Home Use, Remotely Supervised, and Remotely Controlled Transcranial Direct Current Stimulation: A Systematic Review of the Available Evidence

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Objectives: Transcranial direct current stimulation (tDCS) is gaining growing importance in the treatment of neurological and psychiatric disorders and is currently investigated for home-based and remotely supervised applications.

Methods: Here, we systematically review the available evidence from a database search (PubMed, ICTRP, clinicaltrials.gov) from January 2000 to May 2017.

Results: We detected 22 original research papers, trial protocols or trial registrations dealing with tDCS as an add-on intervention to cognitive or physiotherapeutic intervention. Overall, study samples are small; many studies are single-blinded and focus on feasibility and safety. There are two guideline papers setting basic requirements for clinical trials.

Conclusions: Further research needs to focus on home-based treatment from different viewpoints, that is, safety, technical monitoring, reproducibility of repeated applications, feasibility of combined interventions and systematic assessment of efficacy, and safety in large randomized controlled clinical trials (RCTs). However, remotely controlled and supervised tDCS for home use represents a promising approach for widespread use of noninvasive brain stimulation (NIBS) in clinical care.

Keywords: Domiciliary treatment, home based treatment, neurology, neuropsychiatric disorders, psychiatry, randomized placebo controlled trial, remote control, remotely controlled, transcranial direct current stimulation

Conflict of Interest: Ulrich Palm and Frank Padberg received paid speakership from NeuroCare Group, Munich, Germany. Frank Padberg received grants from neuroConn, Ilmenau, Germany, and Brainsway Inc., Jerusalem, Israel. Linda Wulf is part-time employee of NeuroCare Group. Alkomiet Hasan has received paid speakership by Desitin, Otsuka, Lundbeck and Janssen Cilag. He was member of the Roche, Lundbeck and Janssen Cilag Advisory Board. Daniel Keeser received a paid speakership from NeuroCare Group. The remaining authors have no relevant financial relationships to disclose.

INTRODUCTION

Transcranial direct current stimulation (tDCS) is an emerging non-invasive brain stimulation (NIBS) technique that consists in the application of weak currents through electrodes placed on the head. In a simplified model, anodal stimulation leads to a decrease of the resting state membrane potential of cortical neurons with facilitation of the spontaneous firing rate (1). Conversely, cathodal stimulation leads to hyperpolarization and decrease of neuronal activity. This is used to modulate the specific functional state of brain regions close to the stimulation area and remote areas by changes in network connectivity. tDCS is currently used for different purposes, that is, 1) as investigational tool in experimental and clinical neuroscience, 2) as novel therapeutic intervention in neurology and psychiatry, and 3) unfortunately—on a separate track—as a lifestyle application without a sound scientific background.

The experimental use in neuroscience aims at probing hypotheses regarding the functional role of cortical brain regions in neurophysiological and/or neuropsychological paradigms, that is, combining tDCS with electroencephalography (EEG) (2), multimodal imaging techniques (3), motor evoked potentials (MEP) (4) or neuropsychological tests to investigate the impact on cognitive functioning and behavior (5).

Regarding its therapeutic use, tDCS has gained growing interest as easily applicable novel intervention for the treatment of
neuropsychiatric disorders over the last years. There is pilot evidence for a variety of psychiatric disorders, for example, depression, schizophrenia, substance-related disorders, and others (6). Recent research suggests that there are dosage-dependent effects of tDCS, for example, in major depressive disorder (7) and that maintenance treatment should be carried out in short intervals in the postacute treatment of depression (8). Furthermore, there are growing numbers of studies combining tDCS with additional interventions such as cognitive-behavioral therapy, cognitive remediation, physiotherapeutic training etc. in a variety of neuropsychiatric disorders, such as stroke, multiple sclerosis, pain syndromes (9).

The third field of tDCS use is particularly critical, that is, the do-it-yourself (DIY) application with the subjective aim of cognitive enhancement, for example, in online gaming, or an increase in endurance for physical training (see, e.g., www.focus.us). The devices used for these purposes are commercially available from a variety of manufacturers at low budget. DIY tDCS bears various risks, ranging from adverse effects to an interaction with concomitant treatment or even a lack of appropriate therapy which may lead to deterioration of serious clinical conditions (10).

