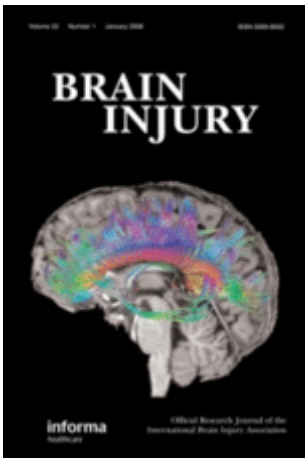

Single tDCS session of motor cortex in patients with disorders of consciousness: a pilot study

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Keywords:	transcranial direct current stimulation, persistent vegetative state, minimally conscious state, primary motor cortex, disorders of consciousness, unresponsive wakefulness syndrome

Abstract

Primary Objective: Patients with disorders of consciousness (DOC) face a lack of treatments and risk of misdiagnosis, potentially due to motor impairment. Transcranial direct current stimulation (tDCS) showed promising results when applied over the prefrontal cortex in patients with DOC and over the primary motor cortex (M1) in stroke. The aim of this pilot study was to evaluate the behavioral effects of M1 tDCS in patients with DOC. **Research Design:** In this randomized double-blind sham-controlled crossover trial, we included 10 patients (49±22 years, 7±13 months since injury, 4 unresponsive wakefulness syndrome [UWS], 6 minimally conscious sate [MCS], 5 traumatic etiologies). **Methods and Procedures:** One session of tDCS (2 mA for 20 minutes) and one session of sham tDCS were applied over M1 in a randomized order with a washout period of minimum 24 hours and behavioral effects were assessed using the CRS-R. At the group level, no treatment effect was identified on the total score (p=0.55) and on the motor subscale (p=0.75). Two patients responded to tDCS by showing a new sign of consciousness (visual pursuit and object localization). **Conclusions:** One session of M1 tDCS failed to improve behavioral responsiveness in patients with DOC. Other application strategies should be tested.

Key words: transcranial direct current stimulation (tDCS), disorders of consciousness, motor cortex, unresponsive wakefulness syndrome, minimally conscious state.

Introduction

Patients with disorders of consciousness (DOC) following severe brain damage represent a challenging population regarding diagnosis and treatment. The gold standard for assessing the level of consciousness is the Coma Recovery Scale – Revised (CRS-R), that relies on behaviors observed at bedside in response to external stimuli (1). It allows to disentangle an unresponsive wakefulness syndrome/vegetative state (UWS/VS – state of intermittent wakefulness without evidence of awareness of the environment or self (2)) from a minimally conscious state (MCS – fluctuating presence of signs of consciousness such as visual pursuit or command following (3)). However, the high dependency on motor abilities represent an issue for a proportion of clinically unresponsive patients showing partial preservation of cortical activity on neuroimaging and/or neurophysiological assessments (4). This specific situation, coined MCS*, cognitive-motor dissociation or covert consciousness characterizes patients unable to display responses at bedside despite being conscious (4–6). Motor function appears, therefore, as one of the key means to increase the patient's chances of showing signs of consciousness and may also allow the use of other behavioral therapies, requiring patients' active participation, to promote recovery. Transcranial direct current stimulation (tDCS), a neuromodulation method known to transiently improve the functions of targeted cortical areas using non-invasive weak electrical currents (1 – 2 mA) can improve various skills in healthy controls and pathological populations (7). When applied on the projection of the primary motor cortex (M1; C3 – C4 according to the 10 – 20 EEG system (8)) in patients with stroke, it has shown to induce improvements in hand function, muscle strength or activities of daily living, among others (9). In patients with DOC, a single session of tDCS over the left dorsolateral prefrontal cortex (DLPFC) can effectively modulate the cortical excitability as measured by TMS-EEG (10). From a clinical standpoint, a randomized

controlled trial performed on 55 patients showed a significant treatment effect in the 30 patients in MCS as measured by the CRS-R when one tDCS session was performed over the DLPFC for 20 minutes at 2 mA and 43% of the patients in MCS showed a new sign of consciousness after the real stimulation that was not present before or after sham however these positive behavioral effects were transient (11). Other studies evaluating the effects of prefrontal tDCS applied for longer period of time have also shown positive results on behavioral improvements (12,13). After these encouraging results and in view of the extensive literature for motor cortex stimulation, we conducted a pilot study investigating the beneficial effects of one session of M1 tDCS in patients with DOC on their behavioral responses as measured by the CRS-R.

