Transcranial direct current stimulation for treatment of depression during inpatient psychotherapy: Results from a psychosomatic hospital.

**Abstract:** Recent studies focusing on the combination of psychotherapy and transcranial direct current stimulation (tDCS) showed debatable results for an additional effect of tDCS in depression. Here we provide data from a psychosomatic hospital where patients were treated for major depressive disorder in a multimodal inpatient psychotherapy setting, including an intensive group and individual psychotherapy and psychopharmacologic treatment, and received tDCS as an individual treatment attempt. Seven patients underwent 11-19 tDCS treatments and 3-5 psychotherapy sessions per week during their inpatient stay. One patient achieved response and remission in the Beck Depression Inventory, another patient achieved response criteria. The other patients had moderate to no improvement. Overall, tDCS was well tolerated but had very limited effect in patients undergoing a multimodal psychosomatic treatment and psychopharmacologic regimen. This case series is limited by the lack of a control group but is in line with previous results questioning the additional effect of tDCS to psychotherapeutic or psychopharmacologic treatment. Furthermore, the combination of multimodal therapies hampers distinction between unspecific effects of care and tDCS.

**Keywords:** non-invasive brain stimulation; depression; tDCS; psychotherapy.

1. Introduction

Major depressive disorder (MDD) is a psychiatric disorder with high global incidence and prevalence [1] which have risen even further during the COVID-19 pandemic. This increase highlights an urgent need for effective and accessible treatment strategies due to the significant health and societal impact of this psychiatric condition. The current first-line treatments for MDD are psychopharmacotherapy and psychotherapy, used alone or in combination, depending on depression severity [2]. About one-third of MDD patients exhibit a treatment-resistant course, despite stepwise therapy involving medication and cognitive-behavioral therapy (CBT) [3]. The search for augmenting, additional therapy methods is therefore necessary. Here, new pharmacological treatment strategies including combined treatment with adjuvant substances, e.g., food supplements or experimental drugs including psychedelics, might bring benefits [4].

Since a couple of years, new non-invasive brain stimulation methods have been investigated as potential treatment options in neuropsychiatric disorders. One of them, transcranial direct current stimulation (tDCS), uses weak direct current applied to the scalp over a brain target region to modulate the respective brain areas and interconnected remote areas. This neuromodulation technique changes neuronal excitation or inhibition following the hypothesis of a dysfunctional activation of the targeted area [5]. In a simplified model, anodal stimulation enhances activation in hypoactive areas whereas cathodal stimulation decreases activation in hyperactive areas. Besides area of stimulation and electrode size, several other technical parameters like duration of stimulation, stimulation intensity, number of stimulations, interval between stimulation, brain state (activation/deactivation), and concomitant medication modulate tDCS effects [6].

The investigation of tDCS for major depressive disorders followed the seminal publication of Nitsche & Paulus [5] with open-label studies and small randomized controlled trials (RCT) in the first years and large RCT over the last decade. However, from the beginning, tDCS was used as an add-on treatment to existing psychopharmacologic regimen [7] and the combination of tDCS to serotonergic medication was suggested to improve symptoms of major depression and cognitive function.

This is underpinned by the data from RCTs for the treatment of MDD, combining tDCS with selective serotonin reuptake inhibitors. Thus, two large RCTs were able to show clear superiority of active tDCS over sham [8], respectively superiority of active tDCS over sham but no non-inferiority of active tDCS compared to escitalopram [9]. However, another recent multicentre RCTs showed no differences between active and sham tDCS as an add-on to psychopharmacologic regimen concerning antidepressant efficacy [10]. In terms of tDCS in combination with psychotherapy, the online combination of tDCS with group cognitive behavioral therapy (CBT) showed a significant improvement of depression symptoms over time in all groups, but there were no significant differences between the groups (tDCS+CBT vs. sham tDCS+CBT) regarding antidepressant effects [11]. Here, we propose a combined treatment approach to include tDCS as an additional treatment in a multimodal psychosomatic therapy setting.