Though, the DIY applications of tDCS may be particularly detrimental for the sound development of the method, the general aspect of home use is also very interesting for evidence-based therapeutic applications, where maintenance treatment is required (e.g., in relapsing or chronic conditions) or and outpatient resources are limited (e.g., for remote areas or rare diseases with highly limited specialized units). For any home use, quality monitoring will be an essential issue, and put into practice using remote supervision and control approaches.

In order to outline the prerequisites and avenues for further methodological development, we systematically review the state of research on home use and remotely supervised tDCS for treatment of neuropsychiatric disorders. Two guideline papers have set benchmarks for the application of home use or remote controlled tDCS (9,11). However, technical issues and safety aspects need to be addressed before this new methodology can offer an alternative to the stimulation in clinical setting.

METHODOLOGY

Search Strategy

The database of the U.S. National Institutes of Health (PubMed/ Medline) was searched without any time frame (last search on 2017/05/16) for the terms “tDCS” and “transcranial direct current stimulation” in cross combination with the terms “remote control,” “domiciliary use,” “remotely supervised,” “self treatment,” and “home treatment.” Furthermore the terms “do-it-yourself brain stimulation” and “noninvasive brain stimulation remote control” were searched. Additionally, the WHO International Clinical Trials Platform (ICTRP) and the U.S. National Institutes of Health Clinical Trials Platform (clinicaltrials.gov) were searched within the time frame January 1, 2000 to May 16, 2017 for the term “transcranial direct current stimulation” (ICTRP) and “transcranial direct current stimulation home treatment” (clinicaltrials.gov). Database searches found 482 hits (PubMed: 261; ICTRP: 201; clinicaltrials.gov: 20). References of retrieved articles were searched for further literature and brought five hits. After manual checking for duplicates, 78 hits remained. After exclusion of 43 records due to topical irrelevance (e.g., no relationship to tDCS or home treatment), 35 abstracts or articles were assessed for eligibility. Of these, 13 were excluded for being out of scope (e.g., papers with ethical aspects on DIY brain stimulation, studies with clinic-based tDCS and home-based other therapy) and 22 remained for analysis. The PRISMA flowchart reporting the search strategy is shown in Fig. 1.

RESULTS

The topic of remotely supervised tDCS for study and home treatment purposes is a quite new field of research, emerging with a case report on schizophrenia treatment in 2013 (12) and a study on trigeminal neuralgia in 2014 (13). However, the available evidence is still sparse as large treatment studies with established protocols are still lacking or are under investigation. Therefore, ICTRP and clinical-trials.gov records and related study protocols were considered in the analysis to give an overview over current research and future directions. Thus, the available literature can be classified into four categories: current clinical trials, published study protocols, published original research, and guideline papers.

Current Clinical Trials

The abstract search on clinicaltrials.gov and ICTRP found several ongoing or not yet recruiting studies dealing with tDCS home treatment in different medical conditions; however for most studies only sparse information is available (abstracts presented here can be accessed via the webpage https://clinicaltrials.gov/cl2/search and are not mentioned in the reference list). For these studies, no study protocols are published yet, however they represent various directions of home use or remotely supervised tDCS in neurologic and psychiatric disorders. In sum, six study registrations reporting on the respective topics were detected:

A single-blind study is assessing the effect of 20 sessions of motor cortex tDCS on chronic neuropathic pain in 45 patients with a cloud-based remote supervision (NCT02346396). Another single-blind study is assessing the effect of motor cortex tDCS on chronic stroke. Three patients are receiving stimulation in clinical setting, another three patients at home with remotely supervised tDCS and finger tracking training, however under supervision of an investigator being at patient’s home (NCT02460809). A third single-blind study is investigating the effects of home-based cognitive training and tDCS in 40 patients with mild cognitive impairment and late life depression. A trained relative administers tDCS over an eight-week period (NCT02959502). Another study entitled home-administered trial of direct current stimulation (HAT-tDCS) will include 36 patients with a major depressive episode (NDE) (NCT02894736). A double-blind, randomized clinical trial will investigate the development of a tDCS device for home use (NCT02408237) with a target sample of 40 healthy participants. Another double-blind, randomized, phase II clinical trial with 32 fibromyalgia patients aims at evaluating home-based tDCS to relieve pain with a stimulation period of 12 weeks and 5 sessions per week (NCT02652988).

