Trial Protocol

Parts of the trial protocol have been published previously (Bajbouj et al., 2018). This protocol is the original and final version. It includes the following sections:

1. Background information
2. Objective/Purpose
3. Study design including list of investigators
4. Selection and Exclusion of Patients
5. Treatment of Patients
6. Assessment of Efficacy
7. Assessment of Safety
8. References

1. Background information

Major depressive disorder (MDD) is a debilitating disease affecting approximately ten percent of the population globally (Malhi & Mann, 2018). Clinical management primarily comprises psychotherapy, pharmacological treatment, and neuromodulatory interventions (Otte et al., 2016).

Cognitive behavioral therapy (CBT) is effective in the treatment of MDD with mean effect sizes of .75 and a sustainable improvement of symptoms (Cuijpers et al., 2020). Thus, it is recommended as first-line treatment in all national and international guidelines. However, about 20 to 30 percent of MDD patients do not sufficiently respond to standard treatment consisting of CBT, pharmacotherapy, or the combination of both (Rush et al., 2006). Therefore, there is an urgent need to develop more effective treatment strategies (Cuijpers et al., 2021).

In recent years, the concept of treatment augmentation (as previously known from pharmacological approaches) has been transferred to behavioral interventions. Here, the basic idea is to enhance their neuroplastic and clinical effects by pharmacological interventions such as psilocybin (Carhart-Harris et al., 2016) or non-invasive brain stimulation (NIBS) techniques (Bajbouj and Padberg, 2014; Sathappan et al., 2019). NIBS comprises transcranial magnetic stimulation (TMS) which has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDD, as well as transcranial direct current stimulation (tDCS). In tDCS, a weak direct current is applied through electrodes placed on the scalp with the aim to modify cortical excitability (Nitsche et al., 2009). As compared to TMS, tDCS has the advantage of flexible usability in various settings, a better safety profile, and lower costs. We previously conducted trials in which we demonstrated that tDCS with electrodes placed over the dorsolateral prefrontal cortex (DLPFC) is capable of enhancing cognitive control, a cognitive mechanism essential for key psychotherapeutic techniques targeting the regulation of negative emotions in both healthy participants (Feeser et al., 2014) and MDD patients (Wolkenstein and

Plewnia, 2013). In concordance, small pilot trials indicate an augmenting effect of tDCS for cognitive-behavioral therapies in patients with MDD (Segrave et al., 2014; Welch et al., 2019).

2. Objective/Purpose

Based on findings mentioned above, we conducted a randomized double-blind placebo-controlled clinical trial called PsychotherapyPlus comparing the efficacy of a tDCS-augmented CBT with CBT plus sham-tDCS and CBT alone in MDD patients. It was hypothesized that tDCS-augmented CBT would be superior to CBT plus sham-tDCS and to CBT alone.

3. Study design

PsychotherapyPlus is a multicenter trial with six German university hospitals involved: Charité - Universitätsmedizin Berlin (leading site, PI: Malek Bajbouj) and the universities of Munich (PI: Frank Padberg), Tuebingen (PI: Andreas Fallgatter), Leipzig (PI: Maria Strauss), Freiburg (PI: Claus Normann) and Mannheim (PI: Andreas Deuschle). Patients were randomized to one of the following three treatment arms: group 1 receiving 12 sessions CBT with tDCS, group 2 receiving 12 sessions CBT with sham-tDCS, and group 0 receiving 12 sessions CBT alone without any stimulation procedure. Involved psychotherapists, raters and patients were blinded for tDCS treatment conditions until the end of the trial. The course of *PsychotherapyPlus* is visualized in **Figure A**. In the *screening phase*, inclusion and exclusion criteria were evaluated. After inclusion, patients attended a baseline visit and a pre-intervention functional magnetic resonance imaging (fMRI), where resting state fMRI and PFC functioning were assessed (reported elsewhere).