Material and Methods

The study was approved by the local ethics committee (CE2009/201). Inclusion criteria were : presenting a DOC (UWS/VS or MCS) as established by international guidelines (14) and a stable vital condition (no recent event requiring hospitalization, change in medication or intubation). Exclusion criteria were the following: documented neurological condition prior to the accident; medication comprising sedative agents, Na^{+} or Ca^{2+} channel blockers or NMDA receptor antagonists, presence of metallic cerebral material, craniectomy under the stimulated area (i.e., prefrontal cortex) and uncontrolled epilepsy. Patients received one active and one sham session of tDCS in a randomized order with a 1:1 ratio. Direct current was applied by a battery-driven current stimulator (DC Stimulator Plus, Neurocare, Germany) using saline-soaked surface sponge electrodes (7 x 5 cm). Impedances were always kept below 10 kΩ and voltage below 26 V through a built-in safety mode. The active electrode (anode) was placed on the area corresponding to C3 or C4 according to the 10-20 international system for EEG placement (the most affected side was stimulated based on the patient's medical records) while the return electrode (cathode) was placed on the contralateral

supraorbital area. During tDCS, the current was increased to 2 mA and applied for 20 minutes while for the sham condition, the same electrode placement was used but the current was applied for 5 seconds and then ramped down. The two tDCS and sham sessions were separated by at least 24 hours of washout, which was estimated as a time interval long enough (above 90 minutes) for potential tDCS-related effects to disappear (15) and short enough for potential spontaneous recovery to not impact the behavioral outcomes. The device used offers a built-in blinding mode using anonymous code numbers provided by a third party which means both the patient and the investigator were blinded to the treatment allocation. Side-effects were collected after each session of tDCS (active and sham) using a questionnaire assessing if any of the following signs were observed during or following tDCS: redness of the skin, irritation/injury of the skin, signs of pain or discomfort, epileptic seizure, increased sleepiness. Behavioral assessments using the CRS-R were performed before and after each stimulation sessions by trained clinicians. The CRS-R is a standardized behavioral assessment scale consisting of 23 items hierarchically-organized within 6 subscales interrogating auditory, visual, motor, verbal, communication and arousal functions and is the only measurement tool recommended for clinical use in patients with DOC by the American Congress of Rehabilitation Medicine with minor reservations (1,16). Our primary outcome measure was the tDCS treatment effect computed using a Wilcoxon match-paired signed rank-test comparing the differences in CRS-R total score (deltas) as follows: [after sham minus before sham] and [after active minus before active]. The statistic Z was used to calculate the effect size (ES) r using the formula $r=Z/\sqrt{2n}$. The treatment effect was calculated only in the absence of a carry-over effect that was tested using the same test but comparing the CRS-R total scores before active tDCS and before sham tDCS. As a secondary outcome, we computed the treatment effect for the motor subscale score. As exploratory analyses, we looked at each CRS-R subscale separately using the method described above.

We also checked for a potential significant difference between baseline and post CRS-R total scores for both active and sham stimulation using a Wilcoxon match-paired signed-rank test. We then computed the treatment effect for patients in MCS only (n=6; based on the baseline diagnosis) to compare our results to the existing literature. As further explorative analysis, we checked for a potential correlation between clinical improvement (i.e., CRS-R total score after active tDCS minus total score before active tDCS – delta active tDCS) and time since injury using a Spearman's Correlation test. Statistical analyses were performed using R (17). Results were considered significant at $p<0.05$.

Results

Ten patients were enrolled (4 UWS and 6 MCS; 8 men; 49±22 years; 7±13 months since injury; 5 traumatic etiologies, 4 anoxic, 1 stroke – see Table 1). The median [IQR] time between the consecutive active and sham tDCS session was 1 [1 – 1.75] days. No side effects were observed after the active or the sham session.

INSERT TABLE 1 AROUND HERE

At the group level, no carry-over effect was identified (Z= -1.33; p=0.22) and we did not find any significant treatment effect (Z= -0.62; p=0.55; ES=0.10). Regarding the motor subscale, no significant treatment was observed (Z=0.56; p=0.75) neither in any other subscale (p>0.05). There was no significant difference in the CRS-R total scores between the baseline condition and post stimulation for both active (Z= -1.73; p=0.25) and sham stimulation (Z= -1.09; p=0.30). For MCS subjects only (n=6), no significant treatment effect was identified either (Z= -0.26; p=0.89; ES=0.06). Regarding the influence of time since injury, no significant correlation between delta active tDCS and days since injury was identified (t= -0.291; p=0.778). At the single subject level, one 64-year-old male patient at a subacute stage

(28 days post stroke) showed visual pursuit after the active stimulation only, that was not observed beforehand or after sham stimulation (only reflexive blinking to threatening stimulus) and his diagnosis therefore changed from UWS to MCS. Another patient, 19-year-old male patient 8 months post traumatic brain injury recovered object localization following active stimulation only but his diagnosis remained MCS. No patient changed diagnosis after the sham stimulation.