Published Study Protocols

O’Neill et al. (14) report on the protocol of a randomized, sham-controlled cross-over trial of anodal and cathodal tDCS over primary motor areas in 24 patients with chronic pain who had undergone repetitive transcranial magnetic stimulation (rTMS) treatment before (12 responders, 12 nonresponders). Electrodes are placed over the same areas as previously defined in the rTMS study, reference electrodes were placed contralaterally supraorbital. Three blocks of stimulation (1.4 mA, 20 min, 5 sessions), separated by a four week wash-out period, will be administered after a training session with photography and written description of the correct placement and
control by the study staff before each new block. Mode of stimulation is preprogrammed by the study team, electrode positioning is performed with specially designed headband after training by the study staff.

Bagg et al. (15) report on the protocol of a randomized, single-blinded (participants are blind to group allocation and study hypothesis), two-arm trial for 275 patients with low back pain and a study duration of 12 (to 18) weeks. One group will undergo sensory and movement training in 12 sessions, the other group will additionally have tDCS (more than 11 weeks, stimulation of motor and prefrontal cortices contralateral to site of greatest pain, further parameters are not reported), cranial electrical stimulation (CES, intervention not otherwise specified, more than eight weeks), low-intensity laser therapy (more than 10 weeks, to the area of greatest pain), and pulsed electromagnetic energy (more than seven weeks, to area of greatest pain). Stimulation methods will partially or fully overlap between weeks 1 and 12. Only the preprogrammed device for CES will be distributed for home use after training by the study staff; however the study protocol does not provide further information on technical settings or on remote supervision.

Our group (16) reported on a multicenter study with remotely controlled tDCS to improve MDE. One hundred and fifty-two patients with stable antidepressant medication will receive either active anodal or sham tDCS (2 mA, 30 min) of the left dorsolateral prefrontal cortex (DLPFC, F3–F4 corresponding to international 10–20 EEG system, positioning with a standard cap) with 24 treatments within 6 weeks. Stimulations are performed by study staff during inpatient and outpatient treatment with remotely controlled activation of active and sham mode for all participating centers. Electrode positioning is performed with a standard EEG cap. Technical data from stimulations is uploaded to the data cloud of the trial coordinating center for quality management and evaluation.

