Aus der

Klinik und Poliklinik für Psychiatrie und Psychotherapie

Klinikum der Ludwig-Maximilians-Universität München

Dissertation

zum Erwerb des Doctor of Philosophy (Ph.D.)

an der Medizinischen Fakultät

der Ludwig-Maximilians-Universität zu München

Transcranial direct-current stimulation of the prefrontal cortex, a multilevel analysis of data from a clinical trial in depression

vorgelegt von:

Aldo Soldini

aus:

Guatemala City / Guatemala

Jahr:

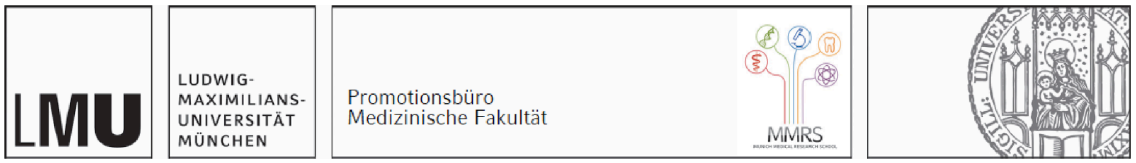
2024

Mit Genehmigung der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

Erstes Gutachten:	Prof. Dr. Frank Padberg
Zweites Gutachten:	Dr. Daniel Keeser
Drittes Gutachten:	Prof. Dr. Antje Grosche
Viertes Gutachten:	Prof. Dr. Stephan Kröger
Dekan:	Prof. Dr. Thomas Gudermann
Tag der mündlichen Prüfung:	03.12.2024

Affidavit



Affidavit

Soldini, Aldo

Surname, first name

Nussbaumstrasse 7

Street

80336, Munich, Germany

Zip code, town, country

I hereby declare, that the submitted thesis entitled:

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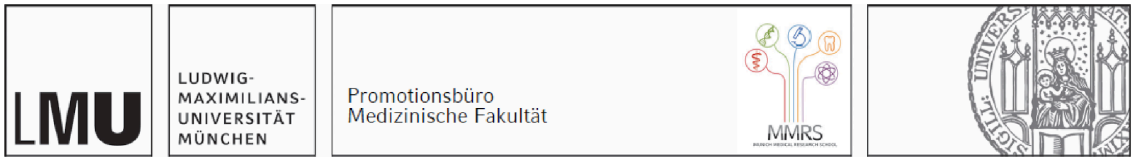

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Soldini, Aldo

Surname, first name

Nussbaumstrasse 7

Street

80336, Munich, Germany

Zip code, town, country

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Table of content

List of abbreviations

ACE	adverse childhood experience
CSV	comma-separated values
CTQ	childhood trauma questionnaire
DICOM	Digital Imaging and Communications in Medicine
DLPFC	dorsolateral prefrontal cortex
E-field	electric field
GABA	gamma-aminobutyric acid
GCBS	German Center for Brain Stimulation
HAMD	Hamilton Depression Scale
M.I.N.I.	Mini-international neuropsychiatric interview
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	major depressive disorder
MRI	magnetic resonance imaging
NIBS	non-invasive brain stimulation
NICUM	NeuroImaging Core Unit Munich
PACS	picture archiving and communication system
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation

List of publications

Subject of this PhD Thesis

Soldini, A., Vogelmann, U., Aust, S., Goerigk S., Plewnia C., Fallgartner A., Normann C., Drase L., Zwanzger P., Kammer T., Schönfeldt-Lecuona C., Vural G., Bajbouj M., Padberg F., Burkhardt G. Neurocognitive function as outcome and predictor for prefrontal transcranial direct current stimulation in major depressive disorder: an analysis from the DepressionDC trial. Eur Arch Psychiatry Clin Neurosci (2024). https://doi.org/10.1007/s00406-024-01759-2

Burkhardt G, Goerigk S, Bulubas L, Dechantsreiter E, Keeser D, Kumpf U, **Soldini A**, Wolf J, Amann BL, Plewnia C, Fallgatter A, Langguth B, Normann C, Frase L, Zwanzger P, Kammer T, Schönfeldt-Lecuona C, Kamp D, Bajbouj M, Falkai P, Brunoni AR, Bertsch K, Jobst A, Reinhard MA, Padberg F. Adverse childhood experiences and clinical effects of transcranial direct current stimulation in major depressive disorder: Results from the DepressionDC trial. Psychiatry Res. 2023 Dec;330:115577. doi: 10.1016/j.psychres.2023.115577. Epub 2023 Oct 29. PMID: 37922733.

Burkhardt G, Goerigk S, Dechantsreiter E, Bulubas L, **Soldini A**, Zwanzger P, Diemer J, Padberg F, Brunnauer A, Kumpf U. Driving-related cognitive skills during antidepressant transcranial direct current stimulation: results in a subsample from the DepressionDC trial. Front Psychiatry. 2023 Dec 7;14:1255415. doi: 10.3389/fpsyt.2023.1255415. PMID: 38130292; PMCID: PMC10733487.

Others

Mizutani-Tiebel Y, Tik M, Chang KY, Padberg F, **Soldini A,** Wilkinson Z, Voon CC, Bulubas L, Windischberger C, Keeser D. Concurrent TMS-fMRI: Technical Challenges, Developments, and Overview of Previous Studies. Front Psychiatry. 2022 Apr 21;13:825205. doi: 10.3389/fpsyt.2022.825205. PMID: 35530029; PMCID: PMC9069063.

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Kumpf U, **Soldini A**, Burkhardt G, Bulubas L, Dechantsreiter E, Eder J, Padberg F, Palm U. Association between Mood and Sensation Seeking Following rTMS. Brain Sci. 2023 Aug 30;13(9):1265. doi: 10.3390/brainsci13091265. PMID: 37759866; PMCID: PMC10527256.

Candidate's contribution to the publications

1.1 Paper I - *Neurocognitive function as outcome and predictor during prefrontal transcranial direct current stimulation in major depressive disorder: An analysis from the DepressionDC trial*

The three selected publications correspond to ancillary studies of the DepressionDC clinical trial (Padberg et al., 2017). A description of the clinical trial can be found in the introductory summary. Although the clinical study began before the candidate initiated his doctoral studies, the involvement of the doctoral candidate spanned multiple stages before the clinical study came to an end.

The candidate performed at a clinical level after receiving a good clinical practice certification (ICH E6 (R2)). In collaboration with other medical residents working in the inpatient wards and the outpatient unit, the candidate screened for potential study patients. Clinical training was provided to ensure that the candidate could carry out standardized clinical assessments such as the Montgomery–Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Scale (HAMD). He interviewed the patients and performed standardized tests to determine if the patients were eligible to participate in the study. He carried out informed consent for the clinical study, magnetic resonance imaging (MRI) acquisition, and genetic sampling. He also performed standard physical and mental state examinations. This included a neurocognitive assessment using the EmoCogMeter, a digital tool described in Paper I. In collaboration with novel Biobank of the psychiatry department, the candidate extracted blood samples that were planned to be used in ancillary genetic analysis. He followed up on the patients, and performed clinical interviews at set intervals to evaluate patient progress and screen for possible adverse effects.

At specific timepoints, the candidate switched to a technical role within the clinical trial. The candidate underwent training by the electrophysiology department of the hospital, where he learned how to apply non-invasive brain stimulation (NIBS) procedures such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). This was later reinforced by participating in a NIBS Workshop in Copenhagen. He prepared, set up, and applied transcranial direct current stimulation on recruited patients using the standardized clinical study protocols. He generated and retrieved electronic data from tablets in compliance with local and institutional data protection regulations, and cleaned the data sets to produce pertinent comma-separated values (CSV) files, that would be later used for the statistical analysis. The candidate is a part of the NeuroImaging Core Unit Munich (NICUM). Guided by Daniel Keeser, he learned to perform MRIs, producing anatomical and functional imaging data. The data was stored in a picture archiving and communication system picture archiving and communication system (PACS) in the Digital Imaging and Communications in Medicine (DICOM) format and used for subsequent ancillary analyses.

Together with Gerrit Burkhardt and Frank Padberg, the candidate proposed a hypothesis to be tested utilizing the aforementioned collected data. The idea of utilizing the cognitive data to determine if baseline cognition was a mediator of response, was brought forward. For paper I, the candidate worked together with Gerrit Burkhardt and Stephan Goerigk to perform the

transformation of the data (winsorization) and the statistical analysis. The original manuscript was written by the candidate under the supervision of Gerrit Burkhardt. The candidate then submitted the article and worked as the corresponding author, interacting with the editor and reviewers to generate the accepted version of the manuscript.

1.2 Paper II - *Adverse childhood experiences and clinical effects of transcranial direct current stimulation in major depressive disorder: Results from the DepressionDC trial*

and

Paper III - *Driving-related cognitive skills during antidepressant transcranial direct current stimulation: results in a subsample from the DepressionDC trial*

The data utilized in these publications corresponds to the DepressionDC clinical trial. The clinical and technical roles performed by the candidate have been detailed in the previous section.

When the experimental part of the clinical trial came to an end, the candidate was involved in regular meetings with staff and colleagues of the other clinical centers, as well as internal meetings within the German Center for Brain Stimulation (GCBS) and the NeuroImaging Core Unit Munich (NICUM), to discuss the analysis of secondary endpoints. Although to a lesser extent than in paper I, the candidate was involved in the conceptualization of the ancillary hypothesis presented in papers II and III. The main manuscripts were written mainly by Gerrit Burkhardt with support of the other co-authors, including the doctoral candidate.

2. Introductory summary

2.1 Background

2.1.1 Transcranial Direct Current Stimulation (tDCS). Definition, history, and physiological effects

Transcranial Direct Current Stimulation (tDCS) is a method within the array of non-invasive brain stimulation (NIBS) approaches, where a direct electrical current of 1-2mA is applied over distinct cortex regions via surface electrodes. This procedure has been proven to be safe and tolerable in humans (Bikson et al., 2016). Most users experience only mild tactile („tingling“) sensations underneath the electrodes (Woods et al., 2016). The electrical current stimulates superficial brain regions and generates electrical fields that modulate underlying targeted brain regions. These changes are usually transient, necessitating repeated sessions or combined interventions for sustained effects (Nitsche et al., 2008).

Historically, first brain stimulation attempts were introduced by electric fish that were used for therapeutic purposes in the 1st Century, as documented by Scribonius Largus (Priori, 2003). However, it wasn't until the 18th and 19th centuries that scientists began systematically investigating the effects of electricity on the nervous system. Ewald Hitzig and Eduard Fritsch in the 1870s used direct current to map motor areas of the brain in animals, highlighting the potential for targeted stimulation (Hagner, 2012). Bindman et al investigated the effects of direct currents on the rat brain, and described how it modulated spontaneous neuronal activity depending on the polarity (Bindman et al., 1964). In the 20th century, Nitsche and Paulus' research demonstrated the ability of tDCS to enhance or diminish cortical excitability, and highlighted its potential for modulating cognitive and motor functions (Nitsche & Paulus, 2000). Since then, tDCS has been employed in different fields, such as neurology and psychiatry. Fregni and Pascual-Leone were among the first to investigate the therapeutic benefits of tDCS for depressive disorders in patients resistant to conventional treatments (Fregni & Pascual-Leone, 2007).

