Controlled clinical trial of repeated prefrontal tDCS in patients with chronic minimally conscious state

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ABSTRACT
Objectives: To assess the effects of repeated transcranial direct current stimulation (tDCS) sessions on the level of consciousness in chronic patients in minimally conscious state (MCS).
Methods: In this randomized double-blind sham-controlled crossover study, we enrolled 16 patients in chronic MCS. For 5 consecutive days, each patient received active or sham tDCS over the left prefrontal cortex (2 mA during 20 min). Consciousness was assessed with the Coma Recovery Scale-Revised (CRS-R) before the first stimulation (baseline), after each stimulation (day 1–day 5) and 1 week after the end of each session (day 12).
Results: A treatment effect (p = 0.013; effect size = 0.43) was observed at the end of the active tDCS session (day 5) as well as 1 week after the end of the active tDCS session (day 12; p = 0.002; effect size = 0.57). A longitudinal increase of the CRS-R total scores was identified for the active tDCS session (p < 0.001), while no change was found for the sham session (p = 0.64). Nine patients were identified as responders (56%).
Conclusion: Our results suggest that repeated (5 days) left prefrontal tDCS improves the recovery of consciousness in some chronic patients in MCS, up to 1 week after the end of the stimulations.

Introduction
Transcranial direct current stimulation (tDCS) delivers a weak (usually 1–2 mA) electrical current through the brain using two electrodes, an anode and a cathode placed on the scalp [1]. It is presumed that anodal tDCS strengthens synaptic connections through a mechanism similar to long-term potentiation, while cathodal tDCS seems to have an opposite effect [2,3]. Better performances were observed on working memory tasks during and after active tDCS over the left dorsolateral prefrontal cortex (DLPFC) in healthy volunteers and in patients with stroke, suffering from Parkinson’s disease, and moderate traumatic brain injury [4–7]. Similarly, tDCS over the left DLPFC seems to have positive effects on attention in patients with stroke [8] and in patients with mild [9] or severe [10] traumatic brain injury suffering from attentional deficits.

We recently reported an improvement in the level of consciousness in patients with disorders of consciousness (DOC), especially patients in a minimally conscious state (MCS; showing reproducible but inconsistent signs of consciousness [11,12]), following a single session of DPLFC tDCS [13]. This finding is noteworthy as there are very few evidence-based guidelines regarding the treatment of patients with DOC [14,15]. Until now, only amantadine has been shown to increase the pace of recovery of patients with severe traumatic brain injury in a subacute population (4–16 weeks post-injury [16]). However, if amantadine enhances the pace of recovery in subacute stage, it may not be as efficient at improving the level of consciousness in patients in a chronic stage [15]. Additionally, amantadine is associated with side effects such as epileptic seizure [17] and may, therefore, not always be supported by the patient [18]. tDCS has been widely studied, and there is no severe side effect when applied within the safety criteria [19]. In this context, tDCS has the advantage to have little to no side effects, even when the stimulations are repeated daily [20,21].

As the effects of a single tDCS stimulation on patients with DOC seem to last a few hours, we here aim to determine whether these short-term effects can be amplified and made more durable by the use of repeated stimulations. Indeed, previous studies on stroke patients or patients with Parkinson disease showed that repeating the number of stimulations (e.g., 5 or 10 days) could increase the duration of the effect from 1 week to 1 month [22–24]. Similarly, Angelakis et al. investigated in a prospective case series trial, the effect of repeated tDCS over the left DLPFC or the primary motor cortex in 7 chronic patients in unresponsive wakefulness syndrome (UWS—i.e., eyes opened, but no awareness of self or environment [25,26]) and three patients in MCS [27]. No behavioural changes were observed in patients in UWS, while the three patients in MCS demonstrated clinical improvement. However, among the patients in MCS, only one received tDCS over the prefrontal cortex. Therefore, in a double-blind randomized sham-controlled crossover study, we assessed the effects of daily sessions of tDCS over the left DLPFC on the level...
of consciousness in chronic patients in MCS. We hypothesized that repeated tDCS over the left DLPFC (i.e., 5 consecutive days of stimulation), as compared to sham stimulations, will improve the level of consciousness (as measured by changes in CRS-R total scores) in a sample of chronic patients in MCS. We focused on chronic patients (>3 months post-insult [13]) to avoid the spontaneous recovery period, which could be a confounding factor. Our second hypothesis is that the effects will last at least 1 week after the end of the active tDCS session, and that these effects will linearly increase over the 5 days of stimulation. Finally, we hypothesized that the number of responders to repeated tDCS sessions will increase as compared to our first study (i.e., single stimulation).