Published Original Research

Available original research is summarized in Table 1. Studies can be divided according to several characteristics, that is, type of study (case report, open label or randomized clinical trial), disease category, primary aim (at-home approach as clinical study or tDCS extension/maintenance treatment of another in-house treatment such as electroconvulsive therapy, ECT, or rTMS), and supply of devices by clinicians (e.g., in compassionate use or maintenance treatment) or by direct-to-consumer programs of manufacturers. It has to be noticed that most studies only report a minority of these characteristics. Therefore, in Table 1, we aimed at assessing quality measures of the reported studies including (A) control of adherence to the study protocol and scheduled stimulations, (Q) quality of stimulation, including electrode positioning and technical handling of the stimulation, (S) assessment of safety, including...
Table 1. Characteristics of Studies in Psychiatric and Neurological Disorders.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study type, disorder</th>
<th>Number of participants, age, gender</th>
<th>Conditions Electrode positioning, intensity, duration, number of stimulations</th>
<th>Operator, mode of supervision</th>
<th>Adverse effects</th>
<th>Outcome parameters, results</th>
<th>Strengths (S) and weaknesses (W)</th>
<th>Quality measures during stimulation series</th>
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<tr>
<td><strong>Psychiatric disorders</strong></td>
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<tr>
<td>Andrade et al. (2013)</td>
<td>Case report, schizophrenia, auditory verbal hallucinations</td>
<td>N = 1, 25 years, woman</td>
<td>Single condition: anode: F3, cathode: Tp3; 1–3 mA, 20–30 min, once to twice per day more than 3 years</td>
<td>tDCS applied by relatives, irregular clinic visits when deterioration occurred</td>
<td>Deterioration when electrode positioning was interchanged or alternate day session spacing was attempted</td>
<td>Clinical judgment, improvement in overall functioning</td>
<td>S: Feasibility and safety of long-term treatment</td>
<td>A = yes (relatives) Q = no S = no T = no V = no</td>
</tr>
<tr>
<td>Schwippel et al. (2017)</td>
<td>Case report, schizophrenia, multimodal hallucinations</td>
<td>N = 1, 31 years, man</td>
<td>Two conditions after a series of 22 cTBS without improvement: (active) anode: F4, cathode: Tp3; 1–2 mA, no improvement (active) anode: Tp3, cathode: F4; 2 mA, 20 min, once per day, 400 stimulations</td>
<td>tDCS applied by patient, irregular clinic visits</td>
<td>No adverse effects observed (skin, brain imaging, neuron specific enolase)</td>
<td>Clinical and cognitive assessment, no relevant change in psychopathology, improvement in cognition</td>
<td>S: Feasibility and safety of long-term treatment</td>
<td>A = no Q = no S = yes (after 400 sessions) T = no V = no</td>
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<tr>
<td>Azevedo et al. (2017)</td>
<td>Case report, Prader-Willi syndrome, hyperphagia and aggression</td>
<td>N = 1, 24 years, man</td>
<td>Single condition: anode: F3, cathode: F4; 2 mA, 20 min, 10 stimulations</td>
<td>tDCS applied by trained professional during at-home visit</td>
<td>No adverse effects observed</td>
<td>Clinical judgment and questionnaires, improvement of hyperphagia and aggression</td>
<td>S: Feasibility of tDCS in a patient with cognitive impairment</td>
<td>A = yes Q = yes S = yes T = yes V = yes</td>
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<td><strong>Neurological disorders</strong></td>
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<td>Pérez-Borrego et al. (2014)</td>
<td>Case report, chronic pain in macrophagic myositis</td>
<td>N = 1, 56 years, woman</td>
<td>Single condition: anode: Two electrodes over both motor cortices, cathode: forehead; 1.5 mA, 20 min, 5 stimulations, 1 maintenance stimulation per week</td>
<td>tDCS applied by trained caregiver, remote supervision by videoconference</td>
<td>No adverse effects reported</td>
<td>Clinical judgment and pain rating (visual analogue scale)</td>
<td>S: Remote supervision</td>
<td>A = yes Q = yes S = yes T = yes V = yes</td>
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<td>Hagenacker et al. (2014)</td>
<td>Cross-over RCT, trigeminal neuralgia</td>
<td>N = 10, 32–77 years, 5 women, 5 men</td>
<td>Two conditions: (active) anode: M1, cathode: Fp2, 1 mA, 20 min, 10 stimulations (sham) anode: M1, cathode: RSO, 1 mA, 20 min, 10 stimulations</td>
<td>tDCS applied by patients with help of relatives, phone backup, electronic protocol of the stimulation quality (not further specified)</td>
<td>No adverse effects observed</td>
<td>PREP, nociceptive blink reflex, verbal pain rating, reduced pain intensity after active treatment, PREP: increased N2 latency, decreased peak-to-peak amplitude after active tDCS</td>
<td>S: High quality study design</td>
<td>A = adherence control, Q = quality of stimulation, S = safety assessment, T = technical monitoring, V = regular visits</td>
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<td>Mortensen et al. (2015)</td>
<td>RCT, upper limb motor impairment following intracerebral hemorrhage</td>
<td>N = 15, 44–76 years, 6 women, 9 men</td>
<td>Two conditions: (active) anode: ipsilesional M1, cathode: contralesional supraorbital, 1.5 mA, 20 min, 5 stimulations (sham) anode: ipsilesional M1, cathode: contralesional supraorbital, 1.5 mA, 20 min, 5 stimulations Combination with occupational therapy (5 × 30 min)</td>
<td>tDCS applied by trained professional during at-home visit</td>
