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Treatment of major depression with a two-step tDCS protocol add-on to SSRI: Results from a naturalistic study

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To the Editor:

Transcranial direct current stimulation (tDCS) has been introduced as a potential treatment for major depressive disorder [1,2]. Recent studies suggest that anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) has a dosage-dependent effect [3] and leads to larger clinical improvement when combined with an antidepressant medication, such as selective serotonin reuptake inhibitors (SSRIs) [4] as they enhance and prolong tDCS-induced cortical neuroplasticity [5,6]. Further neuroplasticity changes might be facilitated through metaplastic mechanisms when applying a second tDCS session during the aftereffects of the first stimulation [7].

The aim of this naturalistic study, acknowledged by the institutional review board and registered with the German Clinical Trials Register (DRKS00008009), was to assess a novel two-step treatment protocol, incorporating recent findings on dosage-efficacy-relationship of tDCS [2] and safety of repeated twice-daily tDCS sessions [8].

Twenty-four patients were recruited after written and oral informed consent.

In the first part (Phase 1), patients received tDCS twice a day within a three-hour interval in the morning, i.e. twenty stimulations in two weeks. In the optional second part (Phase 2), patients received a single stimulation per day in the morning, i.e. 10 stimulations over two weeks (Supplementary Figure 1).

All patients received a treatment with citalopram (CIT, 20–40 mg) or escitalopram (ESC, 10–20 mg). Existing CIT/ESC medication was increased or continued, drug-free patients started CIT/ESC as an add-on to stimulation at the same time (±2 days) with increase to final dosage within one week. Other existing antidepressants were switched to CIT/ESC within 3–4 days in an overlap manner at the beginning of the stimulation series. Co-medications (second-generation antipsychotics, hypnotics, benzodiazepines up to 1.5 mg lorazepam equivalent) were allowed and remained unchanged.

Antidepressant medication at end of Phase 1 was continued in Phase 2 and was grouped into two dosage levels according to medium dosage (CIT < 40 mg or ESC < 20 mg) and high dosage (CIT = 40 mg or ESC = 20 mg).

Stimulations were performed with a CE-certified Eldith-DC-stimulator (NeuroCareGroup, Munich, Germany): anode over left DLPFC (F3, according to international 10–20 EEG system); cathode over F4; electrode size 35 cm^2; current strength 2 mA; duration 30 min + 15 seconds fade-in/fade-out.

At baseline, Edinburgh Handedness Inventory (EHT), Antidepressant Treatment History Form (ATHF; treatment resistance defined as failure of ≥2 adequate trials), Hamilton Depression Rating Scale-21 (HAMD) as primary outcome and Beck Depression Inventory (BDI) as secondary outcome were assessed. Primary endpoint was the number of participants achieving response (≥50% reduction in HAMD), and remission (≤7 in HAMD) at end of Phase 1 and 2. Secondary outcomes were cognitive improvement (Trail Making Test parts A and B, TMT-A/B), general symptom assessment (WHO Quality of Life Bref, WHOQOL), Clinical Global Impression (CGI), and Global Assessment of Functioning (GAF). Side effects were measured by the Comfort Rating Questionnaire (CRQ) [9]. Clinical ratings were repeated at end of Phase 1 and Phase 2. Final ratings of Phase 1 corresponded to baseline ratings of Phase 2. There was no clinical follow-up at a later time point.

For statistical calculation, linear mixed model analyses (LMM) were used. Predictors for clinical outcomes were: duration of illness [less than two years, two to ten years, more than eleven years]; age of onset; treatment resistance (ATHF) [zero to nine vs. ten or more; data-driven binarization]; pre-treatment change of medication; dosage [medium, high]. Results were corrected for multiple comparisons.

Twenty-four patients completed Phase 1 of the study, 16 patients quit after Phase 1, and 8 patients completed Phase 2. Demographic and clinical characteristics are reported in Supplementary Table 1. All patients had the diagnosis of a (recurrent) depressive disorder; one patient had a chronic depression. Number of depressive episodes varied between first episode (11 patients), and 15 episodes (1 patient). Eight patients changed medication at enrolment, 16 patients already were on CIT/ESC or had no medication.

In Phase 1, significant time effects for all clinical outcomes and a reduction of post-treatment scores in HAMD by 34.99% (mean scores before treatment: 23.83 ± 6.34; after Phase 1: 15.65 ± 7.32) were found (Fig. 1A). Six (25%) patients (18.75%) achieved response in HAMD rating; four (16%) patients achieved remission.