**Methods**

**Patients**

We prospectively enrolled medically stable patients in chronic MCS between January 2011 and August 2014. The sample size was based on the duration of the ethic committee approval (i.e., 4 years).

Inclusion criteria were: (1) being in MCS according to the published diagnosis criteria; (2) more than 3 months post-injury; (3) acquired traumatic or non-traumatic etiology [11]. We excluded patients with unclear diagnosis during prescreening assessments and patients with a metallic cerebral implant or pacemaker (in line with the safety criteria for tDCS in human subjects [17]). Patients were studied free of sedative drugs and Na+ or Ca++ channel blockers (e.g., carbamazepine) or NMDA receptor blockers (e.g., dextromethorphan) to avoid interaction with the presumed neuromodulatory effects of tDCS [28]. We did not include patients with a cranioplasty. Medications (two patients were on amantadine) and rehabilitation (e.g., number of sessions per week and type of therapy performed by physical therapists, occupational therapists, and speech therapists or any other type of therapy such as hydrotherapy) were kept unchanged throughout the experiment. If the medication and/or rehabilitation were modified during the protocol, the patients had to be excluded from the study, as well as if two consecutive assessments were missing due to clinical purposes (e.g., nursing or physical therapy cares needed). Clinically, we defined as responders the patients who showed at least one new sign of consciousness (e.g., response to command, visual pursuit, objects recognition or localization, automatic motor reaction, localization of noxious stimuli or intentional communication) during the 5 days of tDCS, and who kept displaying this behaviour 1 week later, as compared to baseline and sham stimulation.

**Materials**

Each patient received both active and sham DLFPC tDCS sessions in a randomized order. A computer-generated randomization sequence was used to assign in a 1:1 ratio the first session as active tDCS or sham stimulation. For the sham session, the employed tDCS device (Neuroconn DC Stimulator Plus, NeuroConn GmbH, Ilmenau, Germany) offers a built-in placebo mode, which is activated by an anonymous code number and includes ramp periods of 5 s at the beginning and the end of sham stimulation to mimic the somatosensory artefact of active tDCS. Two investigators were involved in data collection. The same investigator performed both tDCS and CRS-R assessments on the same patient. For each patient, the experimenter received two blinded codes from a third person, one for the active stimulation and one for the sham stimulation. Thus, active and sham tDCS could not be identified either by the blinded experimenters who administered tDCS and CRS-R, or by the patients.

Direct current was applied by a battery-driven constant current stimulator using saline-soaked surface sponge electrodes (7 × 5 cm) with the anode positioned over the left DLPF cortex (F3 according to the 10–20 international system for EEG placement [29]) and the cathode placed over the right supraorbital region, as previously described [30]. During tDCS, the current was ramping up to 2 mA (in 5 s) from the onset of stimulation and applied for 20 min. For the sham condition, the same electrode placement was used as in the active condition, but the current was applied for 5 s only, and was then ramped down to 0 mA. Impedances were kept <10 kΩ and voltage <26 V.

tDCS was performed daily, at the same time of the day, for 5 consecutive days. tDCS and sham stimulations were tested in a random order in two different block sessions separated by 1 week of washout (as published elsewhere [31]—see Figure 1).

tDCS treatment effect was assessed by means of standardized CRS-R assessments performed by two trained and experienced blinded experimenters [32]. The CRS-R consists of 23 hierarchically arranged items (from reflexes—e.g., visual or auditory startle; to more complex voluntary behaviours—e.g., command following, visual pursuit, object manipulation, recognition or localization) comprising six subscales assessing auditory, visual, motor, verbal, communication and arousal functions. Diagnosis is based on the presence or absence of specific behavioural responses to sensory stimuli administered in a standardized manner as described in the guidelines [32]. The lowest item on

![Figure 1](https://example.com/image1.png)  
**Figure 1.** Protocol of the study. CRS-R, Coma Recovery Scale-Revised; tDCS, transcranial direct current stimulation; BL, baseline; d, day. Active and sham tDCS sessions were randomized.
each subscale represents reflexive activity, whereas the highest
items represent cognitively mediated behaviours. Before inclu-
sion in this study, each patient was assessed at least 4 times
during a 1-week period in order to establish a clear diagnosis.
For the protocol, CRS-R assessments were performed directly
before the first baseline session and after each active tDCS and
sham sessions as well as 1 week later.