<td>Mild transient side effects, no adverse effects observed</td>
<td>JTT, SIS, improvement in JTT in both groups, improvement of grip strength in active group</td>
<td>S: High quality study design</td>
<td>A = yes, Q = yes, S = yes, T = no, V = yes</td>
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<td>Cha et al. (2016)</td>
<td>rTMS open label, followed by tDCS RCT and open label, Mal-de-</td>
<td>N = 24 (rTMS), N = 23 (blinded and open label tDCS), 28–76</td>
<td>All patients had 5 rTMS treatments (1 Hz F4, 10 Hz F3) before undergoing tDCS Two conditions:</td>
<td>tDCS applied by patients, training before first session, all stimulations at-home with online</td>
<td>Skin irritation in one patient in open label phase (2 mA) Questionnaires for mood, anxiety (HADS), and balance (DHI, MBRS)</td>
<td>S: Graded study design of open label rTMS, blinded tDCS, open label tDCS. High adherence and</td>
<td>A = yes, Q = yes, S = yes, T = no, V = yes</td>
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<td>Débarquement syndrome</td>
<td>43, 17–74 years, all women</td>
<td>(active) anode: F3, cathode: F4 (vice versa for left-handed persons), 1 mA, 20 min, 20 stimulations (sham) anode: F3, cathode: F4 (vice versa for left-handed persons), 1 mA, 20 min, each 20 stimulations followed by an open label active phase (same electrode positioning, 1–2 mA, up to 60 stimulations)</td>
<td>symptom tracking and phone calls/visits at-home if needed. Daily online symptom check, phone contact or personal visits at-home by study team, safe electrode positioning by head band and sending picture or videoconference</td>
<td>tDCS</td>
<td>one patient had a skin burn, one patient interchanged polarity and had an increase of tinnitus</td>
<td>Questionnaires for tinnitus (THI, mTQ) and mood (BDI, BAI), both active and sham group clinically improved</td>
<td>S: sham-controlled 3-arm-design with one further control group W: size probably too small to detect differences between active and sham. 3 patients did not complete stimulation series</td>
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<tr>
<td>Hyvärinen et al. (2016)</td>
<td>RCT, chronic tinnitus</td>
<td>N = 43, 17–74 years, 20 women, 23 men</td>
<td>Three conditions: (active) anode: F3, cathode: F4, 2 mA, 20 min, 10 stimulations (active) anode: LT, cathode: F3, cathode: F4, 2 mA, 20 min, 10 stimulations (sham) both electrode montages, 0.3 mA, 20 min, 10 stimulations</td>
<td>tDCS applied by patients, clinic visits at first stimulation and after stimulation series. Diary on stimulation, contact to study staff if needed</td>
<td>No adverse effects observed</td>
<td>Feasibility of home use, cognitive training was performed, clinical results are pending to be reported</td>
<td>S: High quality at-home treatment with high adherence, one drop-out not related to tDCS W: no sham control</td>
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</table>
| Kasschau et al. (2016) | Open label, multiple sclerosis | N = 20, 30–69 years, 17 women, 3 men | Single condition: Anode: F3, cathode: F4, 1.5 mA, 20 min, 10 stimulations | tDCS applied by patients, one clinic visit, one home visit, eight remotely supervised visits by study staff via videoconference | No adverse effects observed | Feasibility of home use, cognitive training was performed, clinical results are pending to be reported | S: High quality at-home treatment with high adherence, one drop-out not related to tDCS W: no sham control | A = adherence control Q = quality of stimulation S = safety assessment T = technical monitoring V = regular visits (active) anode: F3, cathode: F4 (vice versa for left-handed persons), 1 mA, 20 min, 20 stimulations (sham) anode: F3, cathode: F4 (vice versa for left-handed persons), 1 mA, 20 min, each 20 stimulations followed by an open label active phase (same electrode positioning, 1–2 mA, up to 60 stimulations).
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<td>Charvet et al. (2017)</td>
<td>Open label, randomized to two arms (one arm with tDCS), multiple sclerosis</td>
<td>N = 20 (CT + tDCS), mean age 53 ± 9 years, 21 women, 4 men</td>
<td>Single condition: (active + CT) anode: F3, cathode: F4, 1.5 mA, 20 min, 10 stimulations</td>
<td>tDCS applied by patients, one clinic visit, nine remotely supervised visits by study staff via videoconference. Electrode placement by standardized head cap</td>
<td>No adverse effects reported</td>
<td>CT, BICAMS, greater improvement in complex attention and response variability after CT + tDCS</td>
<td>S: Rehabilitation approach by combining tDCS with CT, 96% of stimulations completed</td>
<td>A = yes, Q = yes, S = yes, T = yes, V = yes</td>
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<tr>
<td>André et al. (2017)</td>
<td>RCT, vascular dementia</td>
<td>N = 21, mean age 80 ± 6 years (active), 76 ± 7 years (sham), gender not reported</td>
<td>Two conditions: (active) anode: F3, cathode: RSO, 2 mA, 20 min, 4 stimulations; (sham) anode: F3, cathode: RSO, 2 mA, 20 min, 4 stimulations</td>
<td>tDCS applied by trained professional during at-home visit</td>
<td>No adverse effects observed</td>
<td>Mood (GDS) and cognition (ADAS-cog), verbal working memory (2-back test), executive control (go-no-go task), visual short-term memory (picture naming task), cognitive improvement in both groups, further improvement in n-back test, go-no-go task, and picture naming task only in active group</td>
<td>S: Home treatment approach for dementia, no dropout during treatment W: imbalance in active (V = 13) and sham (V = 8) randomization</td>
<td>A = yes, Q = yes, S = yes, T = yes, V = yes</td>
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</table>