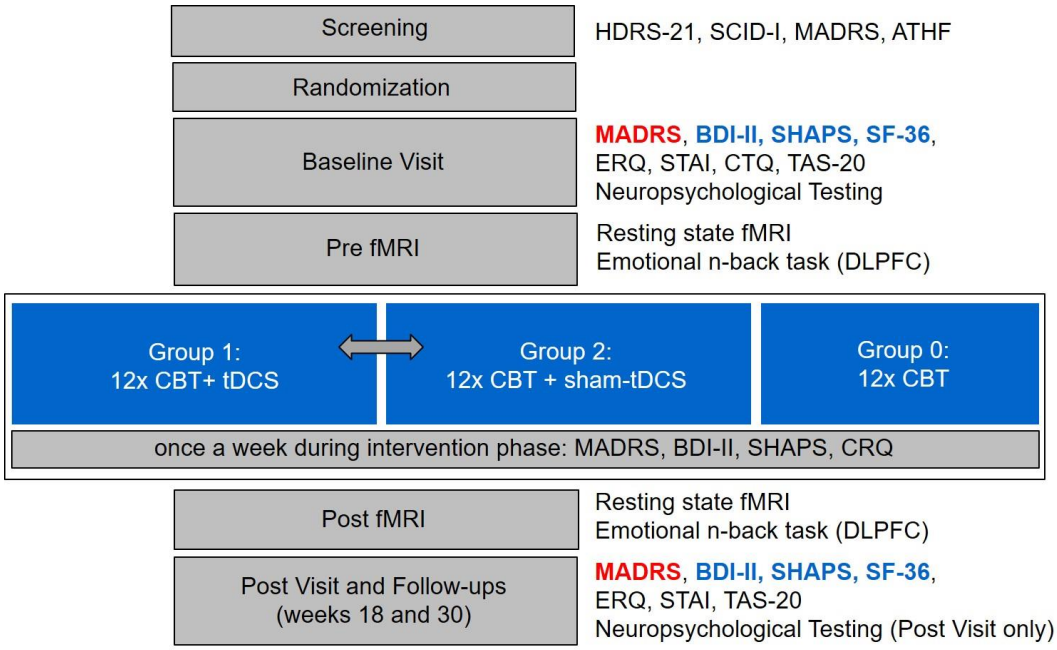

Figure A: Trial course and measured variables. Primary outcome in red, secondary outcomes in blue.

The study was conducted in accordance with the latest version of the Declaration of Helsinki and has been approved by the institutional review board of Charité – Universitätsmedizin Berlin. Local ethics committees at Munich, Tuebingen. Leipzig, Mannheim and Freiburg approved the study protocol. Written informed consent was obtained from all participants prior to inclusion.

The trial initially started with four sites (Berlin, Munich, Tübingen, Freiburg) in June 2016, two additional sites (Leipzig, Mannheim) joined the trial in January 2018 to achieve recruitment goals. Sites were responsible for patient recruiting, screening, assessing the required data and conducting the study intervention. The coordinating center (Berlin) provided tDCS stimulators and equipment, therapy and study manuals as well as tablets with the EmoCogMeter (ECM) for neuropsychological assessment (see Assessments). All psychotherapists conducting the CBT sessions had an expertise in clinical psychology and were trained and certified in CBT. In addition, a full-day study specific CBT training seminar was

provided. tDCS application was standardized across study sites by regulations of the *German Center for Brain Stimulation* (GCBS) research consortium (coordinators: FP and MB) funded by the German Federal Ministry of Education and Research. An instruction video demonstrating all steps of tDCS application and electrode positioning in detail was distributed to the study personnel involved in *PsychotherapyPlus*.

4. Selection and Exclusion of Patients

Outpatients with an age range of 20 to 65 years and a primary diagnosis of major depressive disorder in accordance with DSM-IV criteria were recruited for the study. Patients with a single or recurrent episode were included. Duration of the current depressive episode was less than five years (the definition of an episode is demarcated by a period of ≥ two months in which the patient did not meet full criteria of a major depressive episode). Eligibility criteria included a total score of ≥ 15 in the Hamilton Depression Rating Scale (HDRS-21; Hamilton, 1960) with an item 1 rating of ≥ 2 at the screening visit. Comorbid disorders were assessed by the Structured Clinical Interview for DSM-IV, axis-I and -II. Patients were either medication free or treated with a stable antidepressant medication of an SSRI and/or mirtazapine with "stable" being defined as "no change in antidepressant medication for at least four weeks prior to inclusion". Antidepressants except SSRIs/ Mirtazapine as well as mood stabilizers and antipsychotics were not allowed during the trial. After having completed the intervention and post assessments, patients were allowed to change their medication throughout the follow-up phase. All changes were documented.

