predicts individual memory capacity. 107**,** 7580-7585.

PAPAZOVA, I., STRUBE, W., BECKER, B., HENNING, B., SCHWIPPEL, T., FALLGATTER, A. J., PADBERG, F., PALM, U., FALKAI, P. & PLEWNIA, C. 2018. Improving working memory in schizophrenia: Effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC. *Schizophrenia research,* 202**,** 203-209.

PEIJNENBORGH, J. C., HURKS, P. M., ALDENKAMP, A. P., VLES, J. S. & HENDRIKSEN, J. G. 2016. Efficacy of working memory training in children and adolescents with learning disabilities: A review study and meta-analysis. *Neuropsychological Rehabilitation,* 26**,** 645-672.

PETRIDES, M. & PANDYA, D. 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *European Journal of Neuroscience,* 11**,** 1011-1036.

POLANIA, R., NITSCHE, M. A. & RUFF, C. C. 2018. Studying and modifying brain function with non-invasive brain stimulation. *Nature neuroscience***,** 1.

POPE, P. A., BRENTON, J. W. & MIALL, R. C. 2015. Task-specific facilitation of cognition by anodal transcranial direct current stimulation of the prefrontal cortex. *Cerebral Cortex,* 25**,** 4551-4558.

POWELL, J. L., KEMP, G. J. & GARCÍA-FINAÑA, M. 2012. Association between language and spatial laterality and cognitive ability: an fMRI study. *Neuroimage,* 59**,** 1818-1829.

PRIBRAM, K. H., MISHKIN, M., ROSVOLD, H. E. & KAPLAN, S. J. 1952. Effects on delayed-response performance of lesions of dorsolateral and ventromedial frontal cortex of baboons. *J Comp Physiol Psychol,* 45**,** 565-75.

PRIORI, A., BERARDELLI, A., RONA, S., ACCORNERO, N. & MANFREDI, M. 1998. Polarization of the human motor cortex through the scalp. *Neuroreport,* 9**,** 2257-2260.

RASSOVSKY, Y., DUNN, W., WYNN, J., WU, A. D., IACOBONI, M., HELLEMANN, G. & GREEN, M. F. 2015. The effect of transcranial direct current stimulation on social cognition in schizophrenia: a preliminary study. *Schizophrenia research,* 165**,** 171-174.

RASSOVSKY, Y., DUNN, W., WYNN, J. K., WU, A. D., IACOBONI, M., HELLEMANN, G. & GREEN, M. F. 2018. Single transcranial direct current stimulation in schizophrenia: Randomized, cross-over study of neurocognition, social cognition, ERPs, and side effects. *PloS one,* 13**,** e0197023.

RECKOW, J., RAHMAN-FILIPIAK, A., GARCIA, S., SCHLAEFFLIN, S., CALHOUN, O., DASILVA, A. F., BIKSON, M. & HAMPSTEAD, B. M. 2018. Tolerability and blinding of

