A novel closed-loop EEG-tDCS approach to promote responsiveness of patients in minimally conscious state: a study protocol

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A novel closed-loop EEG-tDCS approach to promote responsiveness of patients in minimally conscious state: a study protocol

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ABSTRACT

Transcranial direct current stimulation (tDCS) applied over the prefrontal cortex has been shown to improve behavioral responsiveness in patients with disorders of consciousness following severe brain injury, especially those in minimally conscious state (MCS). However, one potential barrier of clinical response to tDCS is the timing of stimulation with regard to the fluctuations of vigilance that characterize this population. Indeed, a previous study showed that the vigilance of MCS patients has periodic average cycles of 70 minutes (range 57-80 minutes), potentially preventing them to be in an optimal neural state to benefit from tDCS when applied randomly. To tackle this issue, we propose a new protocol to optimize the application of tDCS by selectively stimulating at high and low vigilance states. Electroencephalography (EEG) real-time spectral entropy will be used as a marker of vigilance and to trigger tDCS, in a closed-loop fashion. We will conduct a randomized controlled crossover clinical trial on 16 patients in prolonged MCS who will undergo three EEG-tDCS sessions 5 days apart (1. tDCS applied at high vigilance; 2. tDCS applied at low vigilance; 3. tDCS applied at a random moment). Behavioral effects will be assessed using the Coma Recovery Scale-Revised at baseline and right after the stimulations. EEG will be recorded throughout the session and for 30 minutes after the end of the stimulation. This unique and novel approach will provide patients' tailored treatment options, currently lacking in the field of disorders of consciousness.

Keywords: transcranial direct current stimulation; minimally conscious state; EEG; vigilance; spectral entropy

INTRODUCTION

A severe injury to the head causing relevant brain damage can lead to an episode of coma (i.e., a state of complete absence of awareness and wakefulness), evolving either to brain death, full recovery or partial recovery with prolonged states of altered consciousness commonly referred to as disorders of consciousness (DOC). These include the Unresponsive Wakefulness Syndrome (UWS), previously called 'Vegetative State', and the Minimally Conscious State (MCS) [1,2]. While patients in UWS only demonstrate reflexive behaviors, yet presenting sleep-wake cycles, patients in MCS present fluctuating but reproducible signs of consciousness, such as visual pursuit or response to command [2]. Although significant progress has been made in understanding the neural correlates of DOC [3,4], current treatment options for DOC patients remain very limited [5]. However, recent studies demonstrating the inherent plasticity of the brain suggest a range of therapeutic possibilities, such as deep brain stimulation of the intralaminar nuclei of the thalamus [6], and some pharmacological agents such as amantadine [7], intrathecal baclofen [8] and zolpidem [9,10], that can improve behavioral signs of consciousness in some DOC patients. During the last 20 years, research on neuromodulation methods such as transcranial direct current stimulation (tDCS) have flourished, as they represent a safe, cost-effective and straightforward technique that can be easily integrated in rehabilitation programs. For DOC, a seminal randomized controlled trial applied 2 mA tDCS over the left dorsolateral prefrontal cortex (DLPFC) for 20 minutes in 30 MCS patients (acute and chronic) and showed positive effects on the level of consciousness, as measured by the Coma Recovery Scale-Revised (CRS-R) [11]. Further trials confirmed clinical effects (as measured by behavioral improvements observed on the CRS-R), even if moderate, of tDCS applied over the DLPFC, especially for MCS patients [12–17]. However, the clinical effects seem inconsistent as several

trials showed no relevant behavioural improvements using the same type of montage [18–20] or multichannel montages [21].

Regarding the electrophysiological effects of tDCS in DOC, several works report significant electroencephalography (EEG) changes following active stimulation (versus sham); both power and connectivity increases were described in the alpha and theta bands [19,22]. The relationship between power and connectivity changes in these bands and the behavioural improvements remains however intricate [23].