The way that tDCS provokes neuroplastic changes has yet to be fully understood. Studies suggest that tDCS modulates brain excitability and alters the release of neurotransmitters. (Monte-Silva et al., 2013) Polarity plays a crucial role on the effects of tDCS. Anodal stimulation has been seen to trigger an excitatory response, whereas cathodal stimulation leads to an inhibitory response (Nitsche & Paulus, 2000). Changes in glutamate and gamma-aminobutyric acid (GABA) have been reported after tDCS sessions (Hone-Blanchet et al., 2016; Mezger et al., 2021). These two molecules are regarded as the main excitatory and inhibitory neurotransmitters (Sohal & Rubenstein, 2019). The reported effects of tDCS on brain metabolites seem to be mixed and inconclusive, meriting further investigation. Epigenetic, gene expression, biochemical cascades, and glial factors have also been reported as mediators of the clinical effects of tDCS (Cirillo et al., 2017). Neuropsychological and neuroanatomical elements, such as gray matter volumes, cortical thickness and surface, and electrical fields have been seen to modify response to tDCS (Bulubas et al., 2019; Filmer et al., 2019; Suen et al., 2021). This hints at the importance of personalized protocols that take individual anatomical traits into account.

2.1.2 The role of tDCS in depressive disorders

Unlike other forms of NIBS such as TMS, tDCS hasn't been FDA approved in the US (Zandvakili et al., 2019), nor is it considered standardized treatment in depressive disorders in many European countries (Härter et al., 2010). Its current use is mostly limited to translational research and clinical studies. The push to use tDCS as a treatment to treat depressive disorders dates back to the 1960s. (Lippold & Redfearn, 1964). Research in the field became somewhat silent until the early 2000s (Nitsche & Paulus, 2000, 2001). Modern protocols took contemporary concepts of physiology and functional neuroanatomy into consideration. Both structural and functional changes of the cortex have been reported in patients with depressive disorders (Boggio et al., 2008; Campbell et al., 2004; Fregni et al., 2006; Hamilton et al., 2008). Both a hypoactivity of the left dorsolateral prefrontal cortex (DLPFC), and a hyperactivity of the right DFPLC have been described. This goes in hand with the customary placement of the electrodes. The 'excitatory' electrode (anode) is usually placed above the left DLPFC while the 'inhibitory' electrode (cathode) is placed above the right DLPFC (Brunoni et al., 2012). tDCS also improves network connectivity and neuroplasticity (Chan et al., 2021; Hordacre et al., 2018). These neurophysiological characteristics seem to be impaired in depressive disorders (Price & Duman, 2020; Tartt et al., 2022)

The effectiveness of tDCS to ameliorate depressive symptoms has been hard to assess. Reported response rates tend to contradict each other. One of the main issues encountered when comparing the multiple studies is the extreme heterogeneity across protocols. Not only do the populations tend to be different (severity of the symptoms, comorbidities, refractory disorders, add-on treatments); but also the length of stimulation, intensity, and number of sessions differ. A few meta-analyses have reported a statistically significant improvement of depressive symptoms after receiving active stimulation over sham stimulation (Brunoni et al., 2016; Kalu et al., 2012; Meron et al., 2015). Contrary to Berlim et al., who showed no superiority of active tDCS over sham tDCS (Berlim et al., 2013). When comparing tDCS to antidepressants, both monotherapies seem to have a similar efficacy; however, a combination of both has been observed to have more favorable results (Brunoni et al., 2013).

2.1.3 The *DepressionDC* trial

The *DepressionDC* trial was a multicenter, randomized, triple-blind, placebo-controlled, parallel group trial involving five German clinical sites (Burkhardt et al., 2023). The study focused on individuals with major depressive disorder (MDD) who had not experienced improvement after receiving at least one treatment with an antidepressant at a sufficient dosage and length during the present episode. Baseline severity of symptoms was assessed utilizing the MADRS. Secondary endpoints such as neurocognitive data, driving skills, genetic data and neuroimaging were also recorded. The protocol consisted of 20 sessions of 30 min daily stimulation over a period of 4 weeks. This was followed by another stimulation block of 4 sessions administered in a 2 week period. The tDCS setup employed a bifrontal configuration, with the anode placed at F3 and the cathode at F4. Participants were randomized to receive either active or sham stimulation. Active stimulation consisted of a direct current of 2mA, while the sham stimulation paradigm constituted a 30 second ramp-up, ramp-down sequence. The data of 150 participants was analyzed. At week 6, there was no significant difference in average improvement scores on the MADRS between the group receiving active tDCS and sham tDCS.

2.2 Project's hypotheses

This thesis consists of three ancillary publications of the *DepressionDC* clinical trial. The effectiveness of tDCS in treating depressive symptoms was assessed in the main study. Our first aim in these ancillary studies was to determine the effects of tDCS on various cognitive domains. This was assessed in Paper I. Processing speed, sustained attention, memory span, selective attention, executive function, and working memory were evaluated utilizing a digital tool (EmoCogMeter). A statistically significant improvement in such domains would indicate that the intervention could be of therapeutic use, regardless of the effects on the depressive symptoms' severity. Determining the safety and tolerability of a medical intervention is crucial to estimating its potential clinical usage. As mentioned before, tDCS has been deemed as physically safe and tolerable. However, long and short-term effects on a patient's mental status are equally as important to assess. Pharmacotherapy remains one of the main pillars of the treatment of depressive disorders. Some psychopharmacological agents impair a patient's driving skills, and patients are advised not to operate vehicles while taking them (Cameron & Rapoport, 2016). Paper III evaluated the neurocognitive effects of repeated sessions of tDCS by testing patients' driving skills by measuring the three neurocognitive domains reaction time, visual perception, and stress tolerance. In regards to driving kills, the intervention would be deemed as safe if there weren't any statistically significant reductions of the cognitive scores.

The second aim of the ancillary studies was the determination of baseline factors that predict clinical response to tDCS. Depressive disorders manifest a variety of symptoms and perturbations of different networks (Kaiser et al., 2015). Measuring secondary endpoints proves useful to determine the global efficacy of the intervention. As described in the background section, variations in neurophysiological and neuroanatomical traits have been observed to influence the effects of tDCS. Looking for proxies of response helps to generate alternative hypotheses as to how (if) such interventions have an effect that might not be measurable directly. For example, cognitive dysfunction is commonly seen in depressive disorders (Lam et al., 2014). Paper I was the evaluation of baseline cognitive scores as a predictive marker of clinical tDCS response. Paper II explored if adverse childhood experiences (ACE) could also be used as predictive factors of clinical tDCS response. Such experiences increase the risk of developing a depressive disorder (Chapman et al., 2004), and significant neuroanatomical and neurophysiological differences have been described when compared to patients with depressive disorders that did not undergo ACEs (Antoniou et al., 2023). The relationship between ACEs and TMS has been explored before (Ng et al., 2023), but not with tDCS. In the main clinical study, a self-reported childhood trauma questionnaire (CTQ) was used to evaluate sexual abuse, emotional neglect, physical neglect, emotional abuse and physical abuse. If there were a statistically significant relationship between these two variables, baseline cognition and ACEs, and an improvement in the severity of depressive symptoms, then such predictive markers could help clinicians and patients decide if tDCS would be a meaningful intervention on a case-by-case basis.

2.3 Project's conclusions

In the *DepressionDC* trial, multiple rounds of traditional bifrontal tDCS to the left DLPFC were found to be no more beneficial than sham stimulation in reducing the intensity of depressive symptoms among patients with depressive disorders, based on changes observed in MADRS scores. The ancillary studies presented in this thesis determined, firstly, that neurocognitive test scores were not influenced by active tDCS vs sham stimulation. Secondly, neither baseline cognitive scores nor adverse childhood experiences were predictors of therapeutic response. Lastly, driving skills were not worsened by repeated tDCS sessions, rendering tDCS a safe intervention regarding motor vehicle operation abilities.

2.4 Future implications

The effectiveness of tDCS in depressive disorders should not be immediately discarded. Instead, the strengths and weaknesses of the clinical study should be explored. The following propositions argue in favor of the need for future studies to evaluate personalized treatment protocols. These propositions could also give an insight as to why no significant changes were observed across the board. Comorbidities are common in psychiatric patients. (Angold et al., 1999). tDCS has been found useful against cravings in patients with substance use and eating disorders. (Goldman et al., 2011; Lapenta et al., 2018). Treating a patient holistically, taking comorbidities into consideration, could prove to be more effective. The *DepressionDC* clinical trial excluded patients with other relevant psychiatric axis I and/or axis II comorbid disorders, as determined by the Mini-international neuropsychiatric interview (M.I.N.I.) and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders. The implication and influence of comorbid diagnoses should be explored in future studies. The variability in individual responses to tDCS, coupled with the need for standardized protocols, underscores the complexity of translating laboratory findings into clinical practice. Reverse-calculation electric field (E-field) modeling has demonstrated that different dosages at an individual level are needed to elicit a target E-field intensity. (Caulfield et al., 2020) We therefore recommend future studies to not only optimize tDCS parameters to modulate cognition better, but to also consider individualized dosages to increase general efficacy and safety parameters. (Esmaeilpour et al., 2018).

Synergistic mechanisms of action might play a crucial role in the effectiveness of tDCS. Tapping into other systems simultaneously might be needed to induce or potentiate meaningful changes. (Talar et al., 2022). An example of an ongoing project testing such hypotheses is the DiSCoVeR project. This is a multicenter clinical trial assessing the effects of cognitive training, utilizing a video game, while tDCS is being remotely administered. (ClinicalTrials.gov Identifier: NCT04953208).

Regarding the identification of refined proxies of therapeutic response. The EmoCogMeter was employed in Paper I. It utilized standard psychometric tests to evaluate specific cognitive domains. The neurocognitive tests utilized in the study might not be the optimal to detect changes elicited by the stimulation. In a similar way, ACEs were assessed in Paper II with 28 self-reported questions. The dichotomous definitions proposed by such a questionnaire might

not reflect the complexity of trauma-related disorders. More fluid traits and definitions could lead to the generation of more optimal baseline markers of response. A holistic spatio-mechanistic framework of tDCS has been proposed. (Yavari et al., 2017). This framework tries to cluster the effects of tDCS into nine groups according to the physiological changes induced and attributes these clusters to local, small-scale, and large-scale networks. Distinguishing the small-scale network effects from the global brain effects of both the neuro-electrical and neuro-chemical modulatory action of tDCS, would lead to the formulation of a more accurate hypothesized proxy of effect over specific brain networks. Although the results of Paper I, and Paper II refute such rationale, the lack of comparative studies still leaves an open-ended question regarding the predictive value of baseline characteristics on the clinical effects of tDCS. Different spatio-mechanistic approaches might facilitate the development of more specific markers of response.

This last segment is reserved for a small reflection regarding the publication of „null-findings“. The DepressionDC clinical trial, as well as the ancillary studies presented in this thesis, fall into this category. The importance of publishing negative findings has resurfaced again in the light of the ongoing replication crisis. (Tackett et al., 2019). Although authors seem to be aware that finding negative results isn't necessarily an undesirable thing, a vast majority refrain from pursuing to publish them. (Echevarría et al., 2021). The reluctance to publish negative results is multifactorial and can be seen at various stages of research.