4x1 high-definition transcranial direct current stimulation (HD-tDCS) at two and three milliamps. *Brain stimulation,* 11**,** 991-997.
REINHART, R. M., ZHU, J., PARK, S. & WOODMAN, G. F. 2015. Synchronizing theta oscillations with direct-current stimulation strengthens adaptive control in the human brain. *Proceedings of the National Academy of Sciences,* 112**,** 9448-9453.
REINHART, R. M. G. & NGUYEN, J. A. 2019. Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nature neuroscience,* 22**,** 820-827.
ROTTSCHY, C., LANGNER, R., DOGAN, I., REETZ, K., LAIRD, A. R., SCHULZ, J. B., FOX, P. T. & EICKHOFF, S. B. 2012. Modelling neural correlates of working memory: a coordinate-based meta-analysis. *Neuroimage,* 60**,** 830-846.
RUF, S. P., FALLGATTER, A. J. & PLEWNIA, C. 2017. Augmentation of working memory training by transcranial direct current stimulation (tDCS). *Scientific Reports,* 7**,** 876.
SALA, G. & GOBET, F. 2018. Cognitive training does not enhance general cognition. *Trends in cognitive sciences,* 23**,** 9-20.
SANISLOW, C. A., PINE, D. S., QUINN, K. J., KOZAK, M. J., GARVEY, M. A., HEINSSEN, R. K., WANG, P. S.-E. & CUTHBERT, B. N. 2010. Developing constructs for psychopathology research: research domain criteria. *Journal of abnormal psychology,* 119**,** 631.
SCHMITT, A., HASAN, A., GRUBER, O. & FALKAI, P. 2011. Schizophrenia as a disorder of disconnectivity. *European archives of psychiatry and clinical neuroscience,* 261**,** 150.
SCHROEDER, P. A., PFISTER, R., KUNDE, W., NUERK, H.-C. & PLEWNIA, C. 2016. Counteracting implicit conflicts by electrical inhibition of the prefrontal cortex. *Journal of Cognitive Neuroscience,* 28**,** 1737-1748.
SCHROEDER, P. A. & PLEWNIA, C. 2017. Beneficial effects of cathodal transcranial direct current stimulation (tDCS) on cognitive performance. *Journal of Cognitive Enhancement,* 1**,** 5-9.
SCHUBERT, M. H., YOUNG, K. A. & HICKS, P. B. 2006. Galantamine improves cognition in schizophrenic patients stabilized on risperidone. *Biological Psychiatry,* 60**,** 530-533.
SCHWAIGHOFER, M., FISCHER, F. & BÜHNER, M. 2015. Does working memory training transfer? A meta-analysis including training conditions as moderators. *Educational Psychologist,* 50**,** 138-166.
SCHWIPPEL, T., HASAN, A., PAPAZOVA, I., FALLGATTER, A. & PLEWNIA, C. 2018a. Verbesserung der kognitiven Leistungsfähigkeit von Patienten mit Schizophrenie durch transkranielle Gleichstromstimulation. *Nervenheilkunde,* 37**,** 340-346.
SCHWIPPEL, T., PAPAZOVA, I., STRUBE, W., FALLGATTER, A. J., HASAN, A. & PLEWNIA, C. 2018b. Beneficial effects of anodal transcranial direct current stimulation (tDCS) on spatial working memory in patients with schizophrenia. *European Neuropsychopharmacology,* 28**,** 1339-1350.
SCHWIPPEL, T., SCHROEDER, P. A., FALLGATTER, A. J. & PLEWNIA, C. 2019. Clinical review: The therapeutic use of theta-burst stimulation in mental disorders and tinnitus. *Progress in Neuro-Psychopharmacology and Biological Psychiatry,* 92**,** 285-300.
SCHWIPPEL, T., WASSERKA, B., FALLGATTER, A. J. & PLEWNIA, C. 2017. Safety and efficacy of long-term home treatment with transcranial direct current stimulation (tDCS) in a case of multimodal hallucinations. *Brain stimulation,* 10**,** 873-874.
SHIOZAWA, P., GOMES, J. S., DUCOS, D. V., AKIBA, H. T., DIAS, Á. M., TREVIZOL, A. P., UCHIDA, R. R., ORLOV, N. & CORDEIRO, Q. 2016. Effect of transcranial direct current stimulation (tDCS) over the prefrontal cortex combined with cognitive training for treating schizophrenia: a sham-controlled randomized clinical trial. *Trends in psychiatry and psychotherapy,* 38**,** 175-177.
SILVANTO, J., MUGGLETON, N. & WALSH, V. 2008. State-dependency in brain stimulation studies of perception and cognition. *Trends in cognitive sciences,* 12**,** 447-454.

SINKEVICIUTE, I., BEGEMANN, M., PRIKKEN, M., ORANJE, B., JOHNSEN, E., LEI, W. U., HUGDAHL, K., KROKEN, R. A., RAU, C. & JACOBS, J. D. 2018. Efficacy of different types of cognitive enhancers for patients with schizophrenia: a meta-analysis. *npj Schizophrenia,* 4**,** 22.

SLIFSTEIN, M., VAN DE GIESSEN, E., VAN SNELLENBERG, J., THOMPSON, J. L., NARENDRAN, R., GIL, R., HACKETT, E., GIRGIS, R., OJEIL, N., MOORE, H., D'SOUZA, D., MALISON, R. T., HUANG, Y., LIM, K., NABULSI, N., CARSON, R. E., LIEBERMAN, J. A. & ABI-DARGHAM, A. 2015. Deficits in Prefrontal Cortical and Extrastriatal Dopamine Release in Schizophrenia: A Positron Emission Tomographic Functional Magnetic Resonance Imaging StudyCortical and Extrastriatal Dopamine in SchizophreniaCortical and Extrastriatal Dopamine in Schizophrenia. *JAMA Psychiatry,* 72**,** 316-324.