A major challenge in the application of tDCS to DOC patients is the variability in the underlying brain state of individuals, impacting their behavioral response. Indeed, DOC patients typically present fluctuations in vigilance impacting their responsiveness to external stimuli [3,24–28]. Piarulli and colleagues used spectral entropy as measured in resting EEG to highlight the periodicity of fluctuations and suggested that spectral entropy variability in MCS could mirror the aforementioned behavioural fluctuations. The 6 MCS patients explored in this study presented a periodicity of 70 minutes (range 57-80 minutes), which could be comparable to the fluctuations in attention observed in healthy controls, while patients in UWS did not present this type of periodicity [28]. Other studies confirmed that EEG spectral entropy reflects the level of consciousness as well as the level of vigilance [29,30]. A key component to tDCS responsiveness might thus be the timing of interventions with respect to the vigilance level, which could explain the inconsistent rate of responders reported in previous trials. The administration of tDCS during specific time windows (i.e., periods of low or high vigilance) could influence its clinical efficacy in MCS patients, since it is known that the positive effects of tDCS are dependent on the brain state [31,32]. To this end, recent advances in tDCS software and hardware enable the implementation of a closed-loop set-up by complex computations performed in real-time. Proof-

of-concept studies showed the efficiency of such approaches using EEG patterns to trigger tDCS in both animal models of epilepsy [33] and healthy subjects [34]. Using this technology to target specific levels of vigilance when applying tDCS in DOC patients could provide insight in the patterns of responsiveness and optimize future applications. This type of approach has not been reported in the literature for DOC patients yet.

The proposed research will test a closed-loop system using EEG-vigilance measures (spectral entropy) to define the best moment for the application of tDCS in MCS patients, on an individual basis. The aim is to investigate whether tDCS applied during high or low vigilance states is more effective in increasing the level of consciousness than intervention during random vigilance states, as measured by behavioural and electrophysiological metrics. The random vigilance state serves the purpose of the control condition, as it is launched independently of the vigilance state, as opposed to what was usually done in previous clinical trials not taking into account patients' level of vigilance when applying tDCS. Thus, we would expect it to provoke less changes compared to the vigilance-based conditions (low or high), at the behavioural and neurophysiological levels. Our primary outcome parameter will be the changes in behavioural responsiveness as measured with the CRS-R after stimulation. We hypothesize a greater increase in the CRS-R total score as well as a larger number of responders in patients receiving tDCS during high vigilance states, than for the other two conditions. Our secondary outcome parameters will be the changes in power spectra and brain connectivity in the alpha and theta bands. We hypothesize to observe enhanced theta activity and alpha activity following active tDCS applied at high vigilance, compared to tDCS applied at low or random vigilance. We will investigate in an explorative manner whether these EEG changes correlate with behavioural outcomes.

METHODS

Study design

This is a prospective multicentric randomized crossover trial. Ethical approval has been obtained by the local ethics committee. The study is registered on ClinicalTrials.gov (NCT03810079) and will be conducted in accordance with the Declaration of Helsinki and with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. All patients' next of kin or legal representative will provide written informed consent to participate after the procedures, risks, and benefits of the study have been explained.

Population

Patients will be screened through our institutional hospital and university databases. Inclusion criteria are as follows: 1) stable diagnosis of MCS provided by the inpatient specialized facility medical staff or by the patient's physician. The stable diagnosis of MCS will be confirmed by the investigators on at least 2 additional CRS-R performed within 1 week prior to tentative inclusion. The MCS condition must be due to acquired brain injury; 2) adult (18 years old – 65 years old); 3) French, English or Dutch-speaking; 4) at least 3 months post injury and; 5) central nervous system-active medication stable for at least a week. Exclusion criteria will be as follows: 1) open craniotomies; 2) ventriculo-peritoneal shunt under the stimulated area (prefrontal cortex); 3) pacemaker; 4) ion channel blockers medication, 5) metallic cerebral implants and; 6) severe medical condition(s) that might influence clinical diagnosis or EEG

activity (e.g., severe hepatic insufficiency, renal failure, or sub-continuous or abundant epileptiform discharges on standard EEG recordings).