Further inclusion criteria comprised:

- no CBT in the current episode or in the past two years (if duration of current episode was > two years)
- no ECT in the current episode

- no more than four sufficient antidepressant treatment trials, each with an ATHF score of ≤ 3, during the current episode
- MRI suitability
- positive tDCS safety screening

Exclusion criteria were:

- substance abuse or dependence in the past six months
- psychotic disorders (lifetime) including schizoaffective disorders or depressive episodes with psychotic symptoms (lifetime)
- bipolar disorders (type I and II)
- post-traumatic stress disorder, currently or within the past 12 months
- current generalized anxiety disorder, obsessive-compulsive disorder, panic disorder or social phobia
- personality disorders
- neurological disorders, such as stroke within the past two years, epileptic seizures (lifetime), epilepsy, dementia, Morbus Parkinson, Chorea Huntington, Multiple Sclerosis, as well as any other neurological disorder leading to increased intracranial pressure, brain lesions or an increased risk for epileptic seizures
- current risk of suicide, based on the personal assessment of the investigator or a score of 3 or more on HDRS-21 item 3 and/or a score of 5 or more on MADRS item 10.

5. Treatment of Patients

Group CBT included guideline-based, well established and empirically validated CBT-oriented strategies (Beck et al., 1979; Hautzinger 2013) enhanced by two selected tools of the Cognitive Behavioral Analysis System of Psychotherapy (CBASP; McCoullough 2003) to increase efficacy of the intervention in both episodic and chronic depression. It was provided

according to a guideline-based, established and validated manual with a total of 12 sessions within six weeks, each with a duration of 100 minutes. Groups were closed and consisted of at least four to a maximum of six patients as well as two psychotherapists. A specific manual was developed for *PsychotherapyPlus* (accessible online: http://dx.doi.org/10.17169/refubium-33631). Previous studies have shown that pre-group preparation is an essential factor for group treatment efficacy leading to a faster development of group cohesion, increased attendance, reduced anxiety and increased faith in group therapy as an effective treatment (Burlingame et al., 2006; Yalom & Leszcz, 2005). Thus, patients attended two individual pre-group sessions with one of the group therapists. In these two sessions (duration of 50 minutes each), patients were prepared for the following group treatment sessions. Patients' compliance with the intervention was strengthened by discussing individual concerns and expectations regarding group therapy, providing detailed information about the treatment program and achieving consensus on individual treatment goals. In the second pre-group session, an individual vulnerability-stress model of depression was developed in collaboration with the patient. Furthermore, the situational analysis as one core method of the treatment group was introduced (CBASP tool #1; McCullough, 2003; Brakemeier et al., 2015) and patients were encouraged to start recalling and collecting difficult social situations in their daily life that can later be analyzed in the group sessions. The intervention phase then started with two introductory group CBT sessions (#1 and 2), followed by eight main sessions including situational analyses with role plays (#3 to 10) and two closing sessions (#11 and 12).

In the two introductory group CBT sessions, patients got to know each other and the therapists assisted in the development of a set of behavioral rules for the group sessions (e.g. to respect others' opinions, the right to remain silent, discretion). Furthermore, patients were encouraged to present their individual concerns and expectations regarding the group treatment. Due to the known link between depression and behavioral inactivity, a daily activity log with mood

monitoring was established for regular use between sessions. At the beginning of each following session, patients were encouraged to report on their use of the activity log and whether they experienced difficult situations that can be used for a situational analysis in the group. Finally, Kiesler's circumplex model of interpersonal behavior (CBASP tool #2; Kiesler, 1983) and the Impact Message Inventory (IMI; Kiesler & Schmit, 1993; see Assessments) were introduced. After session #2, the IMI filled out was filled out by a relative or close friend, the same procedure was repeated after session #11.