SMITH, R. C., BOULES, S., MATTIUZ, S., YOUSSEF, M., TOBE, R. H., SERSHEN, H., LAJTHA, A., NOLAN, K., AMIAZ, R. & DAVIS, J. M. 2015. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. *Schizophrenia research,* 168**,** 260-266.

SNITZ, B. E., MACDONALD III, A. W. & CARTER, C. S. 2005. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophrenia bulletin,* 32**,** 179-194.

STAGG, C. J., ANTAL, A. & NITSCHE, M. A. 2018. Physiology of transcranial direct current stimulation. *The journal of ECT,* 34**,** 144-152.

STAGG, C. J., BEST, J. G., STEPHENSON, M. C., O'SHEA, J., WYLEZINSKA, M., KINCSES, Z. T., MORRIS, P. G., MATTHEWS, P. M. & JOHANSEN-BERG, H. 2009. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *Journal of Neuroscience,* 29**,** 5202-5206.

STAGG, C. J., JAYARAM, G., PASTOR, D., KINCSES, Z. T., MATTHEWS, P. M. & JOHANSEN-BERG, H. 2011. Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. *Neuropsychologia,* 49**,** 800-804.

STAGG, C. J., LIN, R. L., MEZUE, M., SEGERDAHL, A., KONG, Y., XIE, J. & TRACEY, I. 2013. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. *Journal of Neuroscience,* 33**,** 11425-11431.

STEPHAN, K. E., FRISTON, K. J. & FRITH, C. D. 2009. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. *Schizophrenia bulletin,* 35**,** 509-527.

STRUBE, W., BUNSE, T., NITSCHE, M. A., WOBROCK, T., ABOROWA, R., MISEWITSCH, K., HERRMANN, M., FALKAI, P. & HASAN, A. 2015. Smoking restores impaired LTD-like plasticity in schizophrenia: a transcranial direct current stimulation study. *Neuropsychopharmacology,* 40**,** 822.

TANDON, R., GAEBEL, W., BARCH, D. M., BUSTILLO, J., GUR, R. E., HECKERS, S., MALASPINA, D., OWEN, M. J., SCHULTZ, S. & TSUANG, M. 2013. Definition and description of schizophrenia in the DSM-5. *Schizophrenia research,* 150**,** 3-10.

TREMBLAY, S., LAROCHELLE-BRUNET, F., LAFLEUR, L. P., EL MOUDERRIB, S., LEPAGE, J. F. & THÉORET, H. 2016. Systematic assessment of duration and intensity of anodal transcranial direct current stimulation on primary motor cortex excitability. *European Journal of Neuroscience,* 44**,** 2184-2190.

TSENG, P., HSU, T.-Y., CHANG, C.-F., TZENG, O. J. L., HUNG, D. L., MUGGLETON, N. G., WALSH, V., LIANG, W.-K., CHENG, S.-K. & JUAN, C.-H. 2012. Unleashing potential:

transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. *Journal of Neuroscience,* 32**,** 10554-10561.

VERCAMMEN, A., RUSHBY, J. A., LOO, C., SHORT, B., WEICKERT, C. S. & WEICKERT, T. 2011. Transcranial Direct Current Stimulation (Tdcs) Influences Probabilistic Association Learning in People with Schizophrenia. *Schizophrenia Bulletin,* 37**,** 231-232.

VIGNAUD, P., MONDINO, M., POULET, E., PALM, U. & BRUNELIN, J. 2018. Duration but not intensity influences transcranial direct current stimulation (tDCS) after-effects on cortical excitability. *Neurophysiologie Clinique,* 48**,** 89-92.

WACHTER, D., WREDE, A., SCHULZ-SCHAEFFER, W., TAGHIZADEH-WAGHEFI, A., NITSCHE, M. A., KUTSCHENKO, A., ROHDE, V. & LIEBETANZ, D. 2011. Transcranial direct current stimulation induces polarity-specific changes of cortical blood perfusion in the rat. *Experimental neurology,* 227**,** 322-327.