Discussion

We aimed to investigate the effects of one session of M1 tDCS on the behavioral responses of patients with DOC. As for prefrontal tDCS, M1 tDCS seems to be safe for patients with DOC. This aspect still needs to be carefully accounted for since single tDCS-related adverse effects, such as skin burn, have been reported in a healthy subject (18). We did not find any significant treatment effect in CRS-R total scores, or in the motor subscale following the application of a single session of active tDCS as compared to sham. Beside the small sample size, we discuss three potential reasons to explain our results: (i) low dose of tDCS; (ii) sensitivity of CRS-R assessment to evaluate motor function in DOC and (iii) possible absence of effect of M1 tDCS in DOC. The first possibility is that a single session of tDCS is not enough to enhance motor function in patients with DOC. In fact, several studies have shown that the number of sessions is one of the most important factors to determine the dose-effect of tDCS (19,20), but we expected to see at least a transient short-lasting effect. Given the extent of neural lesions in DOC, one can assume that several sessions are necessary even to observe a short-lasting effect in this population. In addition, the growing literature on tDCS in stroke tends to show that tDCS effects are strengthened when combined to behavioral therapies (21,22). More intensive protocols combining repeated sessions of M1 tDCS and rehabilitation program, such as physical therapy or robotic training, should be tested to induce stronger effects on neural plasticity and increase patients' chances to regain motor-related signs of consciousness. The second important issue was whether our assessment was sensitive enough to detect motor changes. Indeed, we only performed one CRS-R evaluation after stimulation while it is known patients with DOC need repeated assessments to obtain an accurate behavioral diagnosis because of the important vigilance fluctuations they are subject to (23,24). Additionally, other assessments, such as electroencephalography (EEG),

electromyography (EMG), or motor evoked potential (MEP) could provide higher sensitivity to detect neural changes. These techniques should be implemented in future trials to detect subtler changes. Finally, another issue explaining the absence of results could be that patients with severe brain injury might require more complex tDCS intervention (e.g., network-based stimulation) to be effective. Given the widespread contribution of areas for the planning (frontal and prefrontal cortices) and execution of a movement (i.e., basal ganglia, thalamus, supplementary motor area, motor and premotor cortices) and the extended lesions observed in our population, it may be possible that targeting the motor cortex may not induce as strong effects on behavioral signs of consciousness as targeting the prefrontal region. There is evidence that when stimulating the left dorsolateral prefrontal cortex (DLPFC) of patients in MCS and assessing the behavioral effects with the CRS-R, effect sizes (ES) are greater (single stimulation – n=30; ES=0.38 (11); 5 days of stimulation – n=16; ES=0.43 (12)) than for posterior parietal cortex stimulation (5 days of stimulation – n= 33; ES=0.31 (25)) or motor stimulation in the present study (n=6; ES= 0.06). Therefore, to date, the DLPFC seems to be the best candidate of the three (DLPFC, posterior parietal cortex and M1) for applying tDCS patients in MCS. This region endorses indeed a lot of executive functions (i.e., planning, attention, working memory, decision making and cognitive flexibility). Another limitation of this study is that both acute and chronic patients were included; time since injury was therefore heterogeneous while acute and chronic patients likely respond differently to motor tDCS, given the dramatic progression of the decline in motor function (26,27). However, we did not observe a significant impact of time since onset on clinical improvement, probably due to the small sample size. Once beyond the proof of concept, future studies should be careful to narrow down the time window following injury in their inclusion criteria. Despite the absence of a significant treatment effect at the group level, relevant clinical results were obtained at the single-subject level. Indeed, one subacute patient

(28 days post stroke) with focal lesions in the left basal ganglia and the left insula showed visual pursuit only after the active stimulation, which had important clinical implications since his diagnosis changed to MCS for the first time. Another chronic patient (8 months post traumatic brain injury) with lesions involving the frontal lobes and the hippocampi responded to tDCS by showing object localization for the first time after active stimulation. It should be noted that the evolution over time of these newly acquired behaviors is unknown. Indeed, no further CRS-R data point could be obtained since the patients were discharged from our facility afterwards. Nonetheless, for these two responders, applying M1 tDCS has improved some oculomotor abilities as measured by the CRS-R visual subscale. Since the parietal visual areas and the frontal motor areas are interconnected through cortical and cerebellar pathways (28), increasing the excitability of one area using tDCS might propagate to distant but connected areas (29). Object localization (i.e., moving a limb toward a presented object) also requires a greater participation of motor abilities and stimulating M1 might have directly improved these abilities. The identification of these tDCS-responders showing significant behavioral improvements remains a key issue. To this end, it is now known that behavioral response to tDCS requires at least a partial preservation of the stimulated area both from a structural and a metabolic standpoint (30). Therefore, future studies should not only focus on the repetition of the sessions but also include patients based on the localization of their lesions (e.g., stimulate patients who do not suffer from significant damage in the motor cortex but present low scores on the CRS-R motor subscale). Combined therapies (e.g., tDCS and motor training) could also be effective to potentiate tDCS effects (31).