At an editorial level, biases towards accepting and publishing positive results have also been found. (Matías-Guiu & García-Ramos, 2011). A bias towards citing studies with positive results has also been reported. (Duyx et al., 2017). When faced with such biases, scientists are sometimes rewarded by pouring resources and investigating things that might be "safe", instead of taking more risks at the cost of not finding any significance. (Ortiz, 2020). These factors reduce the visibility of negative studies and create an overrepresentation of positive data. This can lead to the warping of the narrative of future publications, and the generation of tailor-made hypotheses that disregard evidence that might contradict them. The publication of null finding studies has other benefits that might not be too obvious at first, such as preventing waste and allowing a more transparent allocation of resources. Methods and criteria to disclose negative findings have been elaborated. (Bespalov et al., 2019) Studies that report null-findings, that have been executed thoroughly, are as important as publications with statistically significant results. Hopefully this thesis encourages current and future scientists to not fret negative results; rather to embrace them, publish them, and advocate for their importance.

3. Paper I - Neurocognitive function as outcome and predictor during prefrontal transcranial direct current stimulation in major depressive disorder: An analysis from the DepressionDC trial

European Archives of Psychiatry and Clinical Neuroscience
https://doi.org/10.1007/s00406-024-01759-2

ORIGINAL PAPER

Neurocognitive function as outcome and predictor for prefrontal transcranial direct current stimulation in major depressive disorder: an analysis from the DepressionDC trial

Aldo Soldini[1,2,8] · Ulrike Vogelmann[1] · Sabine Aust[3] · Stephan Goerigk[1,4] · Christian Plewnia[5] · Andreas Fallgatter[5] · Claus Normann[6,7] · Lukas Frase[6,7] · Peter Zwanzger[9] · Thomas Kammer[10] · Carlos Schönfeldt-Lecuona[10] · Gizem Vural[1] · Malek Bajbouj[3] · Frank Padberg[1] · Gerrit Burkhardt[1]

Received: 28 July 2023 / Accepted: 13 January 2024

Abstract
Transcranial direct current stimulation (tDCS) of the prefrontal cortex might beneficially influence neurocognitive dysfunctions associated with major depressive disorder (MDD). However, previous studies of neurocognitive effects of tDCS have been inconclusive. In the current study, we analyzed longitudinal, neurocognitive data from 101 participants of a randomized controlled multicenter trial (DepressionDC), investigating the efficacy of bifrontal tDCS (2 mA, 30 min/d, for 6 weeks) in patients with MDD and insufficient response to selective serotonin reuptake inhibitors (SSRI). We assessed whether active tDCS compared to sham tDCS elicited beneficial effects across the domains of memory span, working memory, selective attention, sustained attention, executive process, and processing speed, assessed with a validated, digital test battery. Additionally, we explored whether baseline cognitive performance, as a proxy of fronto-parietal-network functioning, predicts the antidepressant effects of active tDCS versus sham tDCS. We found no statistically significant group differences in the change of neurocognitive performance between active and sham tDCS. Furthermore, baseline cognitive performance did not predict the clinical response to tDCS. Our findings indicate no advantage in neurocognition due to active tDCS in MDD. Additional research is required to systematically investigate the effects of tDCS protocols on neurocognitive performance in patients with MDD.

Keywords Transcranial direct current stimulation · Non-invasive brain stimulation · Major depressive disorder · Depression · Cognition · Neurocognitive tests

Aldo Soldini and Ulrike Vogelmann authors equally contributed to this work.

Frank Padberg and Gerrit Burkhardt authors equally contributed to this work.

✉ Aldo Soldini
aldo.soldini@med.uni-muenchen.de

1 Department of Psychiatry and Psychotherapy, LMU University Hospital, Munich, Germany

2 International Max Planck Research School for Translational Psychiatry, Munich, Germany

3 Department of Psychiatry and Neurosciences, Charité - Universitätsmedizin Berlin, Berlin, Germany

4 Charlotte Fresenius Hochschule, Munich, Germany

5 Department of Psychiatry and Psychotherapy, German Center for Mental Health (DZPG), Tübingen Center for Mental Health, University of Tübingen, Tübingen, Germany

6 Department of Psychiatry and Psychotherapy, University of Freiburg, Breisgau, Germany

7 Center for Basics in Neuromodulation, University of Freiburg, Freiburg, Germany

8 Department of Psychosomatic Medicine and Psychotherapy, University of Freiburg, Breisgau, Germany

9 Clinical Center for Psychiatry, Psychotherapy, Psychosomatic Medicine, Geriatrics and Neurology, Kbo-Inn-Salzach-Klinikum, Gabersee, Germany

10 Department of Psychiatry and Psychotherapy III, University of Ulm, Ulm, Germany

Published online: 26 February 2024

Introduction

Transcranial Direct Current Stimulation (tDCS) is a form of non-invasive brain stimulation (NIBS) that utilizes electrodes on the scalp to create a weak electrical current in order to modulate cortical excitability [1]. In the treatment of major depressive disorder (MDD), anodal tDCS is usually applied over the left dorsolateral prefrontal cortex (DLPFC) [2], a brain area which contributes to frontoparietal network (FPN) function [3]. The FPN plays a central role for several cognitive domains, like attention[4], working memory [5], memory span [6] executive function [7], processing speed[8], and cognitive control [9]. Poor performance in these cognitive domains has also been associated with depressive disorders [10–14]. Therefore, it seems plausible that stimulation of the FPN could influence performance in these domains and that baseline cognitive performance, as a proxy of FPN functioning, could predict the clinical effects of stimulation.

Previous studies have investigated the neurocognitive effects of tDCS when applied to the DLPFC in patients with MDD reporting significant time-dependent improvements in attention/vigilance, working memory, executive functioning, processing speed, and social cognition when compared to placebo [15–18]. On the other hand, multiple studies report no statistically significant group-by-time interaction effects [19–27]. A recent meta-analysis of the cognitive effects of tDCS across multiple disorders revealed that active tDCS elicited improvements in attention/vigilance, and working memory when compared to sham tDCS [28]. This meta-analysis was based on studies that were very heterogeneous in designs, sample sizes, outcomes, and main findings. Thus, a study with a large sample size would be warranted to further test the effects of tDCS on cognition in patients with MDD. To the best of our knowledge, no studies have investigated baseline cognitive testing as a predictor of affective response to tDCS.

In this ancillary analysis of a triple-blind, randomized, sham-controlled multicenter trial, we investigated whether a standard bifrontal tDCS protocol compared to sham tDCS alters cognitive performance across the domains of memory span, working memory, selective attention, sustained attention, executive functioning, and processing speed. Additionally, we explored whether baseline cognitive performance as a proxy of FPN functioning predicts the antidepressant effects of tDCS versus sham tDCS.

Methods and materials

Study population

We analyzed data from the DepressionDC trial (trial registration number: NCT02530164); a triple-blind, randomized, sham-controlled clinical trial carried out across eight psychiatric centers in Germany [29]. The study investigated the efficacy and safety of tDCS as a treatment for MDD in patients that did not respond to conventional pharmacological treatment with selective serotonin reuptake inhibitors (SSRIs). Patients were originally randomized to receive 24 sessions within 6 weeks of either active or sham tDCS. The montage employed in tDCS involves placing the anode over F3 and the cathode over F4. Active stimulation consisted of a constant 2 mA direct current that lasted for 30 min. The sham paradigm consisted of a ramp-up and ramp-down sequence to induce similar skin sensations as active tDCS. tDCS was applied using a DC-stimulator ('Mobile', neuroConn GmbH, Ilmenau, Germany). Inclusion and exclusion criteria are reported in the supplement. Local ethics committees approved the study at each study site. All participants gave their written informed consent before inclusion in the study. From an initial sample total of 150 patients (intention-to-treat sample), we analyzed the data from 101 patients that had available neuropsychological assessments. Data from 49 patients were missing due to technical errors, organizational difficulties at the local treatment sites, and refusal to participate.

Neurocognitive test battery

Neurocognitive function was assessed longitudinally during the study at baseline, post-treatment (week 6), and at the 6-month follow-up using the EmoCogMeter, a digitalized, validated cognitive test battery developed at the Charite Berlin [30–32]. The EmoCogMeter examines the domains of memory span, working memory, selective attention, sustained attention, executive function, and processing speed. Memory span is tested by a digit-span assessment [33]. Working memory was assessed by an n-back task [13]. A variant of the Stroop test and a working memory component were used to assess selective attention and sustained attention, respectively [34]. executive function was measured by both the Trail Making B [35] and Tower of Hanoi tests [36]. Finally, processing speed was measured using a symbol letter modalities test, a variation of the symbol digit modality test. For additional technical information about the tests, please refer to the supplement.

Further outcome measures

The severity of the depressive episode was assessed by trained clinical staff utilizing the Montgomery-Åsberg Depression Rating Scale (MADRS), which was also chosen for the primary outcome of the study [37]. Severity is classified as an absence of symptoms (0–6 points), mild depressive episode (7–19 points), moderate depressive episode (20–34 points), or severe depressive episode (35–60 points). State and trait anxiety were measured utilizing The State-Trait Anxiety Inventory (STAI) [38], with a threshold of 39–40 for identifying clinically significant anxiety symptoms [39].

Statistical analysis

Statistical analyses were conducted in R, version 4.2.1. results [40]. Results were considered significant at $\alpha = 0.05$. We compared baseline characteristics between treatment groups using Pearson's χ^2 tests and Wilcoxon-rank-sum tests as appropriate. To reduce the effect of extreme test performances, we identified values below the 1% and above the 99% percentile on each task and set them to the respective percentile values (winsorization).

To assess potential treatment effects of active tDCS on cognitive performance, we fitted linear mixed models using the lme4 package [41] to predict change from baseline to week 6 on each cognitive test. Treatment group (active tDCS versus sham tDCS) was included as a fixed effect while controlling for the respective baseline cognitive test score (formula: change in cognitive performance ~ treatment group + baseline cognitive performance). Sensitivity analyses included additional models with sex, age, and baseline MADRS as covariates.

To assess potential predictive influences of baseline cognitive performance on antidepressant treatment effects of active tDCS, we again fitted linear mixed models to predict change from baseline to week 6 on the MADRS. Treatment group, performance on the respective cognitive domain, and their interaction were included as fixed effects while controlling for baseline MADRS scores (formula: MADRS change ~ treatment group x cognitive performance at baseline + baseline MADRS score).

All models included the treatment site as a random effect (formula: ~ 1| site). Significance of the model factors was determined using omnibus tests (Type III ANOVA) with Satterthwaite approximation to degrees of freedom. We did not use imputation since linear mixed models are able to handle missing data. Standardized effect sizes for regression coefficients were computed using the emmeans::eff_size() approach, with the sigma parameter being directly extracted from the regression model [42]. We corrected for multiple testing across predictors using the false-discovery-rate (FDR) method [43].

