Brain Stimulation 14 (2021) 1234–1237

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Transcranial Direct Current Stimulation (tDCS) for major depression – Interim analysis of cloud supervised technical data from the DepressionDC trial

A B S T R A C T

Background: Transcranial direct current stimulation (tDCS) of prefrontal cortex regions has been reported to exert antidepressant effects, though large scale multicenter trials in major depressive disorder (MDD) supporting this notion are still lacking. Application of tDCS in multicenter settings, however, requires measurement, storage and evaluation of technical parameters of tDCS sessions not only for safety reasons but also for quality control. To address this issue, we conducted an interim analysis of supervised technical data across study centers in order to monitor technical quality of tDCS in an ongoing multicenter RCT in MDD (*DepressionDC* trial).

Methods: Technical data of 818 active tDCS sessions were recorded, stored in a data cloud, and analysed without violating study blinding. Impedance, voltage and current were monitored continuously with one data point recorded every second of stimulation.

Results: Variability of impedance was considerable (1,42 kΩ, to 8,23 kΩ), inter-individually and even more intra-individually, but did not significantly differ between the study centre in Munich and all other sites.

Conclusion: Measurement, centralized data storage via data cloud and remote supervision of technical parameters of tDCS are feasible and proposed for future RCTs on therapeutic tDCS in multiple settings.

Dear Editor,

1. Introduction

Transcranial direct current stimulation (tDCS), a form of low intensity transcranial electrical stimulation (tES), is a promising therapeutic tool for the treatment of neurological [1] and psychiatric disorders [2–4]. Due to its beneficial safety profile, cost-effectiveness and suitability for clinical use, including home treatment, tDCS applications are spreading rapidly [5]. However, data on efficacy, stimulation quality and safety are limited due to a lack of large multicenter randomized controlled trials (RCTs). For both, multicenter trials, but also future clinical application of tDCS across settings including home treatment, monitoring of technical parameters (i.e. impedance or current) is essential to maintain technical standards, judge on compliance, and potentially to increase the likelihood of response. Here we present a blind interim analysis of technical parameters in 818 active tDCS sessions from an ongoing multicenter RCT in MDD [2] investigating the efficacy and safety of prefrontal tDCS used in addition to a stable antidepressant medication with selective serotonin reuptake inhibitors (SSRI).

2. Methods

The *DepressionDC* Trial (trial registration at ClinicalTrials.gov: NCT02530164) started in 2015 and is currently in its final phase as the last patient has completed the follow-up phase in January 2021. The study has been carried out in accordance with the Declaration of Helsinki. Informed consent was obtained prior to any study related procedure. Technical data which did not contain any link to a patient identification number of 41 patients were provided by six study sites: LMU Munich (n = 20), Charité Berlin, University of Tübingen, University of Regensburg, University of Freiburg, Isar-Amper-Klinikum Wasserburg.

2.1. Stimulation procedure

Eligible patients were respectively assigned to 24 sessions active or sham tDCS as an add-on to stable SSRI medication, to which patients had not sufficiently responded yet. Patients in both groups received 5 daily tDCS sessions per week for 4 weeks, followed by 2 weeks consisting of 2 treatment sessions per week. tDCS was conducted as previously reported [2]. In brief, a pre-programmed portable stimulation device was used at an intensity of 2 mA with a bifrontal montage of 35 cm^2 saline soaked sponge electrodes

https://doi.org/10.1016/j.brs.2021.08.005

(anode over F3, cathode over F4, 10–20 EEG system), and cap system was used for standardized electrode positioning. Each session lasted 30 min plus 15 sec ramp-in at the beginning and 30 sec ramp-out at the end. Sham condition is described in more detail in the published study protocol [2].

2.2. Technical data

With a sampling rate of one per sec. the stimulator continuously measured the applied current (I) and the adjusted voltage (U), which reflects many non-linear processes at both, electrodes and the tissue. These processes determine the impedance according to Ohm's law ($R = U/I$). For measurement of very low currents < 150μA during early ramp-in and late ramp-out periods, an implemented correction mechanism considered the non-proportional interdependency between current and voltage in lower current levels: If the measured current I was lower than a threshold T, a correction factor C was calculated depending on the difference between T and I and an empirically determined parameter E. The electrode impedance Z for currents lower than threshold T was calculated using the measured voltage V and the measured current I, scaled by the correction factor.