CBT main sessions (#3 to 10) started with a short introductory round and the selection of one situation reported by a patient for the following situational analysis. This method focused on the analysis of problematic interpersonal behavior, where the patient was not able to achieve his or her goal(s) due to automatic negative thoughts, dysfunctional concerns or expectations mostly related to depressive symptoms, such as "If I refuse to do XY, the other person will reject me" or "I do not have the right to express my anger about XY". The aim of the situational analysis was to connect patients' behavior and thoughts to consequences and help the patients modify their behavior and thoughts accordingly to their goals and needs. In the elicitation phase, the social situation in which the patient was not able to achieve his or her goal was analyzed in a classical behavioral analytic way (a non-judgemental, objective description of the situation, accompanying thoughts/ individual interpretations, experienced emotions, bodily perceptions, presented body language, actual and desired outcome of the situation). In the following remediation phase, the goal was to understand why actual and desired outcome of the situation did not match. Therefore, inaccurate and irrelevant thoughts/interpretations were revised and inappropriate behavior was modified. At the end of the remediation phase, patients tested their newly learned, more appropriate thoughts and behavior in a role play in support of other group members. The situational analysis closed with a summary (i.e. the formulation of a "take-home message") to promote generalization and transfer of learning. Between the main

sessions, patients were encouraged to write down at least two situational analyses per week on their own at home in order to internalize the analysis procedure and at the same time prepare for the next group session. Written situational analyses were rated by the investigator to record patients' progress using the Patient Performance Rating Form (PPRF; McCullough et al., 2010), which was specifically designed to assess patients' skills in conducting situational analysis of their own.

Two closing sessions (#11 and 12) focused on relapse prevention, a summing up of patients' individual learning content and behavioral changes, a recapitulation of individual concerns and expectations regarding the therapy group combined with a critical evaluation of these, as well as a group farewell designed according to patients' needs. See **Figure B** for a summary.

Figure B: Short summary of CBT sessions.

Patients were allowed to miss a maximum of two CBT sessions during the intervention phase, missing out on more than two sessions lead to exclusion of the patient. All sessions were videotaped for supervision purposes. Supervision was mandatory for all psychotherapists conducting the CBT intervention in *PsychotherapyPlus* and took place according to a fixed schedule after sessions #1, 4, 7 and 11 by a trained and certified psychotherapist (ELB). In

addition, psychotherapists filled out an adherence questionnaire after each CBT session. The questionnaire was designed to document the content of each session (i.e. which patient did a situational analysis on which topic, whether there were critical situations and if so, which strategies have been applied to resolve them) and to assess adherence to the therapy manual by self-report (i.e. did the session include an introductory round and a behavioral activation exercise? Did the session include a situational analysis? Did the session include a final round with take-home messages? Did the therapists meet the time frame?). Adherence was checked during supervision.

Transcranial direct current stimulation (tDCS) was applied during CBT sessions starting for all patients simultaneously after the introduction and warming-up round (approximately 20 min). This corresponded to the moment when the main psychotherapeutic intervention started (see **Figure C**).

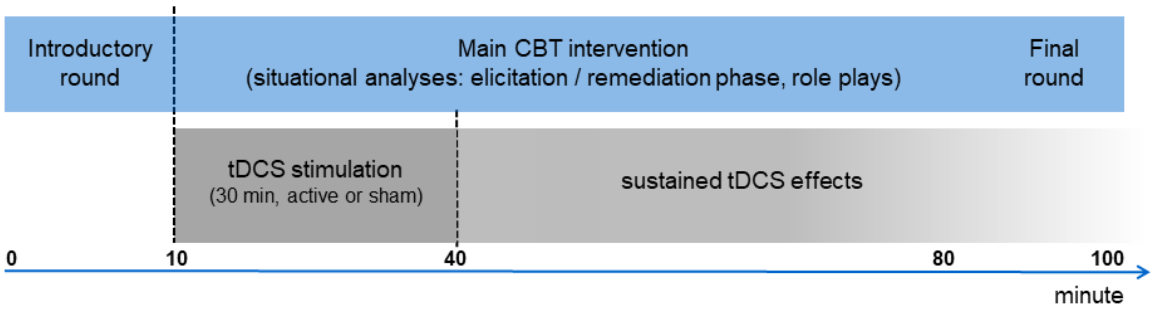

Figure C: Synchronization of tDCS and CBT within one session.

