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<u>Πτυχιακή Εργασία με Θέμα:</u>

Η Επίδραση του Διακρανιακού Ηλεκτρικού Ερεθισμού Σε Ασθενείς με Διαταραχή της Συνείδησης με βάση την Κλίμακα Coma Recovery Scale - Revised

<u>The Effect of transcranial Direct Current Stimulation in Patients with Disorders of Consciousness based on their Coma Recovery Scale – Revised Score</u>

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INTRODUCTION

Disorders of Consciousness (DoC)

For the past decades, progress in medicine has lead to an increase in the survival rate of patients who have suffered heavy brain injuries, but unfortunately after the acute phase, they fall into different categories of awareness. A disorder of consciousness (DoC) is a state where consciousness has been affected by brain damage leading to awareness and wakefulness disruptions. While wakefulness subsumes the ability of basic reflexes like eyes opening and coughing, awareness sustains more complex processes such as physical responses. DoC are further categorized according to their severity.

Usually patients with severe brain damage, get to a state known as coma (either medical induced, or due to the nature of the injury) which can last from days to weeks or even a month or more after the onset. During this time the patient has eyes closed, has no sign of being aware and does not respond to either form of stimuli (voices, pain, environment) (Plum and Posner, 1980). After this state, some patients can lose brain function, motor function, or progress in a state known as Vegetative State (VS) (Laureys et al, 2004).

According to the Multi Society Task Force on PVS (1994), VS patients have not regained awareness. While they are unresponsive to external stimuli, they can open their eyes and have preserved vegetative (autonomous) nervous functioning (sleep-wake rhythm. respiration, digestion and thermoregulation), but have no cognitive function such as responding to voices or experience emotions. After 4 weeks in VS, which is a state that lasts longer than a few weeks, a patient will be classified as in a Persistent Vegetative State (PVS). Patients in PVS due to a traumatic brain injury (TBI) may show improvement within up to 12 months from onset, whereas patients in PVS due to non-TBI are not expected to show improvement after 3 months (UK guidlenes: 6 months). When a patient fails to exit this state, his diagnosis is classified as a Permanent Vegetative State. The term vegetative has been a matter of conflict (Shewmon, 2004; Jennett, 2005) and recently alternated with the term Unresponsive Wakefulness Syndrome (UWS) (Laureys, et al., 2010) denoting that these patients are unresponsive (without response to commands) while awake (showing eye opening).

In 2002, Giacino and associates presented a subgroup of patients that were characterized as in VS but did not meet the diagnostic criteria for this state. They underlined the fact that this group had discernible evidence of consciousness since they presented specific behavioral features and according to their findings they have meaningful differences in their outcome. They proceed by naming this state as Minimal Conscious State (MCS), which is the next step after VS for a patient after brain injury or other degenerative or congenital nervous system disorder, and can be more transient than VS. Later, Bruno and associates in 2011, amplified the term MCS by subcategorizing it, based on the complexity of the patients' behaviors;

MCS+ denotes high-level behavioral responses such as command following, whilst MCS- denotes low level behavioral responses such as visual pursuit.

Clinical and neuroimaging studies have shown strong evidence about the differences in consciousness, the cerebral processes and hence the conscious perception of patients in each state (Boly et al, 2008; Owen et al, 2009; Schnakers et al, 2009; Coleman et al, 2009; Monti et al, 2010; Vanhaudenhuyse et al, 2010).

Dolce et al. in 2008 and Luaute et al. in 2010 demonstrate in their work the importance of a proper diagnosis, since the first signs of recovery of consciousness are too often missed and diagnostic errors and their potential effects on treatment can affect the patients' outcomes.

Neuroimaging studies have shown that sometimes patients may be misdiagnosed as VS/UWS while having conscious experience that is only evident through brain responses rather than behavioral responses. Studies with functional magnetic resonance imaging (fMRI) have shown reliable changes in brain activity in some patients diagnosed as VS/UWS when asked to imagine different activities (e.g., playing tennis vs. walking through the house) (Monti, et al., 2010) or when listening to their own name (Di, et al., 2016). However, such techniques require that the patient is transferred to a specialized diagnostic facility and that the patient is able to cooperate at that particular moment.