Results

Sample characteristics

We analyzed data from 101 patients (active tDCS, n = 50; sham tDCS, n = 51). Mean age (active tDCS 39 [SD 14]; sham tDCS 39 [SD 14]; p = 0.76). Sex: active tDCS 40% male; sham tDCS 40% male. Primary baseline and clinical features across the active and sham-tDCS groups were similar (Table 1 and Supplementary Table 1). Winsorized mean test performances and the number of winsorized measurements per cognitive test are reported in supplementary Table 5 and 6.

Treatment effects on neurocognitive test scores

We observed no significant group-by-time interactions between treatment group and memory span, working memory, selective attention, sustained attention, executive function, or processing speed. Pre- and post-treatment performance across neurocognitive tests for active tDCS and sham tDCS is shown in Fig. 1, and Table 2 provides further statistical information. Results for additional models including sex, age and baseline MADRS yielded similar results (supplementary Table 2–4).

Prediction of clinician-rated depression (MADRS)

We did not detect significant interactions, when predicting MADRS change, between treatment group and memory span, working memory, selective attention, sustained attention, executive function, or processing speed. Table 3 provides the effect size of each neurocognitive test at baseline and Fig. 2 depicts the association between baseline cognitive performance and changes in MADRS scores.

Discussion

In this ancillary analysis of the DepressionDC trial, a randomized, sham-controlled multicenter study assessing the antidepressant efficacy of a prefrontal tDCS as acute treatment in patients with MDD and SSRI treatment, we found no statistically significant group differences between active tDCS and sham tDCS for the change of performance in FPN-associated cognitive domains (i.e. memory span, working memory, selective attention, sustained attention, executive function and processing speed) from baseline to week 6. Furthermore, baseline performance in these domains was not

Table 1 Baseline patient characteristics

Characteristic	tDCS, $n=50$[1]	Sham, $n=51$[1]	p value[2]
Sex			0.76
Female	30 (60%)	29 (57%)	
Male	20 (40%)	22 (43%)	
Age (years)	39 (14)	39 (14)	0.98
Age of onset of depression (years)	32 (12)	34 (15)	0.85
Duration of current episode (weeks)	62 (69)	58 (69)	0.66
Schooling (years)	11.84 (1.93)	11.66 (1.72)	0.56
MADRS score	22.8 (6.1)	23.2 (5.3)	0.60
BDI score	27 (12)	28 (11)	0.52
WHO/DAS score	22 (9)	24 (11)	0.32
GAF score	55 (10)	56 (9)	0.98
SHAPS-D score	4.6 (3.0)	5.7 (3.5)	0.14
State-trait anxiety inventory state score	53 (11)	55 (9)	0.53
State-trait anxiety inventory trait score	57 (10)	55 (10)	0.73
CD-RISC score	16 (7)	17 (7)	0.68

[1] *n* (%); mean (SD). [2] Pearson's Chi-squared test; Wilcoxon rank sum test

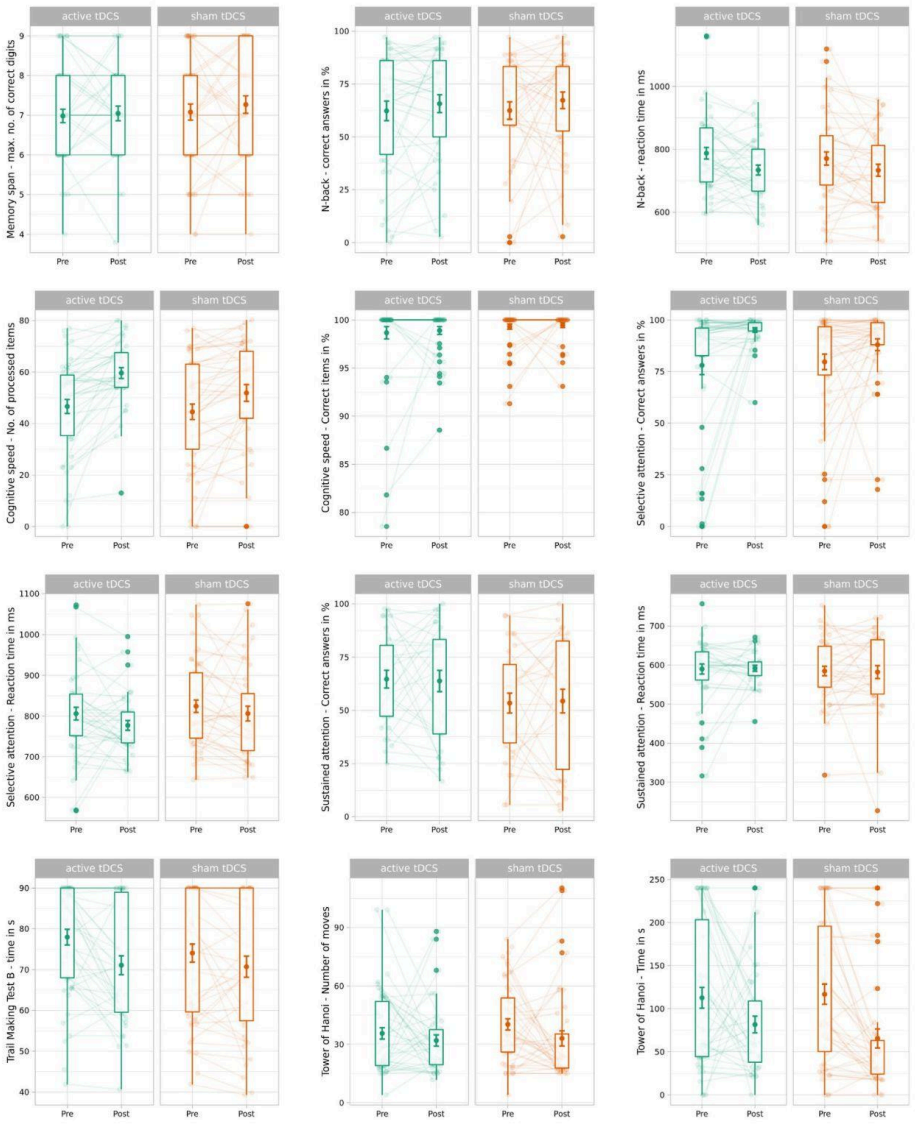
MADRS Montgomery–Åsberg Depression Rating Scale, *BID* Beck Depression Inventory, *WHO/DAS* The World Health Organization Disability Assessment Schedule, *GAF* Global Assessment of Functioning, *SHAPS-D* self- reported anhedonia assessed with the Snaith Hamilton Anhedonia Pleasure Scale, *CD-RISC* Connor-Davidson Resilience Scale

differentially associated with a change in depression severity for active tDCS compared to sham tDCS.

Our results are in contrast to a recent meta-analysis that found significant effects of tDCS on working memory and attention [28]. This meta-analysis was based on studies with sample sizes between n = 18 [15] and n = 127 [26] the number of treatment sessions (one [24] up to 22 [26] and tDCS dosages(0.5 mA [21, 27], 1 mA [15, 20] and 2 mA [16–18, 22–26]) was highly heterogeneous. Among single studies included in this meta-analysis, several authors reported an improvement of attention/vigilance, working memory, executive functioning, processing speed, and social cognition [15, 17], spatial working memory [18] or processing speed [16]. However, other studies in this meta-analysis are rather in line with our findings and did not show significant effects of tDCS on performance in neurocognitive domains [20–27]. The ELECT-TDCS trial, a clinical study with identical stimulation parameters and a larger sample size, did not find significant effects on cognition either [26].

There are several potential reasons for these negative findings. First, our multicenter trial tested only one set of tDCS parameters with the aim of reducing depressive symptoms. However, dose–response curves for single domains of neurocognitive performance have not been established. They may be non-linear and could theoretically vary from one domain to another [44, 45] as well as from dose–response curves of antidepressant effects. While being in line with previous studies on antidepressant tDCS, the administered dosage in our trial might have been insufficient to optimally modulate specific prefrontal cognitive functions. Second, the main trial did not show beneficial antidepressant effects of active tDCS over sham tDCS. Thus, the applied tDCS protocol might have also been not potent enough to modulate neuroplasticity changes in general. Third, high levels of arousal, estimated by using the State-Trait Anxiety Inventory (STAI), have been reported to diminish cognitive practice effects elicited by tDCS, [46] underlining the potential role of arousal in shaping responses to neuromodulation. In our study, both groups had high baseline STAI scores, and such high baseline anxiety could have reduced the effects of tDCS on neurocognitive performance. Lastly, several studies have reported that tDCS might only elicit procognitive effects when simultaneously combined with specific cognitive tasks [47–52]. Thus, passive stimulation, as administered in our trial, might not be sufficient to enhance cognition in patients with MDD.

To the best of our knowledge, this is the first study that investigates whether cognition at baseline may be used to predict improvement of depression during a course of tDCS. Our study has multiple strengths. The study followed the highest possible trial design standards by being triple-blinded, placebo-controlled, and multicenter. We applied a tDCS protocol (2 mA, 30 min) established in previous studies which showed a superior antidepressant efficacy of active over sham tDCS, i.e. the SELECT-TDCS [53] and ELECT-TDCS [26] trials, and our data-set is one of the biggest samples in the field to date (n = 101). Furthermore, we used a validated digital assessment battery that has successfully been used in other previous studies [31, 32, 54]. While efforts are being made to digitize previously validated



Note: Error bars indicate mean (SE). Boxplots include the IQR with whiskers indicating 1.5 times IQR. Thin lines represent patient-individual changes.

Fig. 1 Pre- and post-treatment performance across neurocognitive tests for active tDCS and sham tDCS. Note: Error bars indicate mean (SE). Boxplots include the IQR with whiskers indicating 1.5 times IQR. Thin lines represent patient-individual changes

Table 2 Treatment effects on neurocognitive test scores

Cognitive measure	Slope active tDCS (95% CI)	Slope sham tDCS (95% CI)	F (df)	*p*	p_{fdr}	Standardized effect size (95% CI)
Memory span (maximum number of correct digits)	0.02 (− 0.63 0.66)	0.20 (− 0.44 0.84)	0.72 (1, 73)	0.40	0.80	− 0.19 (− 0.75, 0.37)
Working memory (correct answers in %)	4.86 (− 9.41, 19.1)	6.68 (− 7.47, 20.8)	0.13 (1, 71)	0.72	0.81	− 0.08 (− 0.66, 0.50)
Working memory (reaction time in ms)	-32.8 (− 109, 43.6)	− 38.4 (− 117 40.2)	0.07 (1, 69)	0.79	0.81	0.06 (− 0.71, 0.83)
Cognitive speed (number of processed items)	10.91 (4.12, 17.7)	5.71 (− 1.19, 12.6)	4.69 (1, 73)	**0.03**	0.18	0.49 (− 0.12, 1.09)
Cognitive speed (correct items in %)	0.22 (− 2.90, 3.34)	0.68 (− 3.31, 4.66)	1 (1, 73)	0.32	0.77	− 0.23 (− 1.86, 1.4)
Selective attention (correct items in %)	14.58 (− 3.33, 32.5)	7.83 (− 14.52, 30.2)	4.88 (1, 77)	**0.03**	0.18	0.50 (− 0.92, 1.91)
Selective attention (reaction time in ms)	− 16.9 (− 126, 92.7)	− 11.5 (− 194, 170.9)	0.08 (1, 73)	0.77	0.81	− 0.07 (− 1.96, 1.83)
Sustained attention (correct items in %)	1.52 (− 19.2, 22.2)	− 1.34 (− 27.5, 24.8)	0.18 (1, 56)	0.67	0.81	0.11 (− 0.87, 1.09)
Sustained attention (reaction time in ms)	16.01 (− 75.4, 107)	2.85 (− 155.2, 161)	0.47 (1, 61)	0.50	0.81	0.172 (− 1.61, 1.95)
Trail making B (time in s)	− 5.69 (− 24.6 13.2	− 2.54 (− 25.1, 20.0)	1.78 (1, 75)	0.19	0.76	− 0.31 (− 2.12, 1.51)
Tower of Hanoi (number of moves)	− 4.2 (− 19.7, 11.3)	− 3.05 (− 19.6, 13.5)	0.06 (1, 74)	0.81	0.81	− 0.05 (− 0.73, 0.63)
Tower of Hanoi (time in s)	− 29.8 (− 112, 52.9)	− 44.0 (− 158, 70.4)	1.02 (1, 74)	0.32	0.77	0.23 (− 1.31, 1.77)

p values computed using Type III analyses of variance with Satterthwaite's method. Slope active tDCS = standardized slope parameter for active tDCS. Slope sham tDCS = standardized slope parameter for sham tDCS