tDCS was implemented according to the DepressionDC trial within the GCBS research consortium (Padberg et al., 2017). In brief, montage was bifrontal with the anode over F3 (left dorsolateral prefrontal cortex, DLPFC) and the cathode over F4 (right DLPFC) according to the international 10-20 EEG system. To ensure correct positioning of the electrodes, positioning caps were applied (EASYCAP GmbH, Germany). Caps were available in different

sizes (according to the head circumference) to allow optimal fitting for each patient. Then, Cz (10/20 EEG system) was determined and the cap was placed on the head according to Cz. Predefined spots on the cap allowed marking the correct reference spots for F3 and F4 electrode positioning. Rubber electrodes had a size of 35 cm^2 and were placed in saline-soaked surface sponges with a standardized amount of saline per sponge (15-20 ml). Active or sham stimulation was delivered by tDCS devices according to a previously randomized stimulation ID. The list of stimulation IDs was pre-programmed by the manufacturer (neuroConn GmbH, Ilmenau, Germany). The active tDCS group received 2 mA direct current with a density of 0.0571 mA/cm after a ramp-in-phase of 30 s. The sham group was also exposed to a 30 s ramp-in-phase, however, the direct current stopped right afterwards. After each tDCS session, patients completed the Comfort Rating Questionnaire (CRQ, see section on assessments) to assess potential adverse effects.

6. Assessment of Efficacy

The primary outcome was the change in MADRS scores from baseline to post-intervention as well as an 18- and 30-weeks-follow-up. Secondary endpoints included clinical responses to treatment defined as a ≥ 50% reduction of MADRS scores and remission rates defined as MADRS scores ≤ 10. Further secondary endpoints were changes from baseline to post-intervention regarding self-rated depression severity (BDI-II), anhedonia (SHAPS-D), and health related quality of life (SF-36).

The following measures were assessed during the course of the trial:

HDRS-21. Patients were screened with the Hamilton Depression Rating Scale, 21-item version (Hamilton, 1960). The HDRS was published for the purpose of ‘‘quantifying the results of an interview” on a variety of depressive symptoms. Since it has not been designed for use in

treatment studies, it was only applied during the screening visit measuring one of the inclusion criteria (HDRS-21 total score of ≥15).

MADRS. The Montgomery–Åsberg Depression Rating Scale (Montgomery and Asberg, 1979) is a clinical interview to assess depression severity on 10 items: (1) apparent sadness, (2) reported sadness, (3) inner tension, (4) reduced sleep, (5) reduced appetite, (6) con- centration difficulties, (7) lassitude, (8) inability to feel, (9) pessimistic thoughts, and (10) suicidal thoughts. Each symptom is rated on a scale from 0 to 6. The overall score ranges from 0 to 60 with higher scores indicating higher depression severity. According to the authors, the scale is particularly sensitive to treatment effects. Therefore, it was the primary endpoint of the study and applied at multiple time points during the course of the study.

BDI-II. The Beck Depression Inventory, second version (Beck, Steer & Brown, 1996), is an improved revision of the original BDI, one of the most widely used self-report instruments to assess depression severity. Each of the 21 items is scaled from 0 to 3 with higher scores indicating more severe depression.

SHAPS-D. The Snaith–Hamilton Pleasure Scale (Snaith, 1993) assesses the hedonic capacity of the participants during the course of the treatment with higher scores indicating less anhedonia. It is of special value since the inability to experience pleasure is recognized as a core symptom of depression. It relies on self-report and consists of 14 items.

SF-36. The Short Form Health Survey is a 36-item self-report instrument to assess health related quality of life independent of psychiatric disorders and is a validated tool across treatment studies (http://www.sf-36.org). It comprises the following subscales: physical functioning, social functioning, emotional role functioning, emotional physical functioning, mental health, vitality, bodily pain and general health status.

ERQ. The Emotion Regulation Questionnaire (Gross and John, 1993) was designed to assess individual differences in the use of two common emotion regulation strategies: cognitive reappraisal and emotion suppression. Both strategies can be trained by CBT.