JFK Coma Recovery Scale – Revised

The JFK Coma Recovery Scale-Revised (CRS-R) is a standardized neurobehavioral assessment scale for the determination of a patients' level of consciousness (Giacino et al., 2004)

CRS-R is based on the diagnostic criteria for disorders of consciousness by the Aspen Workgroup (Giacino et al., 2002) and includes six subscales addressing auditory, visual, motor, oromotor/verbal, communication and arousal functions. The total score ranges between 0 (worst) and 23 (best). For each subscale specific operational criteria distinguish patients in VS from patients in MCS, such that the presence of intentional (non-reflexive) responses on a single subscale can suffice to identify patients in MCS (Estraneo et al., 2015)

The CRS-R has shown superior performance in detecting VS and MCS compared to other scales (Giacino et al., 2004; Schnakers et al., 2006; Schnakers et al., 2008) and is recommended by the Brain Injury–Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine since its use reduced the 30–45% consciousness misdiagnosis reported in previous assessments (Schnakers et al., 2009; Seel et al., 2010).

Portacio et al., (2018) showed in their study that when the assessment through the CRS-R was performed early after a severe brain injury, even in the post-acute phase in the Intensive Care Unit, the results could assist the physicians with the communication process and concluded that CRS-R should be included in the panel of demographic, clinical, neuroradiological and electrophysiological parameters applied in the diagnosis of patients with brain injuries.

Consequently, the CRS-R is a sensitive tool for characterizing the level of consciousness and monitoring neurobehavioral recovery in patients with DoC.

Transcranial Direct Current Stimulation

In many neuropsychiatric disorders variation of cortical excitability and neuroplasticity are considered as important pathophysiological factors. Therefore, the ability to modify cortical activities with the use of non invasive techniques such as non-invasive brain stimulation (NIBS) can be of a great assistance as a therapeutic approach. Transcranial Current Stimulation is one of NIBS techniques.

Bindman et al, in 1964, were the first to show that neural activity and cortical excitability in anesthetized rats could be modified by the application of direct current on the sensorimotor cortex, with effects that could persist for hours after the end of stimulation, depending on stimulation polarity. Rush and Driscoll in 1968 and later Dymond et al. in 1975 and Lolas in 1977, managed to achieve physiological and functional effects by inducing a sufficiently large transcranial current in both healthy subjects and patients suffering from psychiatric diseases. Since it was not possible for them to also assess the heterogeneous effects of their method, the technique was left behind until 1998 when Priori et al. and Nitsche and Paulus (2000), started to explore the use of tDCS as a tool to modulate human brain activity and its physiological effects.

It has been shown from early 60s that tDCS can locally affect the resting membrane potentials of neurons towards depolarization or hyperpolarization with respect to the current flow direction in relation to the axonal orientation (Bindman et al., 1962, 1964; Purpura and McMurtry, 1965; Gorman, 1966). Anodal tDCS can increase the excitability of the underlying cortex, when on the other hand, cathodal tDCS decreases it when it is delivered to the motor cortex of healthy subjects (Nitsche and Paulus, 2000). Furthermore, studies showed that short duration stimulation can be sufficient to induce excitability changes without outlasting the stimulation period, whereas a longer stimulation period can induce excitability changes that are lasting for one hour or even more (Priori et al., 1998; Priori, 2003; Nitsche and Paulus, 2000; 2001, Nitsche et al., 2003b).

Several studies describe the connectional effects of tDCS at a non local level. Neuronal networks can respond to DC fields in a more sensitive matter than single neurons (Francis et al., 2003), whilst various cortical and subcortical networks can be interfered with tDCS activities in terms of functional connectivity and synchronization. This has been examined with primary motor cortex (Polanía et al., 2011a,b, 2012), the prefrontal cortex (Keeser et al., 2011a), and during slow wave sleep (Marshall et al., 2004). For what is more, tDCS can also have non synaptic effects since the modulation of the resting membrane potential do not only happen at the synaptic level but to the whole axons as well. This last effect can contribute to the long lasting after effect of tDCS (Ardolino et al., 2005). At a cellular level, alterations in the conformation and the function of various axonal molecules when exposed to DC fields can be responsible for the non synaptic mechanisms of tDCS (Jefferys, 1995).

tDCS could additionally cause changes in non neuronal tissues of the brain like endothelial cells, lymphocytes and glial cells (Ruohonen and Karhu, 2012). These non neuronal effects could be responsible for the therapeutic action of tDCS, but more studies are needed for these to be proved.