Side effects were evaluated by the experimenters after each
stimulation and included (1) the presence of redness of the
skin under the electrodes; (2) signs of discomfort, as assessed
by observation of the facial expression (e.g., grimace or tears
[11,33,34]); and (3) arousal CRS-R subscale (to assess any
possible sedative effect).

Standard protocol approvals, registrations and patient
consents
Written informed consents were obtained by the legal repre-
sentative of each patient. The study was approved by the
ethics committee of the University and University Hospital
of Liège, Belgium (ClinicalTrials.gov NCT02019615).

Statistics
Statistical analysis was performed using SAS (version 9.3 for
Windows) statistical package. The effect of the treatment was
analysed based on the modification of the CRS-R total score. The
differences considered in the present study were: [day 5—base-
line] and [day 12—baseline]. In each situation, the individual
data recorded during the crossover study were analysed accord-
ing to the method described elsewhere [35] and summarized
hereafter. At the group level, we first looked for a period, inter-
action and treatment effect. The period effect refers to the
calculation of active tDCS-sham stimulation response differ-
ences, which were then compared according to the order of
administration using a Mann-Whitney U test. The interaction
effect referred to the calculation of the mean response after active
tDCS and sham session, which was then compared according to
the period using a Mann-Whitney U test. If no period and
interaction effect was found, then treatment effect was assessed
using a Wilcoxon match-paired signed-rank test. Results were
considered significant at \( p < 0.05 \). Multiple comparisons using
Bonferroni correction (six comparisons) had to be performed for
the secondary end-point assessment (i.e., assessment of CRS-R
subscale change according to tDCS/sham), and results were
considered significant at \( p < 0.0083 \) (i.e., 0.05/6). To evaluate
the longitudinal evolution of the CRS-R score between treatment
groups, a mixed model with an undefined covariance structure
was fitted to the data. The covariates included in the model were
the time and the interaction with the treatment indicator. This
statistical method allows the comparison of response curves
between treatments while accounting for dependency of the
data within each patient. The effect size was calculated using
the following expression \( r = \frac{z}{\sqrt{n}} \) where \( z \) is the statistics
obtained from the Wilcoxon signed-rank test [36]. Results
were considered significant at the 5% critical level (\( p < 0.05 \)).
Differences between responders and non-responders were
assessed using a t-test (i.e., age and time since insult) and a
chi-square test (i.e., aetiology).

Results
We assigned 21 eligible patients to receive both active and
sham tDCS in a crossover study design. Two patients were
excluded from the study after the first washout period
because of medical complications that required a modification
of medication (one patient had a pulmonary infection
and the other had epileptic seizures). Three other patients
were also excluded from the study due to missing CRS-R
assessments for 2 consecutive days (i.e., incomplete, missing
or delayed—more than 1 h—CRS-R assessments due to
nursing cares or physical therapy cares for pulmonary con-
gestion, needed after the stimulation session—see Figure 2).
The five drop-outs did not differ from the others in terms of
age (\( p = 0.443 \)), time since injury (\( p = 0.515 \)) or baseline
CRS-R (\( p = 0.669 \)).

Sixteen patients completed the study (mean age of 47 [17–74]
years; 9 men; interval since insult: 85 [5–365] months; 11 post-
traumatic, 5 non-traumatic—i.e., anoxic and stroke). Demographic
data are reported in Table I. Nine patients first
received active tDCS, and seven patients first received sham
stimulation. There was no significant clinical or demographic
difference between the 2 groups. We did not identify any period
or interaction effect (\( p > 0.05 \)), at day 5 nor at day 12. At the
group level, a difference was observed between the two treatment
conditions at day 5 (\( p = 0.013 \)) as well as 1 week after the last
stimulation (day 12 \( p = 0.002 \)) (Figure 3).

We did not observe any significant effect of tDCS on any of
the six CRS-R subscales.

When we looked at the longitudinal change of the CRS-R
scores, an improvement of the CRS-R total scores was found for

![Figure 2. Study flowchart.](image-url)
the active tDCS session across time (p < 0.001), while no change was observed under the sham session (p = 0.64, Figure 4).

At the individual level, 9 of the 16 patients were identified as tDCS responders (i.e., patients who demonstrated a new sign of consciousness). The recovery of signs of consciousness included response to command, recognition and localization of objects, automatic motor response and visual fixation/pursuit. Functional communication, which is a criterion of the emergence of MCS [11], was also observed in two patients after active tDCS.