In various studies, different levels of stringency were applied to maintaining the stability of additional therapies, such as exercise therapy, occupational therapy, and psychotherapy, for varying periods before the start of the study and during the study. In some cases, these additional therapies were simply reported, while in other studies, patients receiving additional therapies besides the primary treatments under investigation, such as tDCS and a specific medication, were excluded. Generally, many studies included both inpatients and outpatients. In clinical practice, it is common for patients with MDD who are connected to a clinic as either inpatients or outpatients to receive more than one form of therapy. This is increasingly the case in psychosomatic treatment settings where therapeutic regimen is multimodal [12]. Although the so-called *milieu* acts as the key factor of inpatient psychosomatic treatment (e.g., social contacts), it is at the same time a relevant confounding factor in any therapeutic process of these patients. Furthermore, contact to healthcare professionals reduces the perceived social exclusion in depressed patients. This is also a confounding factor in standard clinical research setting with a plenty of scheduled study visits. Overall, due to methodological considerations (e.g., exclusion of too many confounding factors in standard clinical research setting), there is a research gap concerning the efficacy of tDCS as an add-on therapy, and even more in a multimodal psychosomatic treatment regimen, where the confounding factors mentioned above are part of the treatment. Thus, regarding the conflicting results of add-on tDCS in a standard clinical research setting, there is further need to explore efficacy and implementation of tDCS in an intensive therapeutic setting. This lack of sufficient evidence is underlined in a recent review paper suggesting some positive effects for the combination of tDCS with psychotherapy and ongoing/concomitant medication, i.e., sertraline, but effect sizes are low and need replication [13].

Here we provide data from a cases series on using tDCS as an add-on to multimodal psychotherapeutic inpatient treatment in a psychosomatic hospital.

2. Materials and Methods

2.1. Treatment attempts and settings

Between 2019 and 2022, inpatients of the Psychosomatic Hospital Medical Park Chiemseeblick, Bernau-Felden, Germany, were offered an optional fee-paying treatment with tDCS for depressive disorders and obsessive-compulsive disorder. Recruitment was done passively by information via website and in the clinic leaflet. Interested persons were screened to fit in one of the diagnoses mentioned above. Patients with other diagnoses and clinically diagnosed personality disorders were excluded. Further exclusion criteria were cranial skin diseases, metal implants in the head, intracranial hypertension, recent stroke, epilepsy, intake of antiepileptic drugs, severe heart, or pulmonary diseases. Overall, 9 patients with (recurrent) major depressive disorder received between 8 and 19 tDCS treatments during their inpatient stay, 2 patients had to be excluded from analysis due to missing data. One further patient was treated for obsessive-compulsive disorder, results are reported elsewhere [14]. Finally, data of 7 patients were used for analysis. They received 11 to 19 stimulations depending on their personal preference, willingness to pay additional fees (~80 € per stimulation), and their date of discharge from hospital. Stimulation series usually began in week 2 or 3 of inpatient stay and was discontinued at patients’ discretion or discharge.

As tDCS was conducted as individual treatment attempt, open-label, and without prefixed study protocol, this case series was not undergoing approval of an ethics committee. Treatment regimen was following the German guidelines on the treatment of unipolar depression [15]. Written and oral informed consent was obtained from all patients to be treated with a new technique which does not have a recommendation of the German guidelines on the treatment of unipolar depression [15].

2.2. Stimulation procedure

Parameters of stimulation were adopted from large studies over the last two decades and are generally sound [7]. Stimulation was delivered by using a CE-certified, pre-programmed DC stimulator (SOOMA Medical, Helsinki, Finland), delivering 2 mA direct current for 30 min. Disposable saline-soaked round sponge electrodes were mounted in a head cap which is placed with its front rim directly over both eyebrows and covers inion with its back rim, following the manufacturer’s guidance. This prefixed montage ensures defined positions for anodal stimulation of the left DLPFC and cathodal stimulation contralaterally. Stimulations were performed once per day, usually on consecutive weekdays within three or four weeks, but without restriction for daytime.

2.3. Inpatient psychotherapy

Inpatients with psychosomatic disorders, including ICD-10 diagnostic groups F3, F4, F5, and F6, with a vast majority of depressive disorders, usually are treated over a six-to-eight-week period with specific group psychotherapy (2-3 h per week), individual psychotherapy up to 3 hours per week (cognitive behavioral therapy, with elements of interpersonal therapy, and acceptance and commitment therapy). Additionally, different trainings of mindfulness, autogenous training, biofeedback training, forest therapy, sailing therapy, QiGong, Feldenkrais, Yoga, creative therapies (dance, music, art), occupational therapy, and physical exercise in various forms, i.e., hydrotherapy, Nordic walking, climbing, gym workouts, Pilates, are performed. Individual psychotropic medication is implemented following patients’ needs and preferences, however the focus of psychosomatic inpatient stay is individual and group psychotherapy and additional body therapies.