Ultimately, tDCS involves the application of a weak direct current, typically through two electrodes inside saline-soaked sponges into the cerebral cortex. Although tDCS does not induce neuronal action potentials, it can affect the resting potential of the neuronal membrane. Anodal (positive) tDCS has excitatory effects, and cathodal (negative) tDCS has inhibitory effects on the underlying cortex. There are no major side effects of tDCS when applied in the existing studies (Zhang and Song, 2018). Some studies have reported skin lesions, slight burning or mild pain at the area under the electrode (Kessler et al, 2012)

In recent years, tDCS has been used as a novel and safe non-invasive therapeutic approach modulating activity of cortical networks in patients with Alzheimer’s disease, stroke or depression (Brunoni et al, 2014; Khedr et al, 2014; Jacquin-Courtois S, 2015; Peters et al, 2016)

tDCS in DOC

Angelakis et al in 2014 were the first to illustrate in their work how tDCS in patients with DoC can affect their recovery. According to their work, there was clinical improvement for patients in an MCS state immediately after treatment. Moreover, there was a patient who received a second round of tDCS after 3 months of his initial participation and who showed a further improvement. On the other hand, no patient in UWS showed any improvement after the intervention.

Later in 2014, Thibaut et al, presented a sham controlled randomize double-blind study where they examined how tDCS can affect the CRS-R score after one session. They concluded that tDCS may transiently improve signs of consciousness in MCS following severe brain damage. In 2017 Thibaut and colleagues had the chance to corroborate their results regarding MCS patients in a randomized double blind sham controlled crossover study since they stimulate for 5 consecutive days.

The following year, in 2015, Naro et al published their work regarding the identification of electrophysiological parameters, by means of a transcranial magnetic stimulation approach, which might potentially express the presence of residual networks sustaining fragmentary behavioral patterns, even when no conscious behavior can be observed. They applied an anodal transcranial direct current stimulation (a-tDCS) protocol over the orbitofrontal cortex and concluded that tDCS could be useful in identifying residual connectivity markers in patients who were clinically defined as in a UWS, who may lack of purposeful behavior as a result of a motor-output failure.

In 2016 they investigated the EEG changes after one single session of tACS (transcranial Alternate Current Stimulation) and tRNS (transcranial Random Noise Stimulation) in DoC patients. (Naro et al, 2016) They concluded that neither tACS nor tRNS induced significant CRS-R changes or side-effects (either during or after the entire experimental session). On the other hand, tACS induced evident changes in some parameters in all the MCS patients, and, notably, in some UWS individuals, whereas tRNS was ineffective. Nonetheless, tACS aftereffects were different according to the site of stimulation.

Another team from Italy (Estraneo et al, 2017), published their work in 2017 in which they aimed to evaluate the effect of tDCS in patients with prolonged DOC. In their work they observed that there were small changes of patients' conditions after the first tDCS session and immediately after the 5 active stimulations. Nevertheless, they concluded that repeated tDCS did not exert remarkable short-term clinical and EEG effects in patients with prolonged DOC.

Zhang et al in 2017 tried to assess the effects of repeated tDCS in patients with prolonged DOCs by Coma Recovery Scale-Revised (CRS-R) score and event-related potential (ERP). Using a sham-controlled randomized double-blind design, 26 patients were randomly assigned to either a real or sham stimulation group. The patients in the real stimulation group underwent 20 anodal tDCS sessions of the left dorsolateral prefrontal cortex (DLPFC) over 10 consecutive working days. They came to the conclusion that there were significant improvements again in MCS patients within attention resource allocation as it was reflected from the P300 amplitude.

Moreover, another team from China brought to fruition their research about the modulation of cortical excitability from tDCS in patients with DoC (Bai Y et al, 2017). According to their research, tDCS could effectively modulate the cortical excitability of patients with DoC, with different kind of changes in MCS and UWS patients.

Based on previous studies, we expected that patients in a MCS would show clinical improvement after multiple tDCS sessions, while patients in a UWS might show improvement with a larger number (in comparison to previous studies) of tDCS sessions. Moreover, it was hypothesized that patients who were in a DoC due to TBI would show greater improvement than non-TBI patients. Similarly, it was hypothesized that patients who were in a MCS before treatment would show greater improvement than patients who were in a UWS. Likewise, it was also hypothesized that time since onset of DoC would be inversely related to improvement.