### Discussion

We identified a positive effect of repeated tDCS over the left DLPFC on level of consciousness in chronic patients in MCS. In addition, these effects lasted at least 1 week after the last stimulation. Our results are in line with previous studies, reporting a positive short lasting effect (1 or 2 h) of tDCS on cognition [5,6,37,38] as well as the longer lasting effect (from 1 week up to 1 month) associated with repeated stimulations, in pain [39], stroke [23,40] and Parkinson disease [22].

As mentioned in the introduction, a previous case series study reported clinical improvement in 10 chronic (>6 months) patients with DOC after repeated tDCS over the left DLPFC (n = 5) or the primary motor (n = 5) cortices [27]. The only patient in MCS who received tDCS over the left DLPFC showed a behavioural improvement characterized by the recovery of pain localization. However, the reappearance of this particular behaviour was not observed in our cohort of 9 responders who presented various new signs of consciousness.

When we looked at the longitudinal changes on the CRS-R scores, we observed a significant increase over time (from day 1 to 12). In addition, we observed an increase in the effect size when comparing the first (single) stimulation (i.e., 0.38) [13] to...
the fifth one (i.e., 0.43). The effect size also increased at day 12 (i.e., 1 week after the end of the stimulation—0.57), suggesting that 5-day stimulation increases the duration and the strength of tDCS clinical effects.

Some authors hypothesized that repeating tDCS every day could improve corticocortical excitability and therefore, strengthen the effect of the stimulation [39]. One study showed that tDCS induced greater motor evoked potential amplitude in healthy subjects when delivered every day rather than every other day [41]. This could reflect superior cumulative effects between stimulation rather than a greater response to each individual tDCS [41]. These studies are in line with our observation, since we identified an increased number of responders with the number of stimulations, together with an increased duration of the effect, lasting up to 1 week after the last stimulation.

Another study investigating the effect of tDCS (over the primary motor cortex) on human consciousness in REM sleep, demonstrated that tDCS could influence motor imagery during this stage of sleep [42]. The authors also suggested that, since REM sleep is involved in motor development and the preparation of movements, tDCS could be used to stimulate motor function, and especially in patients who suffered from immobilization, such as severely brain-injured patients with DOC, highlighting another potential benefit of tDCS for the rehabilitation of patients with DOC.

In our previous trial using a single stimulation, we observed that 43% of MCS (in both acute and chronic stage) was responsive to tDCS [13]. However, when looking at the chronic MCS, only 23% responded to tDCS. In the present study, we noticed that 25% (n = 4) of our sample responded after the first stimulation, which is similar to our previous results. Interestingly, we observed that five other patients showed improvement after 2, 3 or even 4 days of stimulation, resulting in 56% of responders after 5 days of stimulation. These results suggest that repeating tDCS daily could increase the number of responders, and that the first session is not predictive of a future positive effect of the stimulation on the level of consciousness.

The increased effects of tDCS over the sessions could be due to an increase in NMDA receptor excitability, which could improve and strengthen cortical excitability within the stimulated area [1,2]. More distant areas also seem to be involved in tDCS responsiveness. For patients in MCS, we recently identified that responders to a single session of tDCS showed more
grey matter preservation and residual metabolic activity, as compared to non-responders, in the stimulated area (i.e., left DLPFC), in the precuneus, and in the thalamus; areas known to be involved in conscious processes [43]. These results suggest that not only the stimulated area but also areas implicated in consciousness are involved in the mechanisms of action and clinical effects of tDCS in patients with severe brain injured and DOC [44]. However, the stimulated area and the consciousness network need to remain at least partially preserved. Recently, another study also showed that tDCS could be used as a diagnostic tool to disentangle patients in MCS from UWS [45]. The authors identified that active tDCS induced an increase in cortical connectivity and excitability (measured by transcranial magnetic stimulations) in patients in MCS, while improvement was only observed in patients clinically diagnosed with UWS who showed recovery to MCS at follow-up. This study showed that beside the treatment effect of tDCS, this technique could be useful to detect residual connectivity markers in clinically UWS patients who may recover behavioural signs of consciousness later on.

As supported by our findings and previous studies, it is well known that tDCS is a low-risk technique [19,46]. In the 16 patients who completed the study, no seizure or sign of potential pain (e.g., grimace, tears) was observed. No complication related to the protocol occurred during the active tDCS or the sham sessions. Four patients had moderate redness of the skin that disappeared within 30 min. tDCS did not have any effect on the level of arousal on any of the patients. Those observations suggest that tDCS may be applied safely in daily clinical practice. Nevertheless, further studies need to be performed to assess the long-term effect (e.g., 1, 3, and 6 months) of repeated tDCS in patients with severe brain injury.