Table 3 Prediction of changes MADRS

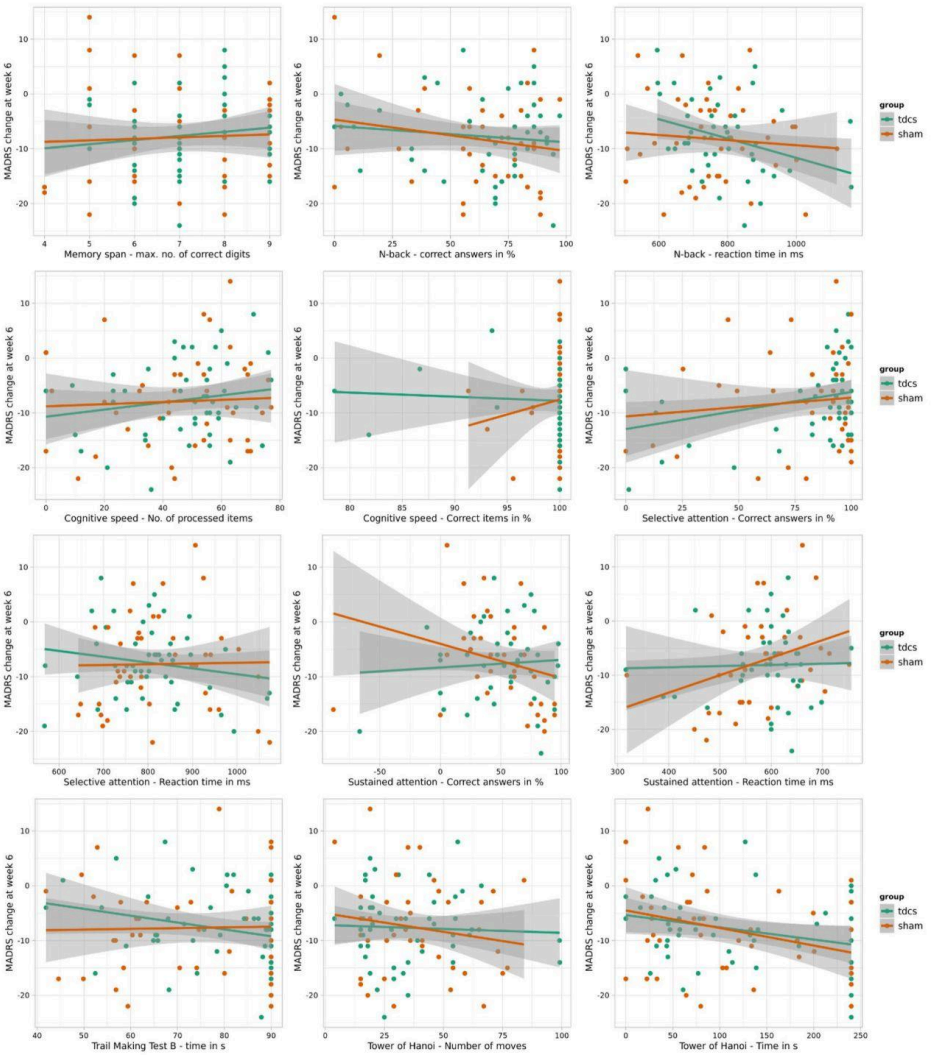
Measure	Cognitive tests							
	Group		Cognitive test score		Group × cognitive test score			
	F (df)	*p*	F (df)	*p*	F (df)	*p*	p_{FDR}	η^2
Memory span (maximum number of correct digits)	0.12 (1, 89)	0.74	0.66 (1, 89)	0.42	0.14 (1, 89)	0.71	0.71	0.001
Working memory (correct answers in %)	0.20 (1, 88)	0.65	2.66 (1, 88)	0.11	0.42 (1, 88)	0.52	0.63	0.005
Working memory (reaction time in ms)	1.54 (1, 81)	0.22	3.10 (1, 64)	0.08	1.43 (1, 81)	0.24	0.63	0.02
Cognitive speed (number of processed items)	0.29 (1, 89)	0.59	0.87 (1, 88)	0.35	0.43 (1, 89)	0.51	0.63	0.005
Cognitive speed (correct items in %)	0.93 (1, 85)	0.34	0,87 (1, 85)	0.35	0.92 (1, 85)	0.34	0.63	0.01
Selective attention (correct items in %)	0.32 (1, 89)	0.57	3.77 (1, 88)	0.06	0.47 (1, 89)	0.49	0.63	0.005
Selective attention (reaction time in ms)	0.40 (1, 85)	0.53	0.42 (1, 85)	0.52	0.40 (1, 84)	0.53	063	0.005
Sustained attention (correct items in %)	0.66 (1,73)	0.42	0.03 (1, 75)	0.86	0.62 (1, 74)	0.43	0.63	0.008
Sustained attention (reaction time in ms)	1.17 (1, 73)	0.28	2.24 (1, 74)	0.14	1.36 (1, 73)	0.25	0.63	0.02
Trail Making B (time in s)	1.59 (1, 85)	0.21	0.80 (1, 87)	0.37	1.59 (1, 85)	0.21	0.63	0.02
Tower of Hanoi (number of moves)	0.47 (1, 88)	0.49	1.37 (1, 88)	0.25	0.55 (1, 88)	0.46	0.63	0.006
Tower of Hanoi (time in s)	0.12 (1, 87)	0.73	8.32 (1, 87)	0.005	0.031 (1, 87)	0.58	0.63	0.004

p values computed using Type III analyses of variance with Satterthwaite's method. MADRS = Montgomery-Åsberg Depression Rating Scale. $\eta^2 = 0.01 \leq 0.06$ (small effect), $0.06 \leq 0.14$ (moderate effect) and ≥ 0.14 (large effect)

cognitive tests [55, 56], such tools which also reduce documentation errors [57, 58], are still underused.

Limitations

First, there is no uniform consensus on what neurocognitive tests are better used to evaluate the performance in domains



Note: MADRS=Montgomery-Åsberg Depression Rating Scale.

Fig. 2 Association between baseline cognitive performance and MADRS change across the trial. *MADRS* Montgomery-Åsberg Depression Rating Scale

associated with FPN function. Our battery included some of the most common tests and slight variations of them. However, other standardized tests could have a higher sensitivity and specificity for detecting neuromodulation effects on cognitive performance [59]. Second, digital tools present a few caveats such as failure of the equipment, corruption of data, and loss of information when retrieving the data. This limited the availability of data in our study. Third, the evaluation of procognitive effects of tDCS and the potential predictive effects of baseline cognition on treatment response were ancillary investigations. Though this data was well balanced across both conditions, there may be latent selection biases making the sample not representative for the whole study population. In addition, the current analysis was likely underpowered to detect small treatment and prediction effects. Lastly, all patients were on a stable SSRI medication for at least 4 weeks prior to inclusion, but not antidepressant-free. Thus, our conclusions regarding the differential effects of SSRI medication and tDCS on performance in distinct neurocognitive domains are limited.

Conclusion

In conclusion, our analysis does not support the notion that acute treatment with active tDCS compared to sham tDCS leads to an improvement in FPN-related neurocognitive functions. In addition, neurocognitive functioning at baseline did not predict the change of MADRS scores over the course of tDCS. Future research should aim at identifying tDCS protocols with optimal dose–response curves for effects on specific neurocognitive domains. Most promising candidates could then be further optimized by adjusting parameters at an individual patient's level.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00406-024-01759-2.

Author contributions Conceptualization: AS, GB, UV; Formal Analysis: GB, SG; Funding Acquisition: FP, AJF; Investigation: AS, UV, GB, LF, CN; Methodology: AS. GB, SA; Project Administration: FP; Resources: FP, AJF, CP, SA; Supervision: GB, FP, AJF, CP, SA; Visualization: GB; Writing – Original Draft Preparation: AS; Writing – Review & Editing: GB, FP, UV, GV, LF, AJF, CSL, SG, SA, CP, CN, LF, PZ, TK, MB.

Funding Open Access funding enabled and organized by Projekt DEAL. The DepressionDC trial was a project of the German Center for Brain Stimulation (GCBS) research consortium, funded by the German Federal Ministry of Education and Research (BMBF; grant number FKZ 01EE1403G). GB has received an internal grant for young researchers from the Medical Faculty of the Ludwig Maximilian University Munich (grant number: FOEFOLE 1127).

Data availability The de-identified individual patient data in this paper will be made accessible after its publication for non-commercial academic projects that have a legitimate research topic and a clearly stated hypothesis. If the application is accepted, researchers will be asked to get the study approved by their institution's ethics board. The authors will subsequently provide the de-identified data sets via a safe data transfer system. You may find the DepressionDC research protocol as well as further extra information at https://osf.io/cpw6f/.

Declarations

Conflict of interest FP has received consulting fees from Brainsway Inc. (Jerusalem, Israel) as a member of the European Scientific. Advisory Board and from Sooma (Helsinki, Finland) as a member of the International Scientific. Advisory Board; honoraria for workshops from Mag&More GmbH (Munich, Germany); and honoraria for lectures from neuroCare Group (Munich, Germany) and Brainsway Inc. (Jerusalem, Israel); and has received equipment from Mag&More GmbH (Munich, Germany), neuroCare Group (Munich, Germany), and Brainsway Inc. (Jerusalem, Israel). BL received honoraria for consultancy and speakers' fees from ANM, AstraZeneca, Autifony Therapeutics, Decibel Therapeutics, Desyncra, Gerson Lehmanns Group, Lundbeck, Merz, MagVenture, Medical Tribune, Neurolite, Neuromod, Novartis, Pfizer, Rovi, Schwabe, Sea Pharma, Servier, Sonova and Sound Therapeutics; research funding from the Tinnitus Research Initiative, Bayhost, the German Research Foundation, the German Federal Ministry of Education and Research, the American Tinnitus Association, AstraZeneca, cerbomed, Neuromod and the European Union; and has received equipment from MagVenture and Deymed Diagnostic. CP is managing partner of PsyKit GmbH, Tübingen, Germany. AS, UV, GV, LF, AJF, GB, CSL, SG, SA, CP, CN, LF, PZ, TK, and MB declare no competing interests.