Electrode positioning (according to 10–20 EEG system): F3, F4, left, right DLPFC; LTA, left temporal area; M1, primary motor cortex; RSO, right supraorbital; Tp3, left temporo-parietal junction. Abbreviations: ADAS-cog, Alzheimer Disease Assessment Scale Cognition; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BICAMS, Brief International Cognitive Assessment in Multiple Sclerosis; CT, cognitive training; cTBS, continuous theta burst stimulation; DHI, Dizziness Handicap Inventory; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; JTT, Jebsen-Taylor-Test; MBRS, MdDS Balance Rating Scale; mTQ, mini-Tinnitus Questionnaire; PREP, pain-related evoked potentials; RCT, randomized controlled clinical trial; SIS, Stroke Impact Scale; THI, Tinnitus Handicap Inventory.
standardized reporting of side effects and adverse events, (T) technical monitoring, referring to a storage of stimulation data in the device, and (V) regular visits during the study phase to foster adherence and assess clinical changes.

Concerning the use of tDCS in psychiatric disorders, there are two case reports on auditory verbal (12) respectively multimodal hallucinations (17), and one case report is dealing with the improvement of hyperphagia and aggressive behavior in patient with Prader-Willi Syndrome and severe intellectual disability (18).

In neurological disorders, there are five randomized controlled clinical trials (RCTs), three open-label studies, and one case report. The single case report by Pérez-Borrego et al. (19) is dealing with the improvement of pain in a patient with macrophagic myofasciitis. A cross-over RCT by Hagenacker et al. (13) investigated with the improvement of trigeminal neuralgia in 10 patients found that anodal tDCS significantly reduced pain intensity compared to sham tDCS after two weeks of treatment. Mortensen et al. (20) report on an RCT in patients with upper limb motor impairment after intracerebral hemorrhage and found an improvement of grip strength in the active group compared to sham. Another study by Cha et al. (21) with graded design including RCT and open-label phases investigated the use of rTMS and tDCS in 24 women with Mal-de-Débarquement-Syndrome and found an improvement of anxiety and balance after active tDCS. Hyvärinen et al. (22) conducted an RCT on the treatment of tinnitus in 43 patients and found an improvement of tinnitus in both active and sham groups with no significant difference between them. Kasschau et al. (23) included 20 multiple sclerosis patients in an open-label study with ten tDCS sessions and concomitant cognitive training. This trial was explicitly designed for testing feasibility of remotely supervised tDCS and did not report on clinical results.

Charvet et al. (24) report on a randomized, open-label clinical trial in multiple sclerosis patients undergoing either computer-based cognitive training or cognitive training + tDCS. The combined treatment was superior to cognitive training alone in terms of cognitive processing.

André et al. (25) conducted a sham controlled study in 21 patients with vascular dementia undergoing four at-home stimulations performed by study staff. Compared to sham group, the active group improved in reaction time at the n-back and go-no-go test and showed improved visual short-term memory in the picture naming task.