METHODS

Participants

Thirty patients (24 males, mean age: 26.5±11.44 years) were enrolled in our study. Ten of them were classified as in a UWS, and 20 as in a MCS, based on their CRS-R. Six patients with TBI were in DOC for less than 10 months and one patient with anoxic encephalopathy was in DOC for less than 6 months, whereas all the rest were chronic patients (more than 6 months for anoxic cases, more than 12 months for TBI cases). Time between brain insult and participation varied with a mean of 4.32±5.37 years. The patients had undergone neurological examination, neuropsychological evaluation, brain imaging (MRI/CT and PET), EEG studies, and sleep studies. For the clinical assessment of the patients, the Greek translation of the CRS-R was used. The study protocol was approved by the Internal Review Board of Evangelismos Hospital and all the legal guardians of the participants had signed an informed consent form.

Procedure

tDCS was applied to all patients. Each tDCS session was performed at the patient's bedside (hospital or home residence). The session time was 30 minutes at 2 mA with the anodal electrode placed over C3 (circular rubber 25cm^2, with sponge cover soaked in saline) and the return over AF8 (rectangular rubber 35cm^2, with sponge cover soaked in saline) (positions of the 10/20 international electroencephalography system). The placements were decided since stimulation of those areas could improve motor function (by stimulation of the primary sensorimotor cortex). The study was carried out with a portable stimulation system (Starstim, Neuroelectrics). IRB approval was obtained before the beginning of the trials.

Although patients differed in their supportive medical treatment (eg, whether they received antiepileptic medication; had an intrathecal baclofen pump to reduce spasticity; had a hydrocephalus shunt; or had a gastrostomy for feeding), these conditions were kept stable throughout participation to minimize confounding factors. Stimulation included 4 consecutive weeks of five 30-minute tDCS sessions, 1 per day (Monday to Friday). Each patient was assessed 1 week before and after the stimulation period with the JFK Coma Recovery Scale-Revised (CRS-R).

Statistical Analysis

Statistical analysis was performed using the SPSS version 25.0 (SPSS, Chicago, IL, USA). The main dependent variable was the CRS-R score (CRS-R), and the main independent variable was tDCS treatment (2 levels: pre vs. post tDCS). The data analysis included the following between-subjects factors: cause of DoC (REASON: TBI vs. non-TBI), DoC state before treatment (STATE: MCS vs. UWS). Moreover, it included time in DoC (MONTHS: number of months) as a covariate. A repeated measures ANOVA based on the GLM was performed to compare the CRS-R score before vs. after tDCS, and to assess the influence to this effect of the other independent variables (REASON, STATE, and MONTHS) (see last paragraph of the Introduction for the rationale).

RESULTS

There was an overall significant increase in CRS-R score for all patients (test of within subjects effects, CRS-R $F=7.478$, $p<0.05$) after tDCS treatment. There was no significant interaction of REASON with CRS-R ($F=0.585$, $p>0.05$). There was no significant interaction of STATE with CRS-R ($F=1.260$, $p>0.05$). There was no significant interaction of MONTHS with CRS-R ($F=2.514$, $p>0.05$) (see table 1, and Figure 1).

Table 1.

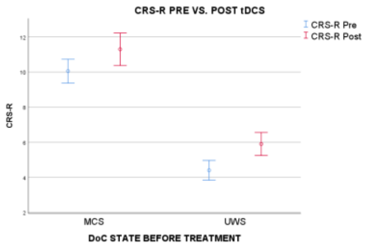
Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	CRSR	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
CRSR	Linear	25.061	1	25.061	7.478	.011	7.478	.748
CRSR * MonthsfromOnsettoProtocol	Linear	8.424	1	8.424	2.514	.125	2.514	.332
CRSR * REASON	Linear	1.960	1	1.960	.585	.452	.585	.114
CRSR * STAGEPRE	Linear	4.223	1	4.223	1.260	.272	1.260	.191
CRSR * REASON * STAGEPRE	Linear	1.055	1	1.055	.315	.580	.315	.084
Error(CRSR)	Linear	83.776	25	3.351				

a. Computed using alpha = .05

Figure 1.


