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

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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 over the prefrontal cortex in DOC and over the primary motor cortex (M1) in stroke. This pilot study aimed at evaluating 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, 6 minimally conscious state, 5 traumatic etiologies).

Methods and Procedures: One session of tDCS (2 mA for 20 min) and one session of sham tDCS were applied over M1 in a randomized order with a washout period of minimum 24 h and behavioral effects were assessed using the CRS-R. At the group level, no treatment effect was identified on the total score ($p = .55$) and on the motor subscale ($p = .75$). 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.

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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 the 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 left DLPFC for 20 min 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. These positive behavioral effects were however transient (11). Other studies evaluating the effects of prefrontal tDCS applied for a 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 in patients with DOC investigating the beneficial effects of one session of M1 tDCS 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 k Ω 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 min while for the sham condition, the same electrode placement was used but the current was applied for 5 s and then ramped down. The two tDCS and sham sessions were separated by at least 24 h of washout, which was estimated as a time interval long enough (above 90 min) 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 $p < .05$.

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.

At the group level, no carry-over effect was identified ($Z = -1.33$; $p = .22$) and we did not find any significant treatment effect ($Z = -0.62$; $p = .55$; ES = 0.10). Regarding the motor subscale, no significant treatment was observed ($Z = 0.56$; $p = .75$) neither in any other subscale ($p > .05$). There was no significant difference in the CRS-R total scores between the baseline condition and post-stimulation for both active ($Z = -1.73$; $p = .25$) and sham stimulation ($Z = -1.09$; $p = .30$). For MCS subjects only ($n = 6$), no significant treatment effect was identified either ($Z = -0.26$; $p = .89$; ES = 0.06). Regarding the influence of time since injury, no significant correlation between delta active tDCS and days since injury was identified ($t = -0.291$; $p = .778$). 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, a 19-year-old male patient 8-month 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:

Table 1. Demographic data, tDCS allocation, CRS-R total scores and main MRI lesions of 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

(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 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-month 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 afterward. 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).

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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Conflicts of interest

The authors declare no conflicts of interest.

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