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Conflicts of interest

The authors declare no conflicts of interest

Conclusions

M1 tDCS in patients with DOC is safe but failed at improving motor responsiveness at the group level. When compared to previous studies, the DLPFC seems to be currently the best candidate for enhancing signs of consciousness, especially patients in MCS (11,12,32). However, it might be important to further investigate M1 tDCS for DOC. For instance, the repetition of sessions, the combination with motor training, or the concurrent stimulation of other areas might be interesting future studies.

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Table I: Demographic data, tDCS allocation, CRS-R total scores and main MRI lesions of the the study sample. TSO= Time Since Onset; CRS-R= Coma Recovery Scale-Revised; TBI= Traumatic Brain Injury; UWS= Unresponsive Wakefulness Syndrome; MCS= Minimally Conscious State

ID	Age (gender)	Etiology	TSO (days)	Baseline Diagnosis	tDCS Allocation	CRS-R Total Score (Sub-scores)				Main MRI lesions
						Before Active	After Active	Before Sham	After Sham	
P1	24 (M)	TBI	286	UWS	active/sham	4 (1-0-0-1-0-2)	4 (1-0-0-1-0-2)	4 (1-0-0-1-0-2)	4 (1-0-0-1-0-2)	left temporo-parietal region
P2	32 (M)	non-TBI	150	MCS	sham/active	20 (3-4-6-3-1-3)	20 (3-4-6-3-1-3)	18 (3-3-5-3-1-3)	22 (4-5-6-3-1-3)	left frontal subcortical region
P3	68 (M)	TBI	45	MCS	sham/active	6 (0-1-3-1-0-1)	7 (0-1-3-1-0-2)	4 (0-0-1-1-0-2)	7 (3-1-1-0-0-2)	cerebellum, frontal lobes
P4	70 (M)	non-TBI	12	MCS	active/sham	7 (0-3-1-1-0-2)	7 (0-3-1-1-0-2)	6 (0-1-2-1-0-2)	9 (0-3-3-1-0-2)	basal ganglia, posterior parietal region
P5	74 (M)	non-TBI	24	UWS	sham/active	2 (0-0-0-1-0-1)	2 (0-0-0-1-0-1)	2 (0-0-0-1-0-1)	2 (0-0-0-1-0-1)	basal ganglia, left thalamus
P6	21 (M)	TBI	1332	MCS	sham/active	9 (1-3-1-1-1-2)	9 (1-3-1-1-1-2)	13 (1-3-5-1-1-2)	8 (1-3-1-1-0-2)	frontal and temporal lobes, thalami, left posterior parietal region
P7	51 (F)	TBI	42	MCS	active/sham	18 (3-3-5-3-1-3)	18 (3-3-5-3-1-3)	15 (3-3-4-3-0-2)	17 (3-3-4-3-1-3)	right frontal lobe
P8	19 (M)	TBI	218	MCS	sham/active	8 (1-3-1-1-0-2)	11 (1-4-2-2-0-2)	8 (1-3-1-1-0-2)	7 (1-2-1-1-0-2)	frontal lobes, hippocampi
P9	64 (M)	non-TBI	28	UWS	sham/active	6 (1-1-1-1-0-2)	7 (1-3-1-1-0-2)	5 (1-1-1-1-0-1)	7 (2-1-1-1-0-2)	left insula, left basal ganglia

P10	68 (F)	non-TBI	39	UWS	active/sham	4 (0-0-2-1-0-1)	4 (0-0-2-1-0-1)	4 (0-0-2-1-0-1)	4 (0-0-2-1-0-1)	bilateral fronto-parieto-temporal areas, right thalamus

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	Title page
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	2-3
	2b	Specific objectives or research questions for pilot trial	3
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	3
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	3
	4b	Settings and locations where the data were collected	1
	4c	How participants were identified and consented	/
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3-4
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	4
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	n/a
Sample size	7a	Rationale for numbers in the pilot trial	/
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	3-4
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	3-4
Allocation concealment mechanism	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	3-4

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3-4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	3-4
	11b	If relevant, description of the similarity of interventions	3-4
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	4
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	/
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	/
	14b	Why the pilot trial ended or was stopped	/
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	See Table I
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	4
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	/
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	4-5
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	4
	19a	If relevant, other important unintended consequences	n/a
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	6-8
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	7-8
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	6-8
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	8
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	n/a
Protocol	24	Where the pilot trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	8
	26	Ethical approval or approval by research review committee, confirmed with reference number	3

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, 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.