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4. Paper II - Adverse childhood experiences and clinical effects of transcranial direct current stimulation in major depressive disorder: Results from the DepressionDC trial

Psychiatry Research 330 (2023) 115577

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Letter to the Editor

Adverse childhood experiences and clinical effects of transcranial direct current stimulation in major depressive disorder: Results from the DepressionDC trial

Dear editor,

Adverse childhood experiences (ACE) are highly prevalent risk factors for major depressive disorder (MDD). A history of ACE predicts psychopharmacological and psychotherapeutic outcomes in post-hoc analyses of randomized controlled trials(Nemeroff et al., 2003; Williams et al., 2016). However, minimal data are available on the relevance of ACE for the efficacy of brain stimulation interventions targeting the left dorsolateral prefrontal cortex, though its structure and function are related to ACE.

We recently reported the results of a multicenter, randomized controlled trial comparing active with sham tDCS over 6 weeks as an additional treatment to selective serotonin reuptake inhibitors(Burkhardt et al., 2023). Despite using an established tDCS protocol(Brunoni et al., 2013), we found no differences between groups. Therefore, we were interested in potential moderators that could explain these negative findings and guide future studies on tDCS in MDD. Specifically, we aimed to assess whether self-reported ACE predicts the clinical effects of active compared to sham tDCS. We obtained data from 126 patients of our trials' intention-to-treat sample. Using the Childhood Trauma Questionnaire (CTQ), we assessed five types of ACE at baseline (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect). We considered patients to have a specific ACE type if they reported at least "moderate to severe" sum scores on the respective CTQ subscale. We then compared patients across three levels of ACE: First, we defined a history of ACE as having experienced at least one ACE type. Second, we further subdivided patients with a history of ACE into patients with a single ACE type versus multiple ACE types. Third, we categorized patients into having experienced low, moderate, or high ACE load using a three-way quantile split on the log-transformed total CTQ score.

Trained clinicians assessed depression severity at baseline, week 6, and the follow-up visits at weeks 18 and 30, using the Montgomery-Åsberg Depression Rating Scale (MADRS). Secondary outcomes measures included the Beck Depression Inventory-II (BDI-II), the State-Trait Anxiety Inventory (STAI), the Snaith Hamilton Anhedonia Pleasure Scale (SHAPS-D), the Global Assessment of Functioning scale (GAF), the Clinical Global Impression Severity scale (CGI-S), and the general health and social functioning subscales of the Short Form Health Survey (SF-36).

Statistical analyses were conducted in R, version 4.2.1. Results were considered significant at α=.05. For each outcome, each visit (weeks 6, 18, or 30) and the three ACE levels (history of ACE; single versus multiple ACE types; low, moderate, or severe ACE load), we fit linear mixed models using the lme4 package to predict change from baseline on the respective scale. Treatment group (active versus sham tDCS), the respective ACE level, and their interaction were included as fixed effects and treatment site as random effect, while controlling for baseline scores. Significance of the model factors was determined using omnibus tests (type III ANOVA) with Satterthwaite approximation to degrees of freedom and false-discovery-rate (FDR) correction for multiple testing across predictors. Baseline characteristics between patients in each ACE level were compared using Pearson's χ^2-tests, Wilcoxon-rank-sum tests or Kruskal-Wallis tests, as appropriate.

Eighty-four (67 %) patients in the overall sample reported a history of ACE, with 50 (40 %) reporting multiple ACE types. ACE frequencies were highest for physical neglect (44 %), followed by emotional neglect (35 %), emotional abuse (32 %), sexual abuse (18 %), and physical abuse (11 %). While there were no significant baseline differences between patients with or without ACE history, patients with multiple ACE types had higher mean scores on the SHAPS-D (5.9 [SD 2.8] vs 4.1 [2.9]; p = .012) and STAI trait (59 [10] vs. 54 [10]; p = .032) compared to patients with single ACE type occurrence. Also, patients with severe ACE load had higher mean BDI-II (31 [11] vs. 25 [11]; p = .028) and STAI trait (59 [10] vs. 52 [11]; p = .016) scores than patients with low ACE load and patients with low ACE load had higher mean GAF scores (58 [7] vs. 54 [8]; p = .04) than patients with moderate ACE load.

We did not find significant interactions between the treatment group and 1.) history of ACE when predicting MADRS change at week 6 ($F_{(1,121)} = 0.11$, $p_{FDR} = .83$, $eta^2 < 0.001$), week 18 ($F_{(1,121)} = 0.11$, p = .83, $eta^2 < 0.001$), or week 30 ($F_{(1,117)} = 0.52$, p = .83, $eta^2 = 0.004$); 2.) single versus multiple ACE types when predicting MADRS change at week 6 ($F_{(1,79)} = 0.37$, $p_{FDR} = .83$, $eta^2 = 0.005$), week 18 ($F_{(1,79)} = 0.04$, $p_{FDR} = .85$, $eta^2 = <0.001$), and week 30 ($F_{(1,77)} = 0.13$, $p_{FDR} = .83$, $eta^2 = 0.001$); and 3.) ACE load when predicting MADRS change at week 6 ($F_{(2,117)} = 0.54$, $p_{FDR} = .83$, $eta^2 = 0.009$), week 18 ($F_{(2,118)} = 1.22$, $p_{FDR} = .83$, $eta^2 = 0.02$), and week 30 ($F_{(2,109)} = 1.04$, $p_{FDR} = .83$, $eta^2 = 0.02$). Results for the secondary outcome domains were in the same direction.

To our knowledge, this is the first investigation of the relationship between ACE and the effects of tDCS. Our negative findings were consistent across all outcomes, time points, and three levels of ACE. Addressing a limitation of previous research (Childhood Trauma Meta-Analysis Study Group, 2022), the baseline differences between patients depending on the severity of reported ACE highlight the need to move beyond dichotomous definitions and incorporate gradual estimates of ACE load in future studies.

Our study has some limitations. First, our findings might not be generalizable to other NIBS techniques. Second, we measured ACE using the retrospective CTQ, which may not align with factual reports of ACE and does not provide information on the age of ACE occurrence. Third, given the sample size of our dataset, we cannot exclude small moderator effects. Lastly, we did not directly measure ACE-associated structural or

https://doi.org/10.1016/j.psychres.2023.115577
Received 24 July 2023; Received in revised form 18 October 2023; Accepted 26 October 2023
Available online 29 October 2023

functional DLPFC changes, e.g., using magnetic resonance imaging.

Data Availability Statement

After the publication of this article, the de-identified individual patient data underlying the findings described here will be made available for non-commercial academic projects with a valid research question and a clearly stated hypothesis for which the data are available. The data can be obtained by submitting a request to the corresponding author. The request will be reviewed by the authors to ensure that the stated requirements are met. In case of approval, researchers will be required to sign a data access agreement that requires them to obtain approval for the project from an institutional ethics board. The de-identified data sets and a data dictionary will then be provided by the authors through a protected data transfer service. The study protocol of the DepressionDC study and additional supplementary material can be found at https://osf.io/cpw6f/.

Role of the funding sources

The DepressionDC trial was undertaken as part of the German Center for Brain Stimulation (GCBS) research consortium, which was funded by the German Federal Ministry of Education and Research (BMBF; grant number FKZ 01EE1403G). GB has received an internal grant for young researchers from the Medical Faculty of the Ludwig Maximilian University Munich (grant number: FOEFOLE 1127). BLA has received a mobility grant (BA21/00002) by the Instituto de Salud Carlos III-Subdirección General de Evaluación y Fomento de la Investigación, Plan Nacional 2008-2011 and 2013-2016. JW has received an internal grant for young researchers from the Medical Faculty of the Ludwig Maximilian University Munich (grant number: FOEFOLE 1150). The sponsors were not involved in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

CRediT authorship contribution statement

Gerrit Burkhardt: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Visualization, Writing – original draft, Writing – review & editing. **Stephan Goerigk:** Conceptualization, Data curation, Formal analysis, Methodology, Validation, Supervision, Writing – original draft, Writing – review & editing. **Lucia Bulubas:** Investigation, Validation, Data curation, Writing – original draft, Writing – review & editing. **Esther Dechantsreiter:** Investigation, Validation, Data curation, Writing – original draft, Writing – review & editing. **Daniel Keeser:** Investigation, Validation, Data curation, Writing – original draft, Writing – review & editing. **Ulrike Kumpf:** Investigation, Validation, Data curation, Writing – original draft, Writing – review & editing. **Aldo Soldini:** Investigation, Validation, Writing – original draft, Writing – review & editing. **Johannes Wolf:** Investigation, Validation, Writing – original draft, Writing – review & editing. **Benedikt L. Amann:** Conceptualization, Validation, Writing – original draft, Writing – review & editing. **Christian Plewnia:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Andreas Fallgatter:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Berthold Langguth:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Claus Normann:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Lukas Frase:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Peter Zwanzger:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Thomas Kammer:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Carlos Schönfeldt-Lecuona:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Daniel Kamp:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Malek Bajbouj:** Conceptualization, Investigation, Funding acquisition, Writing – original draft, Writing – review & editing. **Peter Falkai:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Andre R Brunoni:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Katja Bertsch:** Conceptualization, Writing – original draft, Writing – review & editing. **Andrea Jobst:** Conceptualization, Writing – original draft, Writing – review & editing. **Matthias A. Reinhard:** Conceptualization, Writing – original draft, Writing – review & editing. **Frank Padberg:** Conceptualization, Funding acquisition, Investigation, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

FP has received grants from the German Research Foundation (DFG; grant number: BR 4264/6-1) and the German Federal Ministry of Education and Research (BMBF; grant number: 01EW1903); consulting fees from Brainsway Inc. (Jerusalem, Israel) as a member of the European Scientific Advisory Board and from Sooma (Helsinki, Finland) as a member of the International Scientific Advisory Board; honoraria for workshops from Mag&More GmbH (Munich, Germany); and honoraria for lectures from neuroCare Group (Munich, Germany) and Brainsway Inc. (Jerusalem, Israel); and has received equipment from Mag&More GmbH (Munich, Germany), neuroCare Group (Munich, Germany), and Brainsway Inc. (Jerusalem, Israel). BL received honoraria for consultancy and speakers' fees from ANM, AstraZeneca, Autifony Therapeutics, Decibel Therapeutics, Desyncra, Gerson Lehmanns Group, Lundbeck, Merz, MagVenture, Medical Tribune, Neurolite, Neuromod, Novartis, Pfizer, Rovi, Schwabe, Sea Pharma, Servier, Sonova and Sound Therapeutics; research funding from the Tinnitus Research Initiative, Bayhost, the German Research Foundation, the German Federal Ministry of Education and Research, the American Tinnitus Association, AstraZeneca, cerbomed, Neuromod and the European Union; and has received equipment from MagVenture and Deymed Diagnostic. PF has received research support/honoraria for lectures or advisory activities from Boehringeer-Ingelheim, Janssen, Lundbeck, Otsuka, Recordati, and Richter. CP is a managing partner of PsyKit GmbH, Tübingen, Germany. GB, SG, LB, ED, DKe, UK, AS, JW, BA, AF, CN, LF, PZ, TK, CSL, DKa, MB, AB, KB, AJ, and MR declare no competing interests.