Data were saved on the connected saving tool and automatically transferred via data cloud solution provided by neuroConn Ilmenau to a validated study database implemented by the Münchner Studienzentrum (MSZ), which monitors the principles of ICH Good Clinical Practice and controls the trial conduct. To prevent unblinding the MSZ randomly selected only 20 sessions of active tDCS per patient. The selection followed the criteria, that all patients who received active stimulation and at least 20 tDCS sessions were selected without exception, From patients with more than 20 sessions (i.e. up to possible 24 sessions during the treatment phase), only 20 sessions were randomly selected to prevent unblinding by individually revealing the exact number of tDCS sessions. No further criteria were applied, and both data selection and analysis were kept fully separate from the ongoing trial and study personnel. In each session, technical data of 1844 measurement points were recorded. In two patients, data of only 19 sessions were conducted and used for further analysis.

2.3. Statistical analyses

For further analyses, we excluded ramp-in and ramp-out periods because within such start and shut down intervals, current changes are intended and higher impedance levels are expected to occur. Ramp-in and ramp-out phases were not part of the regular active tDCS session of 30 minutes, but came in addition. The data were evaluated using the open source software “R 3.5.2”. In order to analyse the variability across measurements, we estimated the similarity between all sequences of measures within each participant using dynamic time warping (DTW) as implemented in the “dtw” package. This algorithm estimates the similarity of two sequences by calculating the optimal match between them based on certain restriction and rules (for more information on DTW see Ref. [6]). The resulting scores indicated the variability across trials clustered in participants, days, and study centers. Scores had a minimum of zero indicating no variability across trials whereas higher scores indicated higher variability.

3. Results

The tests for differences in the variability referred to impedances between subjects, sessions and centers, where the analysis of between-centers differences compared the main centre with the other centers due to the better comparability of two similarly sized samples. Considering the phase of the stimulations without ramp-in and ramp-out, impedance minimum was 1,42 kΩ, maximum 8,23 kΩ.

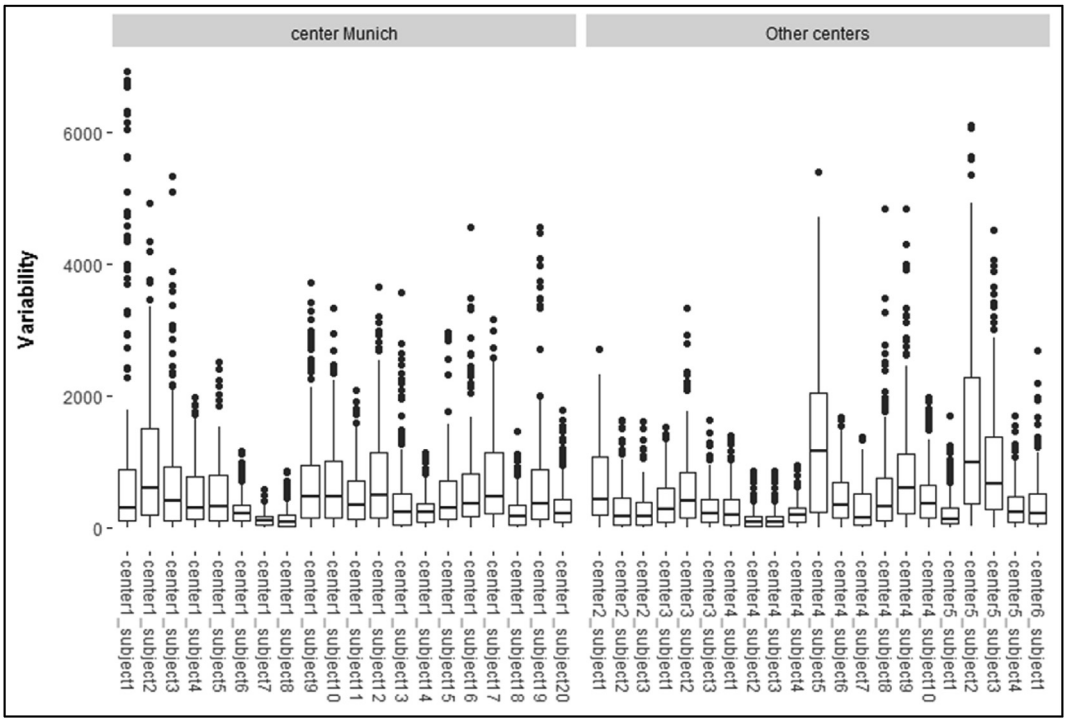

Fig. 1. Distribution of variability in impedance observed in tDCS sessions by subjects (20 sessions per subject) and centers (Munich vs. Other). Each observation represents the distance between two sessions. Boxes represent 25th to 75th percentile with the black bar representing the median variability. Outliers are represented as black dots.