We conducted an a priori sample size estimation based on the individual CRS-R data relative to the chronic (i.e., >3 months post injury) MCS patients included in our previously published randomized clinical trial testing the effect of a single prefrontal tDCS session [11]. The effect size in favor of the active tDCS treatment for this subsample of 21 patients was 1.03 (mean ± SD of the CRS-R total score difference for the active group: 1.048 ± 1.244; for the sham group: -0.095 ± 0.889). Based on this effect size and a power of 0.90 with an alpha error probability of 0.05, the sample size was estimated at 13 patients. To compensate for the potential amount of dropouts (20% based on our previous experience), we will include 16 MCS patients.

Materials

The tDCS closed-loop system will be the Starstim in its 20 channels version (Neuroelectrics, Barcelona). Starstim hybrid tCS-EEG device enables the sensing of neural activity through EEG and is capable of simultaneously delivering non-invasive tCS stimulation. Starstim's software streams in real-time the sensed EEG using Lab Streaming Layer (LSL) communication protocol [35]. LSL technology provides fast transmission and accurate synchronization and time-stamping of EEG samples.

The Closed-Loop Manager (CLM), a software specifically designed for this closed loop application, receives the EEG streaming and analyzes vigilance levels in real-time. Vigilance is assessed by studying spectral entropy fluctuations over the frontal cortex. This analysis, presented in the Analyses Section, is an adaptation of the one introduced by Piarulli et al. [28] to the real-time and experimental constraints (i.e., nursing interventions, prolonged recording

duration, stimulation triggering) of the present study. CLM monitors vigilance levels at a 1-minute rate and analyzes its fluctuations detecting slope changes in the spectral entropy curves.

CLM is also in charge of remotely interfacing the device to start the tDCS onset at 1) high vigilance states (i.e., increasing positive slope), 2) low vigilance states (i.e., increasing negative slope) or 3) random vigilance states (i.e., states in which the stimulation is launched at a random moment, excluding positive and negative slopes). In order to ensure patient's safety and comfort, the total stimulation dose is limited and the impedance levels at stimulation channels are continuously monitored, aborting stimulation if impedances that do not allow the current to stay constant at its configured value are detected. The system architecture is presented in Figure 1.

Figure 1: Closed-loop hardware and software setting.

Procedures

This study is a randomized controlled study, using a crossover design with three sessions performed on three different days spaced by at least 5 days to allow for an appropriate washout period while constraining the total duration of the whole protocol. The three sessions will be as follows: 1. tDCS applied at high vigilance level; 2. tDCS applied at low vigilance level and; 3. tDCS applied at random vigilance level. The investigators will be blinded to the session allocation as the screen will depict the same information for each session. The randomization of the three sessions order will be conducted by a third party not involved in data collection or analysis, in a 1:1:1 allocation ratio. Each session will consist of an initial behavioral assessment performed by experienced and trained clinicians using the Coma Recovery Scale-Revised (CRS-R – [36]). The CRS-R is a standardized neurobehavioral scale that consists of 23 items organized into six subscales that evaluate arousal, auditory, visual, motor, oromotor/verbal, and communication systems. Each subscale is organized hierarchically, with lower items representing reflexive activities and higher items indicative of cognitively-mediated behaviors. CRS-R reliability and validity have been demonstrated in multiple studies [36–38]. The CRS-R will be administered in the patient's native language as validated French and translated Dutch versions are available [37,39] in addition to the original English one [36].

After a screening EEG stage of 30 minutes to 2 hours to monitor the fluctuations in vigilance levels used to trigger the stimulation, a 20-minutes tDCS stimulation session will be performed. Right after the stimulation, post-intervention assessments of behavior (CRS-R) and neural activity (30-minute EEG) will be conducted to evaluate the effects of the neural stimulation. In the case of the random vigilance stimulation, the 20-min tDCS stimulation session starts randomly (within a 30 to 120 minutes time-window), to ensure that the EEG

monitoring phase is similar across all three stimulation conditions. The experimental protocol is described in Figure 2.