Guideline Papers

Currently there is one framework paper to define guidelines of remotely supervised tDCS (9). The authors point out the need of remotely controlled tDCS as a prerequisite of sufficiently powered randomized clinical tDCS trials with adequate duration (relationship between dosage and efficacy) and the need for rigorous quality management, that is, training sessions, trouble shooting, and supervising by the medical staff, to ensure reproducible results and safety. The authors warn against a simple belief that providing patients with devices and instructions could lead to safe and clinically meaningful results. Although tDCS is a safe and easy technique, it is only safe and easy in the hands of trained persons. Therefore, several checklists and guidelines concerning training of staff and participants are presented, as well as algorithms and schedules for study visits and remote control/supervision, and requirements for device equipment. The first one is a checklist for correct preparing of the electrode set-up, device handling, and postprocessing of the stimulation. Another is dealing with training and preparation of study staff to ensure correct handling of standard operation procedures, study equipment, and technical issues. For study purposes, a flowchart with stop criteria is proposed to ensure a maximum of safety if technical difficulties occur. Safety checklists for the study equipment are proposed, as well as guidelines for the safety assessment during the study period. For home application, two different modes of activation are possible: The first is a device with built-in and secured software delivering a certain number of stimulations in limited intervals. Data control and reactivation of a new block after consumption of all stimulations is performed by the medical staff. The second is the activation of stimulations by a code given to the patient via direct contact to the study center. This ensures immediate control of electrode positioning (e.g., by picture or webcam) and controls for number and interval of sessions. Finally, the authors discuss several potential applications of remotely supervised tDCS in attention deficit hyperactivity disorder, depression, multiple sclerosis, and palliative care.

Another publication with focus on visualizing the experimental procedures (11) provides detailed inclusion/exclusion criteria and formal requirements for device kits, headgear, training, video monitoring, and data handling. Training should include a sample video and an instruction manual as well as in-person training. Device set-up is described in detail to avoid typical errors. Although this study is designed for the use in multiple sclerosis patients, algorithms, and visit schedules are exemplary for study design with remotely supervised tDCS.

DISCUSSION

To date there is sparse evidence on the use of home-based tDCS in neuropsychiatric disorders. Most available studies are dealing with multiple sclerosis symptoms and a combination of cognitive training and tDCS. One study is reporting on the improvement of cognition in patients with vascular dementia. For other neuropsychiatric disorders, there are some studies ongoing or not yet recruiting. Interestingly, except for the study of Mortensen et al. (20) in patients with intracerebral hemorrhage, there are no studies published yet addressing domiciliary tDCS use in stroke patients although their disability could serve as a key indication for home treatment. For psychiatric disorders, for example, depression, schizophrenia, and substance related disorders, there is complete lack of evidence except for two case reports in schizophrenia. Overall study samples are small, mostly dealing with feasibility and safety, and are lacking controlled designs. Other papers addressing trial methodology provide elaborated designs but are still ongoing (14,16).

However, two guideline papers by Charvet et al. (9) and Kasschau et al. (11) are setting benchmarks for designing and conducting clinical trials with remotely supervised tDCS. They provide detailed information on study design, quality control, medical supervision, and technical requirements of devices.

Safety, Adherence, and Blinding Integrity

Generally, tDCS is deemed safe when correctly applied and the most important adverse event may be skin lesions which are rarely reported. In the studies dealing with at-home tDCS, Cha et al. (21) reported on a skin irritation without further specification, and Hyvärinen et al (22) reported one skin burn. Apart from this, side effects of tDCS in the analyzed studies do not exceed the well-known sensations of itching, tingling, burning, transient headache, etc. (20,21,23), and probably do not influence adherence rates as patients did not report tDCS as uncomfortable. However, drop-out rates obviously
depend from correct and comprehensive training prior to self-administration of tDCS. This issue has been addressed in the study by Hagenacker et al. (13) where half of the patients dropped out due to discontinuing the treatment at home. Insufficient clinical training, higher age of patients, and lacking remote supervision (optional phone backup) seemed to be the main factors for this result. But also in other studies where relatives were trained to apply stimulations, difficulties of electrode placement or confounding anodal/cathodal may occur (12). On the other side, Cha et al. (21) conducted a sequenced trial with rTMS and tDCS in a blinded and open label design with intensive contact of the study team throughout the randomized treatment phase. They report on high adherence without drop-outs during the randomization and on high satisfaction in participants. Therefore regular visits or phone/video conferences seem to be necessary not only to assess clinical efficacy but also to control for correct performance of stimulations and to avoid drop-outs.

Mortensen et al. (20), Cha et al. (21), and Hyvärinen et al. (22) reported no statistically significant differences in guesses for active or sham treatment. André et al. (25) reported no nominal difference for guesses.