To investigate differences in the variability of impedances we used DTW as described above. 18 % of the variance in the measurements was explained by inter-individual differences between subjects ($F[40,7673] = 42.34$; $p < .001$; $\eta^2 = 0.18$). However, the major portion of the variance was observed in intra-individual differences across trials. There were no significant differences between the study centre in Munich which recruited about half of the patients and the other centers regarding variability of the measured data ($F[1,7712] = 1.80$; $p = .180$; $\eta^2 = 0.00$) and average impedance ($F[1,26] = 1.42$; $p = .245$;. $\eta^2 = 0.05$) (Fig. 1).

Further data for impedance (i.e. mean impedances for individual patients, Fig. S1) as well as current intensity including the distribution of variability (Fig. S2) are reported in the Supplementary Material.

4. Discussion

The presented data show for the first time the course of the technical parameters of tDCS in a multicenter study. 818 stimulations with a total of 1,508,276 measurement points were considered. We present the course of the technical parameters as a possible marker for the stimulation quality and were able to show that online monitoring of technical parameters is feasible and helpful for tDCS quality control. Our data show that variability of impedance was considerable (1,42 kΩ, to 8,23 kΩ), but did not significantly differ between the study centre in Munich and all other sites. Current intensity (raw data) varied between 2.087 mA and 1.875 mA, and there was a difference between centers with a low effect size, which was significant due to the large number of measurements. Nevertheless, there are several issues to be discussed. The first, impedance was calculated from measurements of current and voltage with a formula that was used to correctly map the “real” impedance values even in lower current ranges. Non-linear relationships between current and voltage in relation to the impedance in many areas can principally not be assessed without errors in this way. The direct measurement of the electrode resistance, which largely contributes to impedance, could have been done with the help of a test current and/or the use of a sentinel electrode [7]. However, there are limitations regarding large scale application, e.g. in multicenter RCTs. Another limitation is that we have no previous data from our group nor data from other sources, and to our knowledge, standards for objectively quantifying the variation of technical parameters are lacking. Thus, statements on our data meeting quality criteria would be premature, and we just can compare the variation of technical tDCS parameters e.g. across study sites. We believe, however, that our approach could be useful not only for monitoring tDCS quality in various settings, but also for establishing quality standards and ensuring reproducibility [8].

5. Conclusion

The approach in the *DepressionDC* study, i.e. the central collection and storage of the technical parameters on a data cloud, which can be accessed centrally, was successfully tested in a first sample of study participants. Our approach could leverage quality control in multicenter RCTs on therapeutic tDCS for psychiatric or neurological disorders in various settings including home treatment.

Acknowledgments & Disclosures

This study was supported by the German Centre for Brain Stimulation (GCBS) research consortium (Work Package 7) [grant number 01EE1403G], funded by the Federal Ministry of Education and Research (BMBF).

FP is a member of the European Scientific Advisory Board of Brainsway Inc., Jerusalem, Israel, and has received speaker's honoraria from Mag&More GmbH and the neuroCare Group. His lab has received support with equipment from neuroConn GmbH, Ilmenau, Germany, and Mag&More GmbH and Brainsway Inc., Jerusalem, Israel.

AH has been invited to scientific meetings by Lundbeck, Janssen, and Pfizer, and he received paid speakerships from Desitin, Janssen, Otsuka, and Lundbeck. He was member of Roche, Otsuka, Lundbeck, and Janssen advisory boards.

UP has received speaker's honoraria from neuroCare Group and had a private practice with this company.

MB has receiced speaker fees or honoraria for advisory board participation from Janssen Pharmaceuticals, Lundbeck, Parexel and Biotest. He is member of the scientific advisory board of GH Research.

PZ has received speaker fees or honoraria for advisory board participation from Janssen Pharmaceuticals, Schwabe, Servier, and Neuraxpharm. All these affiliations have no relevance to the work covered in the manuscript.

SB & KS are employees of neuroConn/neuroCare Group. KS is a shareholder in neuroCare Group.

UK, CN, CP, DK, MS, SES report no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.08.005.

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29 June 2021
Available online 13 August 2021