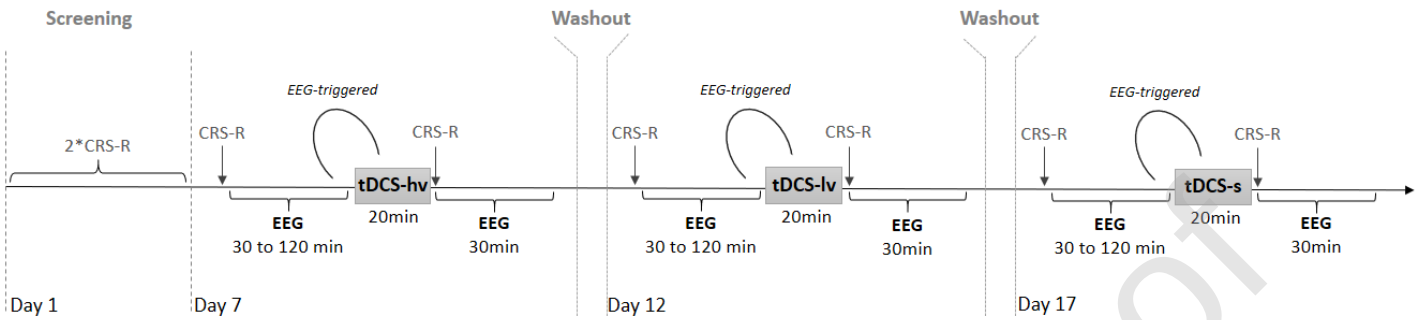

Figure 2: Study protocol timeline. CRS-R = Coma Recovery Scale-Revised; tDCS-hv = high vigilance tDCS session; tDCS-lv = low vigilance tDCS session; tDCS-s = random vigilance tDCS session

Stimulation and EEG assessment

The multi-channel stimulation targets the prefrontal cortex bilaterally and thereby brain executive functions. The stimulation set-up has been optimized to target this area using the Stimweaver algorithm [40]. The optimized montage delivered uses F3, Fz and F4 as anodes, and P7, Cz, P8 as cathodes. Figure 3 shows the placement of the stimulation electrodes (left) along with the induced electric field in the cortex, anodes are represented in red and cathodes in blue. In the figure on the right, both stimulation electrodes (blue) and EEG electrodes (magenta) are represented. This montage corresponds to a standard 19 electrodes in the 10-20 system. It is important to clear up that during non-stimulation intervals all 19 electrodes are used for recording EEG.

