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ORIGINAL ARTICLE

Transcranial Direct Current Stimulation Effects in Disorders of Consciousness

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Abstract

Objective: To assess the efficacy of transcranial direct current stimulation (tDCS) on improving consciousness in patients with persistent unresponsive wakefulness syndrome (UWS) (previously termed persistent vegetative state [PVS]) or in a minimally conscious state (MCS).

Design: Prospective, case series trial with follow-up at 12 months.

Setting: General and research hospital.

Participants: Inpatients in a PVS/UWS or MCS (N=10; 7 men, 3 women; age range, 19–62y; etiology: traumatic brain injury, n=5; anoxia, n=4; postoperative infarct, n=1; duration of PVS/UWS or MCS range, 6mo–10y). No participant withdrew because of adverse effects.

Intervention: All patients received sham tDCS for 20 minutes per day, 5 days per week, for 1 week, and real tDCS for 20 minutes per