The observed positive effects coupled with the absence of adverse events, make tDCS an interesting tool that could be implemented in rehabilitation settings. In addition, it is relatively

Table II. List of CRS-R responses recovered following tDCS in the 9 responders.

| Items                        | Detailed responses during the CRS-R assessment | Number of patients |
|------------------------------|-----------------------------------------------|--------------------|
| Systematic command following | 4 out of 4 responses at “move your right arm” | 1                  |
| Reproducible command following | 3 out of 4 responses at “move your right hand/fingers” | 1                  |
| Sound localization*          | Turn head when presenting your own name behind the head of the patient at least twice | 1                  |
| Object recognition           | Recognize a comb and/or a cup, visually on 3 or more occasions | 2                  |
| Automatic motor reaction     | Spontaneous motor reaction (i.e., grab bed sheet) | 1                  |
| Visual pursuit               | Follow mirror on at least 2 occasions in the same direction | 2                  |
| Visual fixation              | Fixate a ball on at least 2 occasions on the hand | 1                  |
| Object localization          | Reaching ball with the hand on demand at 3 occasions | 1                  |
| Functional communication+    | Accurately respond to 6 autobiographical yes/no questions (e.g., is your name Patrick, do you have 32 years old, is your father’s name Christopher) | 2                  |

CRS-R, coma recovery scale-revised.
*Does not denote MCS.
+Denotes EMCS if observed on two consecutive assessments.

Table III. CONSORT 2010 checklist of information to include when reporting a randomised trial*.

| Section/topic                  | Item No | Checklist Item | Reported on page No |
|-------------------------------|---------|----------------|---------------------|
| Title and abstract            | 1a      | Identification as a randomised trial in the title | P1                  |
|                               | 1b      | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | P1                  |
| Introduction                  | 2a      | Scientific background and explanation of rationale | P3–4                |
| Background and objectives     | 2b      | Specific objectives or hypotheses | P4                  |
| Methods                       | 3a      | Description of trial design (such as parallel, factorial) including allocation ratio | P6–7                |
| Trial design                  | 3b      | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | P9                  |
| Participants                  | 4a      | Eligibility criteria for participants | P5                  |
|                               | 4b      | Settings and locations where the data were collected | P5                  |
| Interventions                 | 5       | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | P6                  |
| Outcomes                      | 6a      | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | P6–7                |
|                               | 6b      | Any changes to trial outcomes after the trial commenced, with reasons | /                   |
| Sample size                   | 7a      | How sample size was determined | P5                  |
|                               | 7b      | When applicable, explanation of any interim analyses and stopping guidelines | /                   |
| Randomisation: Sequence       | 8a      | Method used to generate the random allocation sequence | P5                  |
| generation                    | 8b      | Type of randomisation; details of any restriction (such as blocking and block size) | P5                  |
| Allocation concealment        | 9       | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | P5–6                |
| mechanism                     | 10      | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | P6                  |
| Implementation                | 11a     | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | P6                  |
| Blinding                      | 11b     | If relevant, description of the similarity of interventions | P6                  |
| Statistical methods           | 12a     | Statistical methods used to compare groups for primary and secondary outcomes | P8                  |
|                               | 12b     | Methods for additional analyses, such as subgroup analyses and adjusted analyses | P8                  |

(Continued)
inexpensive and easy to use. Therefore, the use of tDCS in patients with severe brain injury during the rehabilitation program could improve or fasten their recovery. New studies investigating the effect of long-term protocol (e.g., 4 weeks of stimulation) should be performed in order to evaluate the feasibility of a clinical translation of tDCS. In addition, several studies have shown that tDCS coupled with a specific therapy could enhance its effects [47,48]. Therefore, combining tDCS with other therapies, such as physical therapy or occupational therapy, in patients with DOC should be tested as well.

Our study has several limitations. Firstly, we only performed one follow-up assessment after 1 week. It would thus be useful in future tDCS studies to conduct follow-up testing at longer intervals to determine whether treatment effects can last more than 1 week after treatment. In addition, even if the interaction effect was not statistically significant, there is a trend towards a carry-over effect. Therefore, future clinical trials using tDCS should include a longer washout period. Another limitation is the smaller sample of patients included. We were not able to recruit more than 21 patients for this protocol during a 4-year period. Therefore, multicentric and international studies will be necessary to replicate and confirm the results in a larger population of patients.