CTQ. Adverse childhood experiences are assessed in retrospect using the Childhood Trauma Questionnaire (Bernstein and Fink, 1998). This self-report scale consists of 28 items that are assigned to the following five subscales: emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse. Each subscale is composed of five items, each starting with "When I was growing up, ...". Subjects are asked to rate the degree to which they agree with each item on a 1 to 5 scale, from "never true" to "very often true." Thus, scores range from 5 to 25 for each subscale with high scores indi- cating a strong exposure to early life stressors.

TAS-20. The Toronto Alexithymia Scale (Bagby, Parker, Taylor, 1994) assesses different deficits in emotional competences such as difficulty describing feelings, difficulty identifying feelings, and externally oriented thinking. Alexithymia has been shown to influence the outcome of CBT.

STAI. The State Trait Anxiety Inventory (Spielberger et al., 1983) consists of 40 questions on a self-report basis. The STAI measures two types of anxiety: state anxiety, i.e., anxiety about an event, and trait anxiety, i.e. anxiety level as a personal characteristic. Higher scores indicate higher levels of anxiety.

CRQ. The Comfort Rating Questionnaire (Palm et al., 2014) has been developed to assess adverse reactions to tDCS. It consists of 2 × 10 items asking patients about appearance and severity of typical adverse reactions during and after the stimulation such as itching or prickling, feelings of a sharp pain, headaches or fatigue. It served as a safety and tolerability measurement instrument. Subjects completed the self-report scale after each CBT ses- sion with tDCS (active and sham).

ECM. The EmoCogMeter (Fuge et al., 2014) is a tablet-based application to assess an individual's performance on several neuropsychological domains such as learning and memory, working memory, selective and sustained attention, as well as executive functions.

IMI. The Impact Message Inventory (Kiesler & Schmidt, 1993) is based on Kiesler's circumplex model of interpersonal behavior (Kiesler, 1983) and assesses an individual's stimulus character, meaning the emotional, behavioral, and cognitive internal engagement experienced during interactions with a specified interacting partner on the following eight dimensions: dominant, hostile—dominant, hostile, hostile—submissive, submissive, friendly—submissive, friendly, and friendly—dominant. In *PsychotherapyPlus*, patients were encouraged to have the IMI filled out by a close friend or a relative who then rated their impression of the patient on the IMI subscales at the beginning and in the end of the intervention phase.

7. Assessment of Safety

Independent data monitoring was provided by the Koordinierungszentrum Klinische Studien (KKS) of Charité - Universitätsmedizin Berlin. An independent safety monitoring board (SMB; members: Stefan Leucht/ Munich; Katharina Domschke/ Freibug; Carlos Schönfeldt-Lecuona/ Ulm) was established to monitor *PsychotherapyPlus* regarding ethical and safety aspects of study treatment and procedure. The SMB had the authorization to examine whether the study was still ethically justifiable and whether patients' security was warranted throughout the whole trial. Therefore, the SMB was informed about any observed adverse and serious adverse event. Patients had to be withdrawn from the study in case of the occurrence of an increased risk for suicide as assessed by MADRS item 10 at the weekly rating during the intervention phase (a score of 5 or more on MADRS item 10 would fulfill one of the study's exclusion criteria), the occurrence of a serious adverse event or if, according to the belief of the

investigator, it is in the best interest of the patient to stop treatment, e.g., due to an adverse event. There were no such cases to report throughout the whole trial.

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Statistical Analysis Plan

Parts of the statistical analysis plan have been published previously (Bajbouj et al., 2018). This plan is the original and final version. In line with the ICH Good Clinical Practice Guidelines and recent recommendations (Gamble et al., 2017), it includes the following sections:

1. Administrative information
2. Introduction
3. Study methods
4. Statistical Principles and Analysis
5. Trial population
6. References

1. Administrative information

Title and trial registration: “Augmentation of Cognitive Behavioral Therapy with Transcranial Direct Current Stimulation for Depression: A Randomized Controlled Trial”, trial preregistration: NCT02633449. There were no revisions of the statistical analysis plan and no interim analyses.

2. Introduction

Major depressive disorder (MDD) is a debilitating disease affecting approximately ten percent of the population globally (Malhi & Mann, 2018). Clinical management primarily comprises psychotherapy, pharmacological treatment, and neuromodulatory interventions (Otte et al., 2016).