Overall studies vary considerably in reporting tDCS and controlling procedures (Table 1), adverse events, drop-out rates and integrity of blinding and there is a need to uniformly address these issues as proposed by Charvet et al. (9) or consensus statements on reporting study results (e.g., www.ICMJE.org).

Definitions
Throughout the retrieved literature there is no clear distinction between the terms used for describing different methods of controlling and supervising home-based tDCS, although Charvet et al. (9) point out technically different methodologies.

To uniformly address the different methodologies in controlling and supervising tDCS administration, we suggest the following separation:

Home Use (Synonymous: Domiciliary Use) tDCS
This term should be used for application of tDCS by the patient himself or by relatives in compassionate use or in interventional studies. Device function usually is active mode. Frequency and number of stimulations is advised by the medical staff however depends on patient’s compliance if stimulation settings are not preprogrammed and secured by the supervisor. Thus, this option is feasible for patients showing adherence to the intervention. Correct performance is trained in advance by the medical staff and control (e.g., of logged technical data) is performed irregularly during follow-up visits. Some manufacturers already implement controlling of tDCS effects by smartphone applications, daily assessing of mood, appetite, sleep, activity, and others.

Remotely Supervised tDCS
This term should be used for patient/relative-operated tDCS at home using a device with preprogrammed function (active/sham, current strength, duration, frequency), secured against manipulation. Connection to the supervisor is available by online support, for example, phone, webcam, email, and others, or intermediate monitoring, where technical data of each stimulation are logged to the device and uploaded by web connection, for example, to a technical cloud during reloading the stimulation device at the PC (16). For online monitoring, unlocking the stimulator to deliver a stimulation is executed by medical staff via video or phone conference at the beginning of the patient-administered session, for example, after control of correct electrode positioning. Both options can be used in cases where patients cannot easily attend outpatient sessions. However, patients or caregivers’ adherence should be prerequisites.

Remotely Controlled tDCS
This term should be reserved for online tDCS control by trained medical staff during regular or study treatment in a specialized setting (usually a hospital) with preprogrammed devices (active/sham, current strength, duration). Although these devices may be secured against manipulation, device settings are constantly under control of the medical staff. As for remotely supervised tDCS, technical data of each stimulation are logged in the device and could be uploaded to a technical cloud when reloading the stimulator from a PC. This ensures correct application and quality monitoring for tDCS. Moreover, it allows monitoring of treatment conditions by Coordinating Centers for Clinical Trials in RCTs without breaking the blinding of operators or investigators (16).

Future Directions
All of the three different approaches mentioned above have a certain purpose. While home use is generally applicable for compassionate use in severely ill patients or useful for patients living afield or suffering from mobility handicaps, and therefore require help of a trained assisting person, usually a relative, the other methods of remotely supervised or remotely controlled tDCS are required for standardized clinical application or high quality research. Beyond the question of feasibility of home use tDCS, the methodology of remotely controlled tDCS ensures reproducibility of stimulations under laboratory standards in specialized centers, producing high quality data on electro-physical and technical properties of tDCS in a large number of participants (such data are not yet available although tDCS is used all over the world). This also ensures adherence to tDCS as treatment in psychiatry is frequently discontinued by patients regardless of pharmacotherapy or NIBS. In a recent study of transcutaneous vagus nerve stimulation (tVNS) in schizophrenia patients, only 53% of participants showed adherence to protocol-based self-application (26). This shows the need for both technical and motivational support for patients treated with NIBS.

However, there is clear need for larger clinical trials which assess and compare home use, remotely supervised and remotely controlled tDCS in various disorders and settings.

CONCLUSIONS
The treatment of neurological and psychiatric disorders with tDCS is characterized by the need of long-term or repetitive treatment which is difficult for patients suffering from disability or living far away from the hospital. Home-based application of tDCS provides the opportunity for regular treatment or study participation. Remotely supervised tDCS and remotely controlled tDCS of home-based use are feasible approaches for double-blind RCTs. As there are guidelines for technical requirements and methodology, future research will have to incorporate these methods in large scale studies.

Authorship Statement
Ulrich Palm, Alkomiet Hasan, and Frank Padberg designed study and wrote the manuscript. Ulrike Kumpf, Nora Behler, Linda Wulf, Beatrice Kirsch, Jana Wolsching, Daniel Keeser helped with data
gathering and preparation of the manuscript. All authors approved the final manuscript.

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