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Gerrit Burkhardt[a,*], Stephan Goerigk[a,b], Lucia Bulubas[a], Esther Dechantsreiter[a], Daniel Keeser[a], Ulrike Kumpf[a], Aldo Soldini[a], Johannes Wolf[a], Benedikt L. Amann[c,d,e], Christian Plewnia[f], Andreas Fallgatter[f], Berthold Langguth[g], Claus Normann[h,i], Lukas Frase[h,p], Peter Zwanzger[i], Thomas Kammer[k], Carlos Schönfeldt-Lecuona[k], Daniel Kamp[l], Malek Bajbouj[m], Peter Falkai[a], Andre R Brunoni[n], Katja Bertsch[o], Andrea Jobst[a], Matthias A. Reinhard[a], Frank Padberg[a]

[a] *Department of Psychiatry and Psychotherapy, LMU University Hospital, Munich, Germany*

[b] *Department of Psychology, Charlotte Fresenius Hochschule, Munich, Germany*

[c] *Mental Health Institute Hospital del Mar, Barcelona, Spain; Centre Forum Hospital del Mar Research Institute, Barcelona, Spain*

[d] *Pompeu Fabra University Barcelona, Barcelona, Spain*

[e] *Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto Carlos III, Madrid, Spain*

[f] *Tübingen Center for Mental Health, Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany*

[g] *Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany*

[h] *Department of Psychiatry and Psychotherapy, Medical Center, University of Freiburg, Freiburg, Germany*

[i] *Center for Basics in Neuromodulation (NeuroModulBasics), University of Freiburg, Freiburg, Germany*

[j] *kbo-Inn-Salzach-Klinikum, Clinical Center for Psychiatry, Psychotherapy, Psychosomatic Medicine, Geriatrics and Neurology, Gabersee, Wasserburg/Inn, Germany*

[k] *Department of Psychiatry and Psychotherapy III, University of Ulm, Ulm, Germany*

[l] *Department of Psychiatry and Psychotherapy, LVR-Klinikum Düsseldorf, Heinrich-Heine-Universität Düsseldorf, Medical Faculty, Düsseldorf, Germany*

[m] *Department of Psychiatry and Psychotherapy, Charité-Campus Benjamin Franklin, Berlin, Germany*

[n] *Departments of Internal Medicine and Psychiatry, University of São Paulo Medical School, São Paulo, Brazil*

[o] *Department of Psychology, Ludwig-Maximilians-University Munich, Munich, Germany*

[p] *Department of Psychosomatic Medicine and Psychotherapy, Medical Center, University of Freiburg - Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany*

[*] Corresponding author.
E-mail address: gerrit.burkhardt@med.uni-muenchen.de (G. Burkhardt).

5. Paper III - Driving-related cognitive skills during antidepressant transcranial direct current stimulation: results in a subsample from the DepressionDC trial

frontiers | Frontiers in Psychiatry

TYPE Brief Research Report
PUBLISHED 07 December 2023
DOI 10.3389/fpsyt.2023.1255415

OPEN ACCESS

EDITED BY
Huanzhong Liu,
Chaohu Hospital of Anhui Medical University, China

REVIEWED BY
Raffaella Ricci,
University of Turin, Italy
Noomane Bouaziz,
Hôpital de Ville-Évrard, France

*CORRESPONDENCE
Gerrit Burkhardt
gerrit.burkhardt@med.uni-muenchen.de

RECEIVED 08 July 2023
ACCEPTED 24 November 2023
PUBLISHED 07 December 2023

CITATION
Burkhardt G, Goerigk S, Dechantsreiter E, Bulubas L, Soldini A, Zwanzger P, Diemer J, Padberg F, Brunnauer A and Kumpf U (2023) Driving-related cognitive skills during antidepressant transcranial direct current stimulation: results in a subsample from the DepressionDC trial.
Front. Psychiatry 14:1255415.
doi: 10.3389/fpsyt.2023.1255415

Driving-related cognitive skills during antidepressant transcranial direct current stimulation: results in a subsample from the DepressionDC trial

Gerrit Burkhardt[1]*, Stephan Goerigk[1,2], Esther Dechantsreiter[1], Lucia Bulubas[1], Aldo Soldini[1], Peter Zwanzger[3], Julia Diemer[3], Frank Padberg[1], Alexander Brunnauer[1,3] and Ulrike Kumpf[1]

[1]Department of Psychiatry and Psychotherapy, LMU University Hospital, LMU Munich, Munich, Germany, [2]Charlotte Fresenius Hochschule, University of Psychology, Munich, Germany, [3]kbo-Inn-Salzach-Klinikum, Clinical Center for Psychiatry, Psychotherapy, Psychosomatic Medicine, Geriatrics and Neurology, Wasserburg am Inn, Germany

Therapeutic transcranial direct current stimulation (tDCS) is a well-tolerated neuromodulatory intervention. However, there are currently no data on its impact on driving skills. Therefore, we conducted a validated assessment of driving-related cognitive skills in participants of the DepressionDC trial, a multicenter, randomized-controlled trial investigating the antidepressant effects of 6-week prefrontal tDCS in patients with major depressive disorder (MDD). Twenty-one patients (12 women, active tDCS, $n = 11$, sham, $n = 10$) underwent an assessment of driving-related cognitive skills before and after the intervention. Using a Bayesian analysis approach, we found no group differences between active tDCS and sham tDCS in the pre-post treatment changes for *visual perception* (estimated median difference: 3.41 [−3.17, 10.55 89%-CI], BF_{01}: 2.1), *stress tolerance* (estimated median difference: 0.77 [−2.40, 4.15 89%-CI], BF_{01}: 1.6), and *reaction time* (estimated median difference: 2.06 [−12.33, 16.83 89%-CI], BF_{01}: 6.5). Our results indicate that repeated sessions of a conventional bifrontal tDCS protocol do not negatively impact driving-related cognitive skills in patients with MDD.

KEYWORDS

major depressive disorder, transcranial direct current stimulation, tDCS, depression, driving performance

Introduction

Transcranial direct current stimulation (tDCS) of prefrontal cortex regions is increasingly used as a neuromodulatory technique in various scientific and therapeutic applications (1). Conventional tDCS protocols are considered safe and well tolerated (1); however, there are currently no data on their long-term impact on driving skills. Driving is a context-dependent complex cognitive task (2) with high relevance for the daily functioning of many adults. Previous experimental studies have reported less risky driving behavior (3), improved car-following and lane-keeping (4), or no significant improvements in driving-related skills (5) after single tDCS sessions in healthy individuals. However, these results may not be generalizable to repeated tDCS sessions in patients with mental health disorders.

Therapeutic applications of tDCS, e.g., for the treatment of major depressive disorder (MDD), usually target the left dorsolateral prefrontal cortex (lDLPFC), a part of the frontoparietal network (FPN), with multiple treatment sessions across 2–6 weeks (6, 7). Since the FPN is implicated in the function of several cognitive domains like attention and working memory (8, 9), previous research has investigated whether such tDCS protocols elicit short-term effects on cognition. While a recent meta-analysis showed small effects of active tDCS versus sham tDCS on working memory and attention/vigilance across multiple neuropsychiatric disorders (10), another meta-analysis in patients with MDD reported no beneficial cognitive effects but reduced performance gains in processing speed (11). MDD has been associated with cognitive deficits, even following remission from a major depressive episode (12), and constitutes a potential risk factor for dementia (13). Correspondingly, patients with MDD also show impaired driving ability (14). Therefore, it is essential to rule out possible detrimental effects on driving-related cognitive skills and establish the road safety of new interventional methods used in this population.

We investigated the effects of a conventional bifrontal tDCS protocol on driving-related cognitive skills according to legal constraints with a standardized, computerized test battery in a subsample of participants from the recently published DepressionDC trial (7).

Materials and methods

We recruited patients at two study sites (Munich and Wasserburg/Inn) of the recently published DepressionDC trial (Trial registration number: NCT02530164) (7) for an assessment of driving-related cognitive skills, which was optional for study participants. DepressionDC was a multicenter, randomized, sham-controlled trial investigating the efficacy of transcranial direct current stimulation (tDCS) in patients with MDD and no relevant psychiatric comorbidities in addition to a stable but not effective treatment with a selective serotonin reuptake inhibitor (SSRI). The trial comprised a 6-week acute treatment protocol with 2-mA bifrontal tDCS for 20 consecutive weekdays followed by two tDCS sessions a week for 2 weeks or sham treatments at the same intervals; each tDCS session lasted 30 min. Following the international electroencephalogram 10–20 system, two 35 mm^2 sponge-covered rubber electrodes were placed over F3 (anode) and F4 (cathode). While active tDCS comprised a ramp-up phase before and a ramp-down phase after stimulation, sham tDCS consisted of ramp-up-ramp-down phases at the beginning and the end of each session to mimic the sensory artifacts of active stimulation. All treatment sessions were conducted at the respective study site. TDCS devices (DC-Stimulator Mobile, neuroConn, Ilmenau, Germany) were programmed to deliver active or sham tDCS based on a randomization code, without displaying any information on the treatment condition. The local ethics committees approved the study at each study site. All participants gave written informed consent before inclusion in the study.

We assessed participants' driving-related cognitive skills at baseline and in the week after the last treatment session of the 6-week trial. Following the German guidelines for road and traffic safety (15), we applied a standardized, computerized psychomotor test battery comprising the following domains via a validated software[1]: (1) Visual perception was measured as the percentage of correct answers on the adaptive Tachistoscopic Traffic Perception Test (TAVT-MB). During the TAVT-MB, 20 images of typical traffic situations are presented to the test subject for 1 s each. After each image, subjects must respond to a 5-answer multiple-choice question on the contents of the displayed situation. (2) Reactive stress tolerance was measured as the number of omissions on the adaptive Vienna determination test (DT). In three test phases, subjects are presented with visual and acoustic stimuli to which they must respond by pressing several buttons, bars, and pedals using both their hands and feet. (3) Reaction time to simple stimulus constellations was measured as time in ms on the Choice-Reaction Test (RT), in which subjects must respond to a specific combination of visual and acoustic stimuli. Reaching at least a percentage above 15 is defined as a prerequisite to driving a car safely. The assessments lasted about 20–30 min for each participant.

All statistical analyses were conducted in R, version 4.2.1. We descriptively compared the global driving performance of participants in the active tDCS and sham groups using the Index of Psychomotor Performance (IPP) (16). The IPP is calculated by dividing the number of failed tests (participant falls short of the threshold of one standard deviation below the mean of normative data derived from a representative sample of car drivers in Germany) by the number of tests. Failure to more than 40% of tests is considered a severe impairment of driving skills. We then compared the mean changes from pre- to post-treatment between active tDCS and sham tDCS on the three domains using Bayesian linear regression (formula: change ~ treatment group) from the BayesFactor package (17), adjusting for mean centered baseline depression severity [assessed with the Montgomery–Åsberg Depression Rating Scale (MADRS)]. We chose a Bayesian approach to quantify the evidence in favor of the null hypothesis that changes in driving performance are similar between active tDCS and sham. 89%-credible intervals (CI) and Bayes Factors in favor of the null hypothesis (BF_{01}) were computed using the bayestestR package (18). Interpretation of BF_{01} values followed Jeffreys (19).