In conclusion, tDCS applied over the left prefrontal cortex seems to be safe and can enhance the level of consciousness in some chronic patients in MCS. Moreover, the effects appeared to last at least 1 week after the end of the stimulations. In addition, the first session was not predictive of a future positive effect of tDCS on the level of consciousness as the number of responders doubled after 5 days of tDCS as compared with the first day of stimulation. Even though our findings are based on a small sample size, these preliminary results strongly support the need to further investigate the use of tDCS as a therapeutic intervention in patients with DOC.

**Acknowledgments**

The authors thank Pr. Gustave Moonen, Pr. Pierre Maquet, the Neurology Department staff of the University Hospital of Liège, the ISOSL Rehabilitation Center, Centre d’Accueil de Bouge, the Foyer Saint-Anne, the University of Liège, the Duesberg Foundation, the Belgian American Educational Foundation, the Wallonie-Bruxelles International, the James McDonnell Foundation, Mind Science Foundation, IAP research network P7/06 of the Belgian Government (Belgian Science Policy), the European Commission, Human Brain Project (EU-H2020-fetflagship-hbp-sga1-ga720270), and Luminus project (EU-H2020-fetopen-ga686764). AT and OG are post-doctoral fellows, and SL is research director at FRS-FNRS.

**Authorship**

AT and SL designed the protocol. AT and MAB obtained the data. AT, SW and SL interpreted data and wrote the manuscript. SW and AFD analysed the data. CC and OG contributed to the writing of the manuscript. All authors were involved in editing the paper and approved the final text.

**Declaration of interest**

The authors report no conflicts of interest. Funding was provided by: European Commission, James S McDonnell Foundation, Belgian National Fund for Scientific Research (FNRS), Concerted Research Action, the Belgian American Educational Foundation (BAEF), the Fédération Wallonie Bruxelles International (WBI), the Massachusetts General Hospital Department of Neurology and Division of Neurocritical Care and Emergency Neurology, and the University of Wisconsin-Madison. The source of the funding of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. SL is Research Director at FNRS, OG is post-doctoral fellows at FNRS.

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**Table III. (Continued).**

| Section/topic | Item | Checklist item | Reported on page | No |
|---------------|------|----------------|-----------------|----|
| **Results**   |      |                |                 |    |
| **Participant flow (a diagram is strongly recommended)** | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | P9 |
|               | 13b | For each group, losses and exclusions after randomisation, together with reasons | P9 |
| **Recruitment** | 14a | Dates defining the periods of recruitment and follow-up | P5 |
|               | 14b | Why the trial ended or was stopped | / |
| **Baseline data** | 15 | A table showing baseline demographic and clinical characteristics for each group | Table I |
| **Numbers analysed** | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned group | Figure 2 |
| **Outcomes and estimation** | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | P9–10 |
|               | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | / |
| **Ancillary analyses** | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | P10–11 |
| **Harms** | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | P11 |
| **Discussion** | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | P14 |
| **Limitations** | 21 | Generalisability (external validity, applicability) of the trial findings | P14–15 |
| **Generalisability** | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | P14–15 |
| **Interpretation** | 23 | Registration number and name of trial registry | P7 |
| **Other information** | 24 | Where the full trial protocol can be accessed, if available | P7 |
| **Protocol** | 25 | Sources of funding and other support (such as supply of drugs), role of funders | / |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.*
References

1. Nitsche MA, Paulus W. Transcranial direct current stimulation—update 2011. Restor Neurol Neurosci [Internet]. 2011;29(6):463–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22085959

2. Nitsche MA, Frick K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, Henning S, Tergau F, Paulus W. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol [Internet]. 2003;09/02 ed. 2003;553(Pt 1):293–301. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12949224

3. Nitsche MA, Liebetanz D, Schlitterlau A, Henschke U, Frick K, Frommank K, Lang N, Henning S, Paulus W, Tergau F. GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. Eur J Neurosci [Internet]. 2004/05/19 ed. 2004;19(10):2720–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15147306

4. Fregni F, Boggio PS, Mansur CG, Wagner T, Ferreira MJ, Lima MC, Rigonatti SP, Marcolin MA, Freedman SD, Nitsche MA, et al. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. Neuroreport [Internet]. 2005/09/09 ed. 2005;16(14):1551–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16184743

5. Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, Fregni F. Effects of transcranial direct current stimulation on working memory in patients with Parkinson’s disease. J Neurol Sci [Internet]. 2006/07/18 ed. 2006;249(1):31–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16843494