Significant time effects were observed for BDI with a reduction by 31.89% (mean scores before treatment: 26.62 ± 9.97; after Phase 1: 18.25 ± 10.62) (Fig. 1B). For BDI, seven patients (29%) achieved

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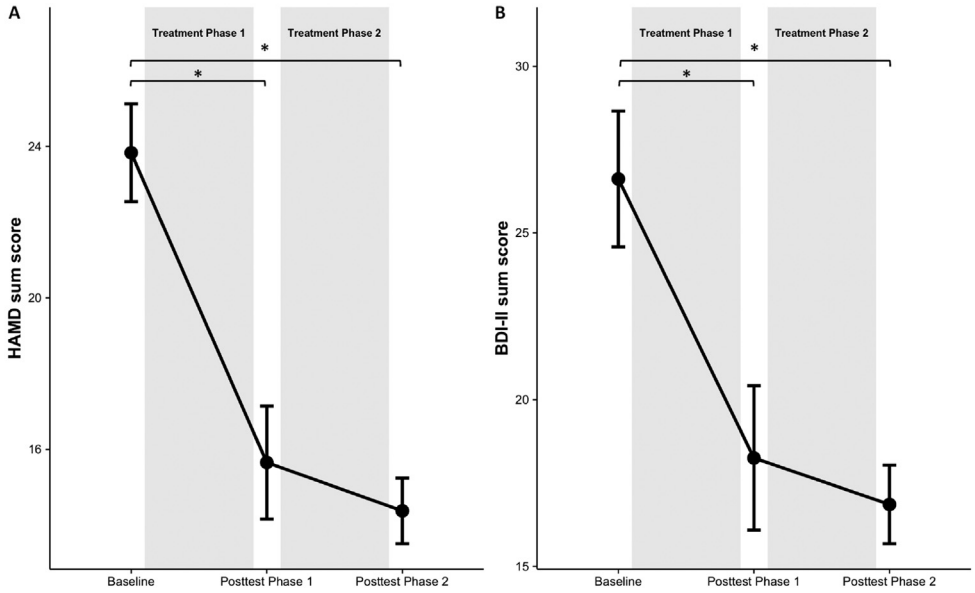

Fig. 1. HAMD (A) and BDI (B) changes.

response criteria and five (20%) achieved remission. CGI improved by 16.22% and GAF showed higher post-treatment scores by 22.78%. WHOQOL dimensions showed significant time effects, except for social relationships and environment. TMT-A/B results did not change. Treatment resistance and change rate of the HAMD showed a significant interaction effect ($\beta = 7.96$, $t_{(16.00)} = 2.40$, $p = .029$), i.e. patients with lower treatment resistance showed larger improvement. Furthermore, patients already treated with CIT/ESC prior to tDCS series had a larger HAMD reduction than those who changed medication at enrolment, and patients receiving high doses of CIT/ESC had significantly higher improvement in CGI and in the WHOQOL environment dimension than patients with medium doses of CIT/ESC. Model parameters are summarized in Supplementary Table 2.

In Phase 2, HAMD scores showed a significant improvement (mean scores before treatment: 23.83 ± 6.34; after Phase 2: 14.38 ± 4.24). Only one patient achieved remission during Phase 2, none achieved response within Phase 2. Overall, patients undergoing Phases 1 and 2 showed two responses and one remission in terms of HAMD. There was a significant reduction in BDI sum score over time (mean scores before treatment: 26.62 ± 9.97; after Phase 2: 16.86 ± 5.76). tDCS was well tolerated with only mild side effects such as tingling and itching.

In summary, this novel study protocol was designed as an open-label study to investigate the feasibility and tolerability of an enhanced stimulation protocol. Results showed a significant improvement of HAMD and BDI in 24 patients undergoing Phase 1 and a significant improvement in 8 patients undergoing Phase 2. There was no relevant change in cognitive measures, a finding that is in line with a recent meta-analysis [10].

Small sample size, open label design, and lack of follow up assessments are limitations of this study.

It can be discussed that enhanced protocols may lead to a quicker symptom relief but, as not exceeding standard protocols in total applied charge, do not show a better outcome. It is likely that short enhanced protocols also need a sufficient maintenance phase with repeated stimulations in the following weeks to evoke sustained changes.

Conflicts of interest

U.P. received paid speakership from NeuroCareGroup and has a private practice with NeuroCareGroup, Munich, Germany. F.P. received research support from NeuroConn GmbH, Ilmenau, Germany, and Brainsway Inc., Jerusalem, Israel, as well as speaker's honorarium from Mag&More GmbH, Munich, Germany, and NeuroCareGroup. A.H. received paid speakerships from Desitin, Janssen-Cilag, Otsuka and Lundbeck. He was member of Roche, Otsuka, Lundbeck and Janssen-Cilag advisory boards. A.R.B. is recipient of a CAPES/Alexander von Humboldt fellowship award for experienced researchers and a consultant of the NeurocareGroup GmbH, Munich, Germany.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.10.003.

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