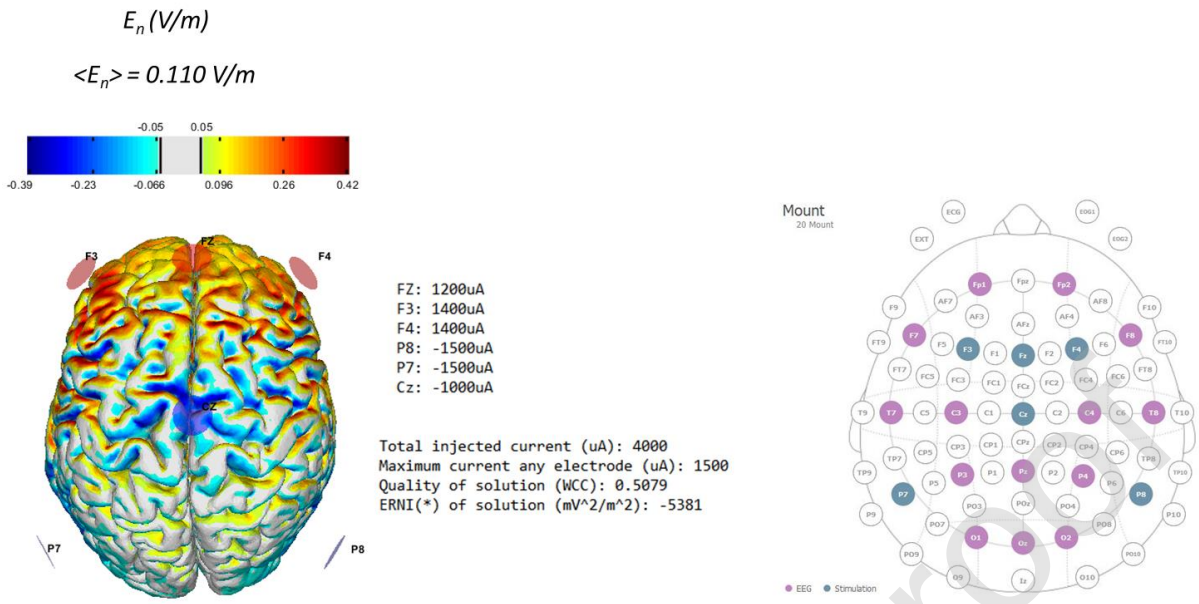

Figure 3: Optimized stimulation montage based on current modelling (left) and montage configuration that will be used for both EEG recordings and stimulation (right)

Stimulations will be applied for 20 minutes using six 3.14 cm2 Ag/AgCl gelled electrodes, each one delivering a constant current as shown in Figure 3 with a 15 seconds ramp up/down period for a smooth current transmission and somatosensory perception. The patients will be kept awake during the stimulation through auditory and/or tactile stimulation.

Data collection and management

Demographic and clinical data relating to the past and current medical history will be collected either via review of the medical records or discussion with family members and clinicians familiar with the case to supplement the data acquired from the medical chart. All information collected during this study will be kept confidential. Data management will comply with the General Data Protection Regulation (EU 2016/679) and a specific information sheet will

inform patients' legal representative of the nature of collected data and their rights regarding this data.

Analyses

Behavioral data

Statistical analyses on the behavioral data will be performed using R software using Kruskal Wallis rank sum tests to calculate the differences in delta CRS-R total scores between the three conditions (high vigilance, low vigilance and random vigilance). In case of significant results ($p < 0.05$), post hoc Dunn tests will be performed for pairwise comparisons. Bonferroni correction will be applied for multiple comparisons. In an exploratory manner, we will also investigate the impact of etiology (i.e., traumatic or non-traumatic) and time since injury on intervention effects using Fisher's test and Spearman correlation, respectively.

Electrophysiological data

The spectral entropy feature calculation algorithm has been implemented from [28] to integrate the CLM real-time platform. After computing the instant value of the Spectral Entropy, it is normalized and smoothed after polynomial fitting with previous samples. Depending on the particular protocol a maximum or a minimum threshold is applied over the smoothed signal to trigger the tDCS. Stimulation at random vigilance levels is achieved by randomly selecting the stimulation starting point between the 30 to 120 min time interval.

For the statistical analysis on the EEG effects of tDCS, the relative power of delta (1 – 4 Hz), theta (4.5 – 8 Hz), alpha (8.5 – 12 Hz) and beta (12.5 – 30 Hz) will be calculated by dividing each frequency band power by the total power of the broadband signal (0.5 – 45 Hz) for each electrode. Changes in power and connectivity values after high, low and random vigilance

stimulations will be analyzed at the group level using t-tests with related cluster permutation tests [41].

DISCUSSION

Patients with DOC need targeted individual interventions to optimize their responsiveness to interventions such as tDCS. This study will be the first of its kind to use a closed-loop EEG-tDCS approach to determine the optimal time window to apply stimulation, based on the patient's own vigilance level. Fluctuations in vigilance represent a well-known challenge for clinicians and researchers working with this clinical population which may prevent optimal diagnostic assessments and therapeutic interventions. Online EEG provides a relatively affordable tool to tackle this issue and to sharpen the use of non-invasive brain stimulation techniques. Several teams already used EEG as an outcome measure to evaluate the effects of tDCS. Schestatsky and colleagues [42] showed that the effects of tDCS, whereas mostly occurring on the underlying cortex, could also be detected in distant connected brain regions. They strongly supported the importance of EEG markers as a trigger for a closed-loop tDCS stimulation protocol. So far, many studies have found consistent EEG changes accompanying tDCS. For instance, Luna et al. found a modulation of alpha power that was different according to the region stimulated and was not correlated with changes in performance [22]. In another recent pilot study, Carrière and colleagues identified a tendency for higher power in the alpha and theta band at the group level after active tDCS and higher connectivity in the alpha band between left and right parietal regions, and in fronto-parietal regions [19]. In a study investigating tDCS with TMS-EEG [20], reduced slow-wave activity and response slope were found following tDCS; both these measures are proxies of cortical bistability and correlated with