WALLACE, D., COOPER, N. R., PAULMANN, S., FITZGERALD, P. B. & RUSSO, R. 2016. Perceived comfort and blinding efficacy in randomised sham-controlled transcranial direct current stimulation (tDCS) trials at 2 mA in young and older healthy adults. *PloS one,* 11**,** e0149703.

WANG, M., YANG, Y., WANG, C.-J., GAMO, N. J., JIN, L. E., MAZER, J. A., MORRISON, J. H., WANG, X.-J. & ARNSTEN, A. F. T. 2013. NMDA receptors subserve persistent neuronal firing during working memory in dorsolateral prefrontal cortex. *Neuron,* 77**,** 736-749.

WEICKERT, T. W., SALIMUDDIN, H., LENROOT, R. K., BRUGGEMANN, J., LOO, C., VERCAMMEN, A., KINDLER, J. & WEICKERT, C. S. 2019. Preliminary findings of four-week, task-based anodal prefrontal cortex transcranial direct current stimulation transferring to other cognitive improvements in schizophrenia. *Psychiatry research,* 280**,** 112487.

WEINSTEIN, J. J., CHOHAN, M. O., SLIFSTEIN, M., KEGELES, L. S., MOORE, H. & ABI-DARGHAM, A. 2017. Pathway-Specific Dopamine Abnormalities in Schizophrenia. *Biol Psychiatry,* 81**,** 31-42.

WHITEFORD, H. A., DEGENHARDT, L., REHM, J., BAXTER, A. J., FERRARI, A. J., ERSKINE, H. E., CHARLSON, F. J., NORMAN, R. E., FLAXMAN, A. D. & JOHNS, N. 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *The Lancet,* 382**,** 1575-1586.

WHITLOCK, J. R., HEYNEN, A. J., SHULER, M. G. & BEAR, M. F. 2006. Learning induces long-term potentiation in the hippocampus. *science,* 313**,** 1093-1097.

WYKES, T., HUDDY, V., CELLARD, C., MCGURK, S. R. & CZOBOR, P. 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American Journal of Psychiatry,* 168**,** 472-485.

WYKES, T. I. L., BRAMMER, M., MELLERS, J., BRAY, P., REEDER, C., WILLIAMS, C. & CORNER, J. 2002. Effects on the brain of a psychological treatment: cognitive remediation therapy: functional magnetic resonance imaging in schizophrenia. *The British Journal of Psychiatry,* 181**,** 144-152.

ZHOU, Y., LIANG, M., JIANG, T., TIAN, L., LIU, Y., LIU, Z., LIU, H. & KUANG, F. 2007. Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI. *Neuroscience letters,* 417**,** 297-302.

ZWISSLER, B., SPERBER, C., AIGELDINGER, S., SCHINDLER, S., KISSLER, J. & PLEWNIA, C. 2014. Shaping memory accuracy by left prefrontal transcranial direct current stimulation. *Journal of Neuroscience,* 34**,** 4022-4026.

8. Declaration of contribution

The work was carried out in the University Clinic for Psychiatry and Psychotherapy Tübingen under the supervision of Prof. Dr. med. Christian Plewnia. In the following, the declaration on the personal contribution to each publication is listed separately. I assure that I have written this dissertation to the best of my knowledge and that I have not used any other sources than those cited in this dissertation.

(1) **Schwippel T**, Papazova I, Strube W, Fallgatter AJ, Hasan A, Plewnia C. Beneficial effects of anodal transcranial direct current stimulation (tDCS) on spatial working memory in patients with schizophrenia. European Neuropsychopharmacology. 2018;28(12):1339-50.

Tobias Schwippel was involved in the planning of the experiment, carried out the experiments and programmed the working memory task used. He also carried out the statistical evaluation. He wrote the first version of the manuscript and was involved in its completion.

(2) Papazova I, Strube W, Becker B, Henning B, **Schwippel T,** Fallgatter AJ, et al. Improving working memory in schizophrenia: Effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC. Schizophrenia research. 2018;202:203-9.

Tobias Schwippel was involved in the planning of the experiment. He programmed the working memory task used, was involved in the statistical evaluation and participated in the completion of the manuscript.

Tübingen, 9th January 2020

Tobias Udo Schwippel

9. Publications

(1) **Schwippel T**, Papazova I, Strube W, Fallgatter AJ, Hasan A, Plewnia C. Beneficial effects of anodal transcranial direct current stimulation (tDCS) on spatial working memory in patients with schizophrenia. European Neuropsychopharmacology. 2018;28(12):1339-50.