6. Zaalhe T, Sandmann P, Thorne JD, Jancke L, Herrmann CS. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci [Internet]. 2011/01/08 ed. 2011;12:2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21211016

7. Jo JM, Kim YH, Ko MH, Ohn SH, Joen B, Lee KH. Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehabil [Internet]. 2009/07/22 ed. 2009;88(5):404–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19620953

8. Kang EK, Baek MJ, Kim S, Paik NJ. Non-invasive cortical stimulation improves post-stroke attention decline. Restor Neurol Neurosci [Internet]. 2010/01/01 ed. 2010;28(6):645–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20042788

9. Kang EK, Kim DY, Paik NJ. Transcranial direct current stimulation of the left prefrontal cortex improves attention in patients with traumatic brain injury: A pilot study. J Rehabil Med [Internet]. 2012/03/22 ed. 2012;44(4):346–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22434324

10. Sacco K, Galetto V, Dimitri D, Geda E, Perroti F, Zettin M, Geminiani G. Concomitant use of transcranial direct current stimulation and computer-assisted training for the rehabilitation of attention in traumatic brain injured patients: Behavioral and neuroimaging results. Front Behav Neurosci. 2016;10:57.

11. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002/02/13 ed. 2002;58(3):349–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11839831

12. Giacino JT, Fins JJ, Laureys S, Schiff ND. Disorders of consciousness after acquired brain injury: the state of the science. Nat Rev Neurol [Internet]. 2014;10(2):99–114. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24488878

13. Thibaut A, Bruno MA, Ledoux D, Demertzi A, Laureys S. tDCS in patients with disorders of consciousness: sham-controlled randomised double blind study. Neurology. 2014;82(13):1112–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24616561

14. Bernat JL. Chronic disorders of consciousness. Lancet [Internet]. 2006/04/18 ed. 2006;367(9517):1181–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16616561

15. Gosseries O, Charland-Verville V, Thinonard M, Bodart O, Laureys S, Demertzi A. Amantadine, apomorphine and zolpidem in the treatment of disorders of consciousness. Curr Pharm Des [Internet]. 2014;20(26):4167–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24025057

16. Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, Eifert B, Long D, Katz DI, Cho S, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med [Internet]. 2012/03/02 ed. 2012;366(9):819–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22375972

17. Gualtieri T, Chandler M, Coons TB, Brown LT. Amantadine: a new clinical profile for traumatic brain injury. Clin Neuropharmacol [Internet]. 1989 Aug [cited 2015 Sep 20];12(4):258–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2680078

18. Nickels J, Schneider W, Dombovy M, Wong T. Clinical use of amantadine in brain injury rehabilitation. Brain Injury 1994;8(8):709–18.

19. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol [Internet]. 2011;14(8):1133–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21320389

20. Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol [Internet]. 2003/10/29 ed. 2003;114(11):2220–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14580622

21. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, Edwards DJ, Valero-Cabre A, Rotenberg A, Pascual-Leone A, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul [Internet]. 2012;5(3):175–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22037126

22. Doruk D, Gray Z, Bravo GL, Pascual-Leone A, Fregni F. Effects of tDCS on executive function in Parkinson’s disease. Neurosci Lett [Internet]. 2014;582:27–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25179996

23. Marangolo P, Fiori V, Calpagnano MA, Campana S, Razzano C, Caltagirone C, Marini A. tDCS over the left inferior frontal cortex improves speech production in aphasia. Front Hum Neurosci [Internet]. 2013;7:539. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24046740

24. Fiori V, Coccia M, Marinelli C V, Vecchi V, Bonifazi S, Ceravolo G. Concomitant use of transcranial direct current stimulation and computer-assisted training for the rehabilitation of attention in traumatic brain injured patients: Behavioral and neuroimaging results. Front Behav Neurosci. 2016;10:57.

25. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS. N Engl J Med [Internet]. 1994/05/26 ed. 1994;330(21):1499–508. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7818633

26. Laureys S, Celesia GG, Cohodon F, Lavrijsen J, Leon-Carrion J, Sannita WG, Saabon L, Schnutzehard E, von Wild KR, Zeman A, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apalic syndrome. BMC Med [Internet]. 2010/11/03 ed. 2010;8:68. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20946060

27. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS. N Engl J Med [Internet]. 1994/05/26 ed. 1994;330(21):1499–508. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7818633

28. Caltagirone C, Marini A. tDCS over the left inferior frontal cortex improves word retrieval in healthy and non-fluent aphasic subjects. J Cogn Neurosci [Internet]. 2011;23:95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21040571

29. Engelakis E, Liouta E, Andreadis N, Korfias S, Ktonas P, Stranjalis G. Concomitant use of transcranial direct current stimulation and computer-assisted training for the rehabilitation of attention in traumatic brain injured patients: Behavioral and neuroimaging results. Front Behav Neurosci. 2016;10:57.