2.4. Measurements

All inpatients were assessed with the Beck Depression Inventory (BDI) [16] at admittance and discharge. Additionally, patients undergoing tDCS treatment were assessed with BDI before first and after last stimulation. The Epworth Sleepiness Scale (ESS) [17] was used to screen for sleep disturbances and the Comfort Rating Scale (CRQ) [18] was used to monitor side effects of stimulation.

2.5. Statistics

Due to the small number of individuals in this case series, no further statistical analyses except for descriptive statistics were performed.

3. Results

This case series reports on seven patients undergoing tDCS as individual treatment attempt to alleviate major depressive disorder during inpatient psychotherapy in a psychosomatic hospital.

3.1. Demographic data

Seven patients (4 female, 3 male, mean age 46.1 ± 14.2 y, age range 28-68 y) with moderate to severe depressive disorder underwent 11 to 19 tDCS treatments within their psychosomatic inpatient stay. Mean duration of hospitalization was 55.7 ± 9.4 days with a range from 42 to 70 days. No patient quitted tDCS treatment for side or adverse effects. The number of stimulation sessions varied due to patients' preferences and discharge dates. Antidepressant and/or concomitant medication was kept stable or changed to the actual medication reported in Table 1. Most patients were on combined antidepressant treatment, except for one patient who chose to forgo medication. Demographic data of patients is reported in Table 1.

3.2. BDI results

Mean BDI was 29.2 ± 8.3 at admittance of patients (2 values were missing and were imputed from the following timepoint) and 21.6 ± 10.8 at discharge (4 values were missing and were imputed from the previous timepoint; last observation carried forward). Between admittance and beginning of tDCS, 3 patients showed slight improvement of BDI (3-7 points), four patients showed no change or light deterioration (1-6 points). For the timepoints from admittance to after tDCS, one patient achieved response, and one patient showed response and remission. Regarding only changes during tDCS treatment, one patient achieved response and remission. See Figure 1 for individual changes of BDI values in each patient. Detailed clinical results are reported in Table 2 and Figure 1.

response

**Figure 1.** BDI scores for each patient. x-axis: Time course of treatment; y-axis: BDI = Beck Depression Inventory (0-9 points: no depression/remitted depression; 10-18 points: mild depression; 19-29 points: moderate depression; 30-63 points: severe depression [19])

**Table 1.** Demographic characteristics of patients.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Female  39y | Female  32y | Male 50ya | Female  58y | Male 28y | Male  48ya | Female  68y |
| ICD diagnosis | F33.1 | F33.2 | F33.1 | F32.2 | F32.1 | F33.1 | F33.2 |
| Age of onset | 25 | 30 | 30 | 58 | 27 | 30 | 66 |
| Number of episodesb | 3 | 2 | 4 | 1 | 1 | 3 | 2 |
| Number of inpatient treatmentsb | 2 | 3 | 4 | 2 | 1 | 3 | 2 |
| Duration of actual hospitalization (d) | 50 | 70 | 57 | 50 | 42 | 57 | 64 |
| Current medication | citalopram 20 mg;  mirtazapine 30 mg;  pipamperone 10 mg | venlafaxine 300 mg;  quetiapine 50 mg | St John’s wort 900 mg | bupropion 300 mg; mirtazapine 45 mg; milnacipran 50 mg;  trazodone 100 mg; quetiapine 250 mg | none | bupropion 300 mg | escitalopram 5mg;  mirtazapine 45 mg;  quetiapine 50 mg |

a same patient treated twice (2 years interval).  b including current episode/inpatient treatment.

3.3. ESS results

There was a small decrease in sleep disturbances reported by patients, with mean ESS scores of 8.4 ± 7.3 points before tDCS (range 1-20 points) to 6.7 ± 6.5 after tDCS (range 0-16 points). Overall, sleep disturbances were on a low level except for two patients reporting severe sleep disturbances before tDCS (16 respectively 20 points) and after tDCS (15 respectively 16 points). Detailed ESS scores are reported in Table 2.

3.4. CRQ results

Side effect ratings during and after tDCS were on a low level as shown by scores between 1.25 and 3.1 (mean score of eight questions on 1–10-point Likert scales) during tDCS and between 1.0 and 2.5 after tDCS. General discomfort of stimulation was rated between 1 and 2 on a 1–10-point Likert scale. Phosphenes or sleep disturbances following stimulation were not reported by any patient. Overall, tDCS was well tolerated and did not result in discontinuation. Detailed CRQ scores are reported in Table 2.

**Table 2.** Clinical characteristics of patients.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Female 39y | Female 32y | Male 50ya | Female  58y | Male 28y | Male  48ya | Female  68y |
| Number of stimulations | 15 | 14 | 16 | 15 | 15 | 11 | 19 |
| ***BDI*** |  |  |  |  |  |  |  |
| -admittance | 22 | 17b | 33 | 42 | 26b | 31 | 34 |
| -before tDCS | 23 | 17 | 27 | 39 | 26 | 37 | 27 |
| -after tDCS | 19 | 12 | 28 | 38 | 6 | 31 | 16 |
| -discharge | 19b | 12b | 27 | 38b | 6b | 29 | 20 |
| ***ESS*** |  |  |  |  |  |  |  |
| -before tDCS | 3 | 3 | 16 | 5 | 11 | 20 | 1 |
| -after tDCS | 1 | 3 | 15 | 4 | 8 | 16 | 0 |
| ***CRQ*** |  |  |  |  |  |  |  |
| -during tDCS | 1.25 | 1.4 | 2.2 | n/a | 1.7 | 3.1 | 2.9 |
| -after tDCS | 1.0 | 1.25 | 2.0 | n/a | 1.7 | 2.5 | 2.25 |
| -general discomfort | 1 | 1 | 2 | n/a | 2 | 2 | 1 |
| -phosphenes | none | none | none | n/a | none | none | none |
| -sleep disturbances | none | none | none | n/a | none | none | none |

BDI = Beck Depression Inventory; ESS = Epworth Sleepiness Scale; CRQ = Comfort Rating Questionnaire.

a same patient treated twice (2 years interval). b missing data imputed (last observation carried forward). n/a = not assessed.

4. Discussion

In this case series, seven inpatients underwent a variable number (11-19) of tDCS stimulations during inpatient stay in a psychosomatic hospital. tDCS was well tolerated and there was no drop out due to side effects. Regarding the effects of tDCS and the inpatient psychotherapeutic treatment separately, each intervention showed only a very modest effect. All patients except for one were under psychopharmacologic medication and all patients received a multimodal treatment with psychotherapy as key element. Only one patient, i.e., the patient without psychopharmacologic regimen, achieved response and remission criteria on the BDI scale during tDCS treatment. Another patient met the response criteria from admission to the end of tDCS treatment, but the effect was lost by discharge. The response criteria were not met when considering only the pre- and post-tDCS periods. The number of stimulation sessions did not have an obvious influence on magnitude of BDI changes. Furthermore, there is no evident correlation between diagnoses, medication or duration of inpatient stay and BDI changes. Here, a variety of confounding factors prevent drawing causal conclusions about the relationships between severity of illness, treatment regimen with medication and tDCS, and changes in the clinical course. We assume that the complex and multimodal treatment regimen with the focus on group and individual psychotherapy is the main confounding factor for a clear delineation. Also, the small improvement in mean ESS might be due to the general stress relief during inpatient stay.

Unfortunately, several BDI data points were missing at both admission and discharge and were imputed with the following (before tDCS) or previous (after tDCS) timepoint. This hampers validity of the effectiveness of the inpatient stay itself, but not the validity of the tDCS treatment. And here, no response in BDI could be found for the timepoint before tDCS and after tDCS except for the patient mentioned above. Interestingly, there was no obvious placebo effect of tDCS treatment although patients had to pay an extra fee which is not reimbursed from health insurances and therefore patients probably had high expectancies on the efficacy of the treatment [20]. It is likely that the multimodal treatment regimen causes a ceiling effect which hampers discriminability of different interventions.

This case series observed a modest improvement of sleep during tDCS treatment which is in line with a recent meta-analysis suggesting an improvement of sleep quality and sleep efficiency in patients undergoing tDCS treatment [21]. On the other hand, this effect might have been mediated by the stress relief during inpatient treatment over several weeks.