(2) Papazova I, Strube W, Becker B, Henning B, **Schwippel T**, Fallgatter AJ, et al. Improving working memory in schizophrenia: Effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC. Schizophrenia research. 2018;202:203-9.

(3) **Schwippel T,** Hasan A, Papazova I, Fallgatter A, Plewnia C. Verbesserung der kognitiven Leistungsfähigkeit von Patienten mit Schizophrenie durch transkranielle Gleichstromstimulation. Nervenheilkunde. 2018; 37(05):340-6.

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11. Curriculum vitae

General Information

Name: Tobias Udo Schwippel

Date of Birth: 25.12.1986

Place of Birth: Salzgitter

Professional Experience

University Hospital Tübingen | Psychiatry Residency (Prof. Dr. A. J. Fallgatter)	01/2015 – present

Research Experience

University Hospital Tübingen | Interventional Neuropsychiatry (Prof. Dr. C. Plewnia)	01/2015 – present

- Influence of tDCS on working memory in schizophrenia
- Treatment of auditory hallucinations with theta-burst stimulation
- Modulation of implicit associations by tDCS in alcohol dependency

University Hospital Tübingen | Neuroprosthetics (Prof. Dr. A. Gharabaghi)	2010 – 2015

- Modulation of implicit and explicit motor learning by tDCS

Education

University Tübingen | Medical school | Ärztliche Prüfung 5th June 2014	2007 – 2014
Brown University, RI, USA | Clinical electives	2012 – 2013
German Air Force | Military service	2006 – 2007
Gymnasium Munster | Secondary education	1997 – 2006
Grundschule Salzgitter / Munster | Primary education	1993 – 1997

Awards and Scholarships

WPA Early Career Psychiatrists Fellowship	2019
Posterblitz Award, German Society of Neurophysiology	2018
Sino-German Summer School, Guangzhou, China	2017
DAAD scholarship, Brown University, Rhode Island, USA	2012 - 2013
Friedrich Ebert Foundation scholarship for gifted students	2010 – 2014
German College Champion Cross Country	2010

Publications

Papazova I, Strube W, Wienert A, Henning B, Schwippel T, Fallgatter A.J, Padberg F, Falkai F, Plewnia C, Hasan A. Effects of 1 mA and 2 mA transcranial direct current stimulation on working memory performance in healthy participants. 2020. Consciousness and Cognition, 83, 102959

Schroeder P.A, Schwippel T, Wolz I, Svaldi J. Meta-analysis of the effects of transcranial direct current stimulation on inhibitory control. 2020. Brain Stimulation, 13, 1159-1167.

Schwippel T, Schroeder P.A, Fallgatter AJ, Plewnia C. Clinical review: The therapeutic use of theta-burst stimulation in mental disorders and tinnitus. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2019; 92, 285-300.

Schwippel T, Papazova I, Strube W, Fallgatter AJ, Hasan A, Plewnia C. Beneficial effects of anodal transcranial direct current stimulation (tDCS) on spatial working memory in patients with schizophrenia. European Neuropsychopharmacology. 2018; 28(12):1339-50.

Papazova I, Strube W, Becker B, Henning B, Schwippel T, Fallgatter AJ, et al. Improving working memory in schizophrenia: Effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC. Schizophrenia research. 2018; 202:203-9.

Schwippel T, Hasan A, Papazova I, Fallgatter A, Plewnia C. Verbesserung der kognitiven Leistungsfähigkeit von Patienten mit Schizophrenie durch transkranielle Gleichstromstimulation. Nervenheilkunde. 2018; 37(05):340-6.

Schwippel T, Wasserka B, Fallgatter AJ, Plewnia C. Safety and efficacy of long-term home treatment with transcranial direct current stimulation (tDCS) in a case of multimodal hallucinations. Brain stimulation. 2017; 10(4):873-4.

Plewnia C, Brendel B, Schwippel T, Martus P, Cordes J, Hasan A, et al. Treatment of auditory hallucinations with bilateral theta burst stimulation (cTBS): protocol of a randomized, double-blind, placebo-controlled, multicenter trial. European archives of psychiatry and clinical neuroscience. 2017; 1-11