Cognitive behavioral therapy (CBT) is effective in the treatment of MDD with mean effect sizes of .75 and a sustainable improvement of symptoms (Cuijpers et al., 2020). Thus, it is recommended as first-line treatment in all national and international guidelines. However, about 20 to 30 percent of MDD patients do not sufficiently respond to standard treatment consisting of CBT, pharmacotherapy, or the combination of both (Rush et al., 2006). Therefore, there is an urgent need to develop more effective treatment strategies (Cuijpers et al., 2021).

In recent years, the concept of treatment augmentation (as previously known from pharmacological approaches) has been transferred to behavioral interventions. Here, the basic idea is to enhance their neuroplastic and clinical effects by pharmacological interventions such as psilocybin (Carhart-Harris et al., 2016) or non-invasive brain stimulation (NIBS) techniques (Bajbouj and Padberg, 2014; Sathappan et al., 2019). NIBS comprises transcranial magnetic stimulation (TMS) which has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDD, as well as transcranial direct current stimulation (tDCS). In tDCS,

a weak direct current is applied through electrodes placed on the scalp with the aim to modify cortical excitability (Nitsche et al., 2009). As compared to TMS, tDCS has the advantage of flexible usability in various settings, a better safety profile, and lower costs. We previously conducted trials in which we demonstrated that tDCS with electrodes placed over the dorsolateral prefrontal cortex (DLPFC) is capable of enhancing cognitive control, a cognitive mechanism essential for key psychotherapeutic techniques targeting the regulation of negative emotions in both healthy participants (Feeser et al., 2014) and MDD patients (Wolkenstein and Plewnia, 2013). In concordance, small pilot trials indicate an augmenting effect of tDCS for cognitive-behavioral therapies in patients with MDD (Segrave et al., 2014; Welch et al., 2019). Based on these findings, we conducted a randomized double-blind placebo-controlled clinical trial called *PsychotherapyPlus* comparing the efficacy of a tDCS-augmented CBT with CBT plus sham-tDCS and CBT alone in MDD patients.

3. Study methods

Trial design. *PsychotherapyPlus* is a double-blind, randomized, placebo-controlled multicenter trial with six German university hospitals involved: Charité - Universitätsmedizin Berlin (leading site, PI: Malek Bajbouj) and the universities of Munich (PI: Frank Padberg), Tuebingen (PI: Andreas Fallgatter), Leipzig (PI: Maria Strauss), Freiburg (PI: Claus Normann) and Mannheim (PI: Andreas Deuschle). Patients were randomized to one of the following three treatment arms: group 1 receiving 12 sessions CBT with tDCS, group 2 receiving 12 sessions CBT with sham-tDCS, and group 0 receiving 12 sessions CBT alone without any stimulation procedure.

Randomization and blinding. The study started with a pre-randomization determining the treatment arm running next. If treatment arm (1) or (2) were randomized to run next, the CBT group had to comprise three patients receiving active tDCS and 3 receiving sham-tDCS to

balance group effects: given our primary hypothesis that CBT with active tDCS is superior to the other treatment arms, it needed to be ruled out that this effect is solely due to greater treatment responses and a mutually induced positive development within one treatment condition as compared to the other conditions. This undesirable effect was supposed to be reduced by patients receiving active tDCS and sham-tDCS attending the same group. There was no CBT group comprising patients with and without tDCS devices to avoid different treatment efficacy expectations among patients within one group. Secondly, randomization to active or sham-tDCS was performed via random assignment of stimulation IDs by an independent clinician not involved in the trial. If treatment arm (group 0) was randomized to run next, no further randomization was necessary. In groups 1 and 2, double-blinded tDCS treatment was used to reduce bias during data collection and evaluation of clinical endpoints. All study personnel, CBT therapists and patients had no knowledge of tDCS conditions. Patients were instructed not to talk to other group members about the stimulation. In addition, all patients were tDCS-naïve. Patients were asked whether they believe having received active or sham stimulation after completing the last follow-up visit at week 30 (blinding check). Psychotherapists performed a blinding check at the end of the intervention phase.