In psychosomatic clinics, the focus of treatment is on non-pharmacological therapies, although psychopharmacotherapy is also utilized. Patients who prefer psychosomatic therapy with predominantly non-pharmacological approaches may have a positive expectation towards the non-pharmacological approach of tDCS and therefore are supposed to benefit more compared to patients of a psychiatric clinic. However, meta-analyses reveal that inpatient psychotherapy has only a small to moderate effect on severity of depression and seems to be less efficient than outpatient psychotherapy [22, 23]. This might be due to several reasons like higher severity of illness, chronicity, and treatment resistance of inpatients, lower global functioning and more comorbidities (somatic and mental). A large German study analyzing demographic and clinical data of 19 Departments for Psychosomatic Medicine at German University Hospitals found a high level of “complex patients” with more than one (DSM-IV) axis-I-diagnosis, additional axis-II-diagnoses, and somatic comorbidity [12]. Furthermore, there is data from a large German cohort showing that inpatient psychotherapy improves major depression with large effect size but that there are stable (personality) factors like suicidality, agoraphobia, life dissatisfaction, physical disability, and pain that stay unchanged over treatment course [24]. This is probably the reason why 20-30% of patients do not experience improvement after inpatient psychotherapy in Germany [25]. Although suicidality, personality disorders, and physical disability were not clinically present in patients of our case series, we cannot rule out further harmful demographic factors and life-events.

Considering concomitant medication of patients, no patient received sertraline which was found to be associated with some beneficial effects in a recent review [13]. However, three patients received other serotonergic medication (citalopram, escitalopram, milnacipran) and one patient had venlafaxine as a serotonin-norepinephrine reuptake inhibitor. Only the patient receiving escitalopram had a relevant improvement of depression with response after tDCS series which is in line with a study comparing the effects of escitalopram versus tDCS, where each escitalopram and active tDCS were superior to sham tDCS [9]. It is likely that a combination of both resulted in an additional improvement of depressive symptoms, however the effect was lost after discontinuation of tDCS. Interestingly, only one patient showed response and remission over the whole inpatient stay and this patient was drug-free. Therefore, it must be questioned if this effect was mediated by the multimodal setting without specific additional benefit of tDCS or if this was a combined effect of tDCS and psychotherapy. Regarding the study of Aust et al. [11] where psychotherapy combined with active respectively sham tDCS improved depressive symptoms in both interventional groups, it is likely that the effect seen in our patient was mediated by the multimodal regimen with psychotherapy as key intervention.

Limitations of the case series are the small and heterogenous sample, the lack of a standardized and sham-controlled study design, the lack of a standardized medication, the vast amount of different psychotherapeutic and additional interventions, and the imputation of missing data. It is likely that the high costs of the stimulation prevented patients from participation. The number of stimulations delivered was in line with the suggested number of about 10-15 stimulations in 2-3 weeks in previous studies [7], however the observation period could have been too short as recent investigations suggested a longer observation period of at least 6 weeks as patients with (recurrent) major depression might have slower response to interventions [16, 27].

This case series is certainly not suitable for conclusive statements about tDCS as an add-on treatment to multimodal psychosomatic treatment. However, it could be shown that tDCS as an add-on treatment is well tolerated and accepted by the patients. Albeit there is some evidence from earlier studies that combination of tDCS with serotonergic medication could have an additive effect [8, 28], this was not replicated in a recent large RCT [10]. Overall, recent research showed a mixed body of evidence on tDCS in the treatment of depressive disorders which supports the notion that tDCS can only achieve moderate effects at least and/or is probably only effective as a combination treatment with another procedure, e.g., pharmacology or psychotherapy. Therefore, the establishment of tDCS as an add-on therapy in the inpatient psychotherapy setting proposed here might expand the multimodal armamentarium of psychosomatic hospitals by neuromodulation therapy but needs more evidence of its efficacy. This encompasses further research on optimal stimulation parameters, e.g., current strength and duration of stimulation, number of stimulations, interval between stimulation, and the combination with an optimal psychopharmacologic treatment, as well as the impact of stimulation on non-pharmacologic treatments as psychotherapy or additional trainings of mindfulness, autogenous training, biofeedback training, etc.

**5. Conclusion**

As tDCS had a very limited effect in recent studies where it was combined with pharmacologic or psychotherapeutic interventions, it might be rather applied in patients who are unable or unwilling to undergo established interventions. Yet, a large placebo effect might shadow any beneficial tDCS effects even when applied in monotherapy. As there is still insufficient evidence, no conclusion can be made whether tDCS should be used as a stand-alone intervention or should be combined with psychopharmacologic or non-pharmacologic interventions.

**Institutional Review Board Statement:** Approval by the Institutional Review Board was not obtained for this case series due to non-systematic and open label design as being individual treatment attempt.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the individual treatment attempt. Written informed consent has been obtained from the patients to publish this paper.

**Data Availability Statement:** All data is reported in the text.

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