30. Hertwig U, Satrapi P, Schonfeldt-Lecuona C. Using the international 10–20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr [Internet]. 2004/02/24 ed. 2003;16(2):95–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14977202
30. Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, Brunelin J, Moller HJ, Reiser M, Padberg F. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J Neurosci [Internet]. 2011/10/28 ed. 2011;31(43):15284–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22031874

31. Baker JM, Rorden C, Fridriksson J. Using transcranial direct current stimulation to treat stroke patients with aphasia. Stroke [Internet]. 2010;41(6):1229–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20395612

32. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil [Internet]. 2004/12/18 ed. 2004;85(12):2020–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15605342

33. Arif-Rahu M, Grap MJ. Facial expression and pain in the critically ill non-communicative patient: State of science review. Intensive Crit Care Nurs. 2010;26(6):343–352.

34. Schnakers C, Chatelle C, Demertzi A, Majerus S, Laureys S. What about pain in disorders of consciousness? AAPS J. 2012;14(3):437–444. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22528502

35. Altman DG. (1990). Practical statistics for medical research. London: Chapman & Hall.

36. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. J Exp Psychol Gen [Internet]. 2012;141(1):2–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21823805

37. Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MT, Paulus W, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res [Internet]. 2005/07/07 ed. 2005;166(1):23–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15999258

38. Javadi AH, Walsh V. Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. Brain Stimul [Internet]. 2011/08/16 ed. 2011; Available from: http://www.ncbi.nlm.nih.gov/pubmed/21840287

39. Antal A, Terney D, Kuhl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manage [Internet]. 2010/05/18 ed. 2010;39(5):890–903. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20471549

40. Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. Restor Neurol Neurosci [Internet]. 2007;25(2):123–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17726271

41. Alonzo A, Brassil J, Taylor JL, Martin D, Loo CK. Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation. Brain Stimul [Internet]. 2012;5(3):208–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22037139

42. Speth J, Speth C. Motor imagery in REM sleep is increased by transcranial direct current stimulation of the left motor cortex (C3). Neuropsychologia 2016;86:57–65.

43. Laureys S, Faymonville ME, Luxen A, Lamy M, Franck G, Maquet P. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. Lancet [Internet]. 2000/06/01 ed. 2000;355(9217):1790–1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10832834

44. Thibaut A, Di Perri C, Chatelle C, Bruno M, Bahri M, Wannez S, Piarulli A, Bernard C, Martial C, Heine L, et al. Clinical response to tDCS depends on residual brain metabolism and grey matter integrity in patients with minimally conscious state. Brain Stimul [Internet]. 2015 Jan [cited 2015 Nov 23];8(6):1116–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26471400

45. Naro A, Calabro R, Russo M, Leo A, Pollicino P, Quartarone A, Bramanti P. Can transcranial direct current stimulation be useful in differentiating unresponsive wakefulness syndrome from minimally conscious state patients? - PubMed - NCBI. Restor Neurol Neurosci [Internet]. 2015 [cited 2015 Sep 20];33(2):159–76. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26471400

46. Fregni F, Nitsche MA, Loo CK, Brunoni AR, Marangolo P, Leite J, Carvalho S, Bolognini N, Caumo W, Paik NJ, et al. Regulatory Considerations for the Clinical and Research Use of Transcranial Direct Current Stimulation (tDCS): review and recommendations from an expert panel. Clin Res Regul Aff [Internet]. 2015;32(1):22–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25983531

47. Straudi S, Fregni F, Martinuzzi C, Pavarelli C, Salvioli S, Basaglia N. tDCS and robotics on upper limb stroke rehabilitation: Effect modification by stroke duration and type of stroke. Biomed Res Int [Internet]. 2016 Jan [cited 2016 May 19];2016:5068127. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = 4830702&tool = pmcentrez&rendertype = abstract

48. Mendonca ME, Simis M, Grecco LC, Battistella LR, Baptista AF, Fregni F. Transcranial direct current stimulation combined with aerobic exercise to optimize analgesic responses in fibromyalgia: A randomized placebo-controlled clinical trial. Front Hum Neurosci [Internet]. 2016 Jan [cited 2016 Mar 29];10:68. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = 4785149&tool = pmcentrez&rendertype = abstract