CRS-R PRE VS. POST tDCS
CRS-R Pre
CRS-R Post
CRS-R
12
10
8
6
4
2
MCS
UWS
DoC STATE BEFORE TREATMENT

DISCUSSION

Our results showed that multiple sessions of anodal tDCS over the left primary motor cortex improved the clinical status of patients with DoC. While our results replicate previous findings of clinical improvement in patients with DoC with repeated sessions of tDCS (Angelakis, et al., 2014; Thibaut, et al., 2017; Estraneo, et al., 2017), this is the first study to report statistically significant improvement in a group of patients who were in a UWS. One explanation for this new finding may be the cumulative effects of increased amount of stimulation. In the present study, we stimulated for a longer period of time and for more sessions then in previous studies. We applied tDCS for 30 minutes and we provided 20 or more sessions, while older studies have stimulated for 20 minutes, and for a maximum of 10 sessions. Some researchers have hypothesized that repeated tDCS daily could improve corticocortical excitability and thus strength the stimulation effect (Antal et al, 2010). In another study from Alonzo et al in 2012, it was shown that tDCS induced greater motor evoked potential amplitude in healthy subjects when it was delivered every day, a finding that could suggest superior effects after cumulative sessions. Furthermore, the excitability of NMDA receptors is increased during tDCS, a fact that can contribute to the increased effects of repeated stimulation resulting to the improvement and strengthen of the cortical excitability within the stimulated areas (Nitsche et al, 2003; 2011).

Similarly, it remains to be shown whether multiple tDCS session within each day are more efficient than single sessions per day. Zhang et al (2018) explored how the patients could react to double intervention since they administered tDCS (anode placed over the left DLPFC and the cathode placed over the right supraorbital region) twice a day for 20 min per session for 10 consecutive working days.

Another question that remains open is the optimal location for applying tDCS in patients with DoC. All existing studies (including the present one) have applied a standardized protocol for all patients, either left DLPFC or left M1. Since both electrode placements – left DLPFC (Angelakis, et al., 2014; Thibaut, et al., 2014; Thibaut, et al., 2017; Estraneo, et al., 2017) and left M1 (Angelakis, et al., 2014; and the present study) – show clinical benefits in patients with DoC, it remains to be tested in future research whether one or the other placement is more efficient. Moreover, although current studies agree that tDCS of the left frontal cortex may benefit some patients with DoC, there are no data yet to show possible benefits of tDCS in the right hemisphere, or even individualized tDCS based on each patient's brain damage (possibly according to neuroimaging).

Finally, the present study showed that multiple sessions of tDCS do not present immediate side effects in patients with DoC. During our study there was no sign of potential pain to the patients, or any sign of epileptic episodes. It has been shown that tDCS is a low risk technique (Brunoni et al., 2011; Fregni et al., 2015). Thus, based on this and on previous studies, it could be suggested that tDCS is safe in daily clinical practice. Nevertheless, further studies need to be performed to assess the long-term effect of repeated tDCS in patients with severe brain injury.

Limitations

It should be noted that due to recruitment difficulties, we could not be very selective with our participants. This may have hidden possible effects of cause of DoC, DoC state, and time since onset on treatment. Future studies could attempt to employ a more homogeneous sample of participants in respect to other factors such as age, type and location of brain insult, or pharmaceutical treatment (e.g., anti-epileptic drugs).

Another limitation of our study was that we only had one follow up assessment after 1 week. It is necessary for future studies to conduct follow-up testing at longer intervals to determine whether treatment effects can last more than 1 week after treatment.

Lastly, the number of participants was not large enough to support statistical power for multiple factors/variables; therefore, multicentric and international studies will help replicate and confirm the results in a larger sample of patients.

Larger, controlled, randomized, blinded and prospective studies are needed. Some issues that must be addressed are what are the long-term effects of the protocol or what will be the effects of a more long term tDCS protocol; what would be the effects of tDCS coupled with other forms of therapy such as occupational or physical therapy. Lastly, from a neuroscientific point of view, there is a need for studies that combine neurophysiological and/or functional neuroimaging techniques with non-invasive brain stimulation to further evaluate the neuro-modulatory effects of stimulation in patients with DoC.

Conclusions

In conclusion, tDCS applied over the left primary motor cortex seems to be safe in the short-term, and shows clinically significant improvements by enhancing the level of consciousness in some chronic patients with DoC. The combination of the presentation of the positive effects with the absence of adverse effects can produce an interesting rehabilitation tool relatively inexpensive and easy in its use that can improve the recovery of patients with DoC.

Disorders of consciousness, such as the Minimally Conscious State (MCS) and the Unresponsive Wakefulness Syndrome (UWS), are highly challenging clinical conditions for treatment. A few recent studies have shown that there is a possibility for clinical improvement of these patients. Still, further investigation is needed in order to identify how this treatment can become a standard clinical practice of rehabilitation.

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