high-frequency suppression. This latter component, however, was not found to be modulated by tDCS and the authors hypothesized that reducing slow activity might not be sufficient to translate in a behavioral improvement in consciousness. Bai and colleagues also explored tDCS effects with TMS-EEG and found a global cerebral excitability increase in early time windows and that these neuromodulatory effects significantly changed in spatial and temporal features between patients in MCS and UWS [43].

Neuroimaging and neurophysiological approaches have therefore a relevant role in identifying different response patterns. Regarding EEG brain connectivity, tDCS responders (compared to non-responders) showed higher theta betweenness centrality in theta, using graph theory analysis, indicating that this new feature can be used to predict tDCS response in DOC patients [44]. Metabolic, structural and electrophysiological patterns of responsiveness have thus been investigated in DOC, but the literature is scarce regarding brain-state dependent application of tDCS, although the effects of tDCS are dependent on ongoing cortical activity [45]. Selectively administering tDCS during specific EEG states, in a closed-loop fashion, is therefore a promising approach. For DOC patients, these patterns should reflect the level of vigilance, as these patients are prone to fluctuations, conditioning responsiveness at the bedside [3,25]. The spectral entropy of the frontal EEG signals has been shown to reliably indicate the level of consciousness [29], while periodic fluctuations have only been observed in MCS patients [28]. Applying tDCS at selected vigilance moments can lead to several scenarios which we aim to investigate here. Even though our hypothesis is that tDCS applied at high vigilance is more efficient (as measured with the CRS-R), we might also consider that a period of high vigilance represents a plateau in the cognitive abilities of patients in MCS and that no additional effects of tDCS will be observed. Conversely, while our hypothesis is that tDCS applied at a low vigilance

state will not lead to any relevant effect as the patient is less responsive, it might be that tDCS applied during low vigilance will increase their level of vigilance sufficiently enough to benefit from the neuromodulatory effects translated into relevant behavioural changes. As these scenarios will need to be confirmed or not, we need an additional reference point within our study with this random control condition independent of the patient's vigilance level.

From a feasibility perspective, recent works show that scalp-recorded low-density EEG is able to detect patterns of interest based on a pre-defined algorithm and to trigger tDCS within a milliseconds time frame [34]. The implication of feasibility of brain state-triggered interventions hereby goes beyond the application of tDCS. A couple of studies on transcranial alternating current stimulation (tACS) employed a closed-loop system to modulate specific brain oscillations. During sleep for instance, tACS was triggered during fast spindles to enhance motor memory consolidation [46]. The effects of closed-loop tACS in memory consolidation have been confirmed in other studies [47,48] and this setup has shown therapeutic benefits in sleep quality [49], and tremor suppression [50]. The field of closed-loop application of non-invasive brain stimulation is still subject to important challenges such as development of accurate and optimized triggering algorithms, translation to clinical use and correct identification of inputs to feed the system with. Nevertheless, the potential clinical applications are multiple, and could enrich the therapeutic options for DOC patients, that are still limited. The present study will be the first proof of concept towards this application. It is difficult for DOC patients to actively engage in conventional rehabilitation tasks and thereby prompt their brain to be in an "active state". Using a closed-loop EEG-tDCS approach to monitor patients' vigilance and determine the most appropriate moment to trigger the stimulation represents an important step forward in the management and care of this population.

Declarations of interest: none

The authors have no conflict of interest relevant to the present study to declare.

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