Sample size calculation. A parallel group study design with three treatment arms (CBT + tDCS, CBT + sham-tDCS, CBT alone), a significance level of 1%, a power of 80%, and an estimated drop-out rate of 10% resulted in a sample size of 64 patients per arm for a total of 192 participants. A significance level of 1% was chosen to minimize the occurrence of a type-I error, i.e. to reject the null hypothesis (in particular: no difference between CBT + tDCS and CBT + sham-tDCS) although it is correct. We estimated a 3-point difference (effect size of Cohen's d = 0.5) for CBT alone and an additive effect in the combined treatment group (i.e., six-point difference, with an effect size of Cohen's d = 1.0). Eligible patients were recruited via outpatient clinics associated with the study sites. Additional procedures such as local

advertising in newspapers or in the public transport system were applied to achieve adequate patient enrolment.

Interim Analysis. There was no interim analysis in the present trial. Also, significance levels were not adjusted during the trial.

Timing of analyses and outcome assessments. Primary and secondary outcome data were analysed by one co-author of the study who was blind to study group assignment during the time of analysis. Analyses started after data management had been finalized. The primary outcome was the change in MADRS scores from baseline to post-intervention as well as an 18- and 30-weeks-follow-up.

4. Statistical Principles and Analysis

The primary outcome was the change in MADRS scores from baseline to post-intervention as well as an 18- and 30-weeks-follow-up. Secondary endpoints included clinical responses to treatment defined as a ≥ 50% reduction of MADRS scores and remission rates defined as MADRS scores ≤ 10. Further secondary endpoints were changes from baseline to post-intervention regarding self-rated depression severity (BDI-II), anhedonia (SHAPS-D), and health related quality of life (SF-36).

Linear mixed models were calculated for intention-to-treat (ITT) and per-protocol (PP) samples. Missing values were replaced via last observation carried forward. In both samples, post-intervention MADRS scores (weeks 6, 18 and 30) were predicted by the variables "group", "time" as well as their interaction. Logistic multilevel models were calculated to investigate whether there was an increased likelihood of a clinically relevant response or remission as a function of treatment arm. To specify efficacy, *Cohen's d* was calculated for

ITT and PP samples. Group differences regarding tolerability and safety were analysed using t-Test statistics.

5. Trial population

Outpatients with an age range of 20 to 65 years and a primary diagnosis of major depressive disorder in accordance with DSM-IV criteria were recruited for the study. Patients with a single or recurrent episode were included. Duration of the current depressive episode was less than five years (the definition of an episode is demarcated by a period of ≥ two months in which the patient did not meet full criteria of a major depressive episode). Eligibility criteria included a total score of ≥ 15 in the Hamilton Depression Rating Scale (HDRS-21; Hamilton, 1960) with an item 1 rating of ≥ 2 at the screening visit. Comorbid disorders were assessed by the Structured Clinical Interview for DSM-IV, axis-I and -II. Patients were either medication free or treated with a stable antidepressant medication of an SSRI and/or mirtazapine with "stable" being defined as "no change in antidepressant medication for at least four weeks prior to inclusion". Antidepressants except SSRIs/ Mirtazapine as well as mood stabilizers and antipsychotics were not allowed during the trial. After having completed the intervention and post assessments, patients were allowed to change their medication throughout the follow-up phase. All changes were documented.

Further inclusion criteria comprised:

- no CBT in the current episode or in the past two years (if duration of current episode was > two years)
- no ECT in the current episode
- no more than four sufficient antidepressant treatment trials, each with an ATHF score of ≤ 3, during the current episode
- MRI suitability

- positive tDCS safety screening

Exclusion criteria were:

- substance abuse or dependence in the past six months
- psychotic disorders (lifetime) including schizoaffective disorders or depressive episodes with psychotic symptoms (lifetime)
- bipolar disorders (type I and II)
- post-traumatic stress disorder, currently or within the past 12 months
- current generalized anxiety disorder, obsessive-compulsive disorder, panic disorder or social phobia
- personality disorders
- neurological disorders, such as stroke within the past two years, epileptic seizures (lifetime), epilepsy, dementia, Morbus Parkinson, Chorea Huntington, Multiple Sclerosis, as well as any other neurological disorder leading to increased intracranial pressure, brain lesions or an increased risk for epileptic seizures
- current risk of suicide, based on the personal assessment of the investigator or a score of 3 or more on HDRS-21 item 3 and/or a score of 5 or more on MADRS item 10.

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