Results

Twenty-one patients (12 women, active tDCS, $n = 11$; sham, $n = 10$) underwent an assessment of their driving-related cognitive skills. The mean age in our sample was 39.1 years (SD 13.1). Further baseline characteristics are reported in Table 1. At baseline, 6 participants showed mild and 2 participants severe impairment of global driving skills. After the 6-week trial, one patient in the active tDCS group showed a relevant worsening (passed to mild impairment), and one patient in the sham group had a relevant improvement of global driving skills (severe impairment to passed). Comparisons of active tDCS and sham indicated anecdotal evidence against group differences for *visual perception* (estimated median difference: 3.41 [−3.17, 10.55 89%-CI], BF_{01}: 2.1) and *stress tolerance* (estimated median difference: 0.77 [−2.40, 4.15 89%-CI], BF_{01}: 1.6), as well as moderate evidence against group differences for *reaction time* (estimated median difference: 2.06 [−12.33, 16.83 89%-CI], BF_{01}: 6.5). Group differences are visualized in Figure 1 and reported in Table 2. Single participant data are reported in

1 https://www.schuhfried.com/vienna-test-system/

Supplementary Table S1 and Supplementary Figure S1. A post-hoc sensitivity analysis adjusted for baseline duration of MDD episode did not change the overall results (Supplementary Table S2).

Discussion

Our results indicate that repeated sessions of a conventional bifrontal tDCS protocol do not negatively impact driving-related cognitive skills in patients with MDD. These results were consistent across three relevant standardized psychomotor test battery domains. All participants were on a stable dose of SSRI medication, which was continued during the tDCS trial. Thus, findings are unlikely to be confounded by pharmacological treatment effects. Furthermore, we controlled our analysis for depression severity to exclude potential effects of psychopathology on task performance.

Since patients in our study were aware they were participating in a driving skill assessment, the applied measures of visual perception, stress tolerance, and reaction time were context-dependent and might not have detected general cognitive effects of tDCS in these domains. For example, in contrast to a prior meta-analysis reporting a significant decrease in reaction time following tDCS stimulation of the DLPFC (20), our data showed moderate evidence against a group difference on this measure. Given that previously reported cognitive effects of tDCS were generally small (10, 20), future research should aim to investigate their real-world impact.

Our cohort consisted of patients with a mean age of 39 (SD 13.1) years, representing a typical MDD cohort. While our sample was too small to apply meaningful subgroup analyses, single-participant data showed that most patients with global baseline driving impairment were 55 and older, with heterogeneous performance trends across the study. MDD shows a significant overlap with mild cognitive impairment and manifest neurodegenerative disorders in older age groups (13, 21, 22). For DepressionDC, we excluded patients with relevant manifest comorbidities like dementia but did not apply more fine-grained assessments of prodromal or subthreshold cognitive and neurological impairments. Thus, our results indicate that a more specific focus on an older population is needed to ensure the road safety but also identify potential pro-cognitive effects of tDCS interventions in this age group.

TABLE 1 Baseline characteristics of patients in the active tDCS and sham groups.

Characteristic	tDCS, $N = 11$	Sham, $N = 10$
Sex		
Female	8 (73%)	4 (40%)
Age—years	41 (13)	43 (15)
Age of depression onset—years	36 (12)	42 (14)
Duration of episode—weeks	33 (34)	53 (37)
SSRI		
Citalopram	2 (18%)	0 (0%)
Escitalopram	4 (36%)	7 (70%)
Fluoxetin	1 (9.1%)	0 (0%)
Paroxetin	1 (9.1%)	0 (0%)
Sertralin	3 (27%)	3 (30%)
MADRS at baseline	22.7 (7.7)	21.6 (5.2)
MADRS change at week 6	-6 (9)	−9 (8)

Mean (SD); n (%).

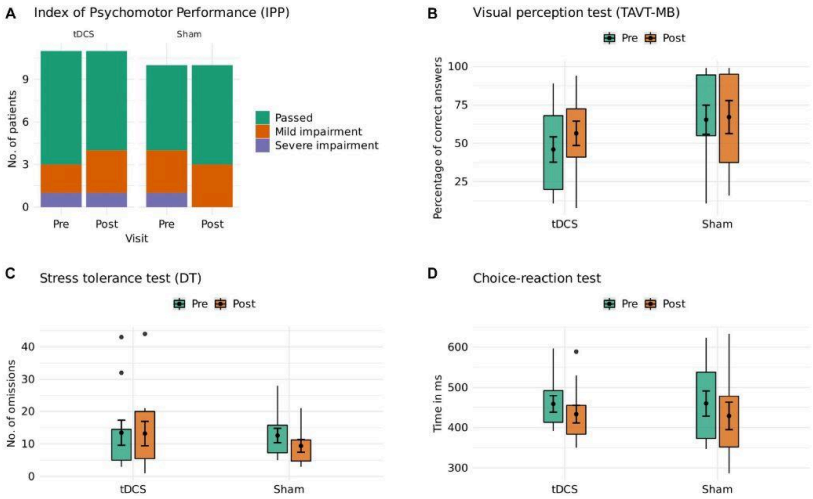

FIGURE 1
Driving-related cognitive skills.

TABLE 2 Driving-related cognitive skills results.

Characteristic	tDCS, $N = 11$			Sham, $N = 10$			Between-group comparison of pre-post change		
	Baseline	Week 6	Pre-post change	Baseline	Week 6	Pre-post change	Baseline-adjusted median difference	89% CI	BF_{01}
IPP class									
Passed	8 (73%)	7 (64%)	–	6 (60%)	7 (70%)	–	–	–	–
Mild impairment	2 (18%)	3 (27%)	–	3 (30%)	3 (30%)	–	–	–	–
Severe impairment	1 (9.1%)	1 (9.1%)	–	1 (10%)	0 (0%)	–	–	–	–
Visual perception test—correct answers	43 (20, 68)	67 (41, 72)	16 (−2, 24)	65 (30)	81 (38, 95)	0 (0, 5)	3.41	[−3.17, 10.55]	2.1
Stress tolerance test—no. of omissions	7 (5, 14)	8 (6, 20)	−2 (−7, 0)	12.0 (7.2, 15.8)	8.5 (4.8, 11.2)	−4 (−6, 0)	0.77	[−2.40, 4.15]	1.6
Choice-reaction task—time in ms	428 (413, 492)	414 (384, 455)	−19 (−58, −1)	446 (373, 538)	418 (352, 478)	−20 (−71, −6)	2.06	[−12.33, 16.83]	6.5

Median (ICR); n (%). 89%-CI, 89%-Credible Interval; BF_{01}, Bayes Factor in support of the null hypothesis; IPP, Index of Psychomotor Performance.

Our study has several limitations. First, given the small sample size, these results may not be robust and should be considered as preliminary evidence. Second, compared to the overall trial sample, we recruited participants from the active tDCS group with lower MADRS change at week 6 (−6 vs. −8 points). This selection of participants with worse antidepressant response might have masked beneficial effects of tDCS on driving-related cognitive skills. However, this would not change our results in regards to driving safety. Third, our sample reached comparable high global driving skills at both time points; thus, the results might not be generalizable to more severely affected patient groups, like patients with schizophrenia (23). Last, we have not directly observed real-life driving behavior but used a validated test battery that has been shown to identify poor driving-related cognitive skills correctly.

In conclusion, we provide first evidence supporting the road safety of a conventional repeated tDCS protocol in patients with MDD. Further trials are needed that systematically assess the effects of non-invasive brain stimulation protocols (e.g., tDCS, but also repetitive transcranial magnetic stimulation) on driving-related cognitive skills in clinical samples as additional safety assessment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethikkommission der Medizinischen Fakultät, Ludwig-Maximilians-Universität München. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GB: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. SG: Conceptualization, Data curation, Methodology, Writing – review & editing. ED: Writing – review & editing. LB: Writing – review & editing. AS: Writing – review & editing. PZ: Writing – review & editing. JD: Conceptualization, Methodology, Writing – review & editing. FP: Conceptualization, Supervision, Writing – review & editing. AB: Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing. UK: Conceptualization, Supervision, Writing – review & editing.

Funding

The DepressionDC trial was undertaken as part of the German Center for Brain Stimulation (GCBS) research consortium, which was funded by the German Federal Ministry of Education and Research (BMBF; grant no. FKZ 01EE1403G). GB has received an internal grant for young researchers from the Medical Faculty of the Ludwig Maximilian University Munich (grant no. FOEFOLE 1127).

Conflict of interest

FP has received grants from the German Research Foundation (DFG; grant no. BR 4264/6–1) and the German Federal Ministry of Education and Research (BMBF; grant no. 01EW1903); consulting fees from Brainsway Inc. (Jerusalem, Israel) as a member of the European Scientific Advisory Board and from Sooma (Helsinki, Finland) as a member of the International Scientific Advisory Board; honoraria for workshops from Mag&More GmbH (Munich, Germany); and honoraria for lectures from neuroCare Group (Munich, Germany) and Brainsway Inc. (Jerusalem, Israel); and has received equipment from Mag&More GmbH (Munich, Germany), neuroCare Group (Munich, Germany), and Brainsway Inc. (Jerusalem,

Israel). Over the last 3 years. PZ has received speaker fees or honoraria for advisory board participation from Janssen Pharmaceuticals, MedTrix, Hennig, Schwabe, Servier, Sympatient, and Neuraxpharm. All these affiliations have no relevance to the work covered in the manuscript. AB received speakers honoraria, financial research support, and travel grants from Recordati Pharma GmbH and Schuhfried GmbH within the last 3 years. He received royalties from Medizinisch Wissenschaftliche Verlagsgesellschaft Berlin, is a member of the executive board of the Deutsche Gesellschaft für Verkehrsmedizin and in the panel of experts of the Bundesanstalt für Straßenwesen (BASt).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1255415/full#supplementary-material

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Acknowledgements

I express my gratitude to my supervisor, Frank, and my thesis committee advisors Dani and Sergi, for their guidance, support, and encouragement throughout the entire process. I also extend my thanks to my fellow colleagues at GCBS and NICUM: Kai-Yen, Gerrit, Esther, Lucy, Uli, Yuki, Eva, Stephan, the imaging, stimulation and electrophysiology teams, and all the research staff and assistants, students, fellow residents, and HiWis whose vital contributions made this possible. Special thanks go to the Max Planck staff and coordinators, particularly Bettina, Isabel, Janhvi, and my fellow C4 batch colleagues. Lastly, I wish to express heartfelt thanks to Gizem, whose support has been invaluable to my career in research.

I dedicate this thesis to my mother, my sister, and my father; to my loving partner Chris, who has been by my side for these last three years; and finally, to Nina, Koko, and our mischief of rats: Mr. Fred, Mr. Tobi, Mr. Marx, and Mr. Æ.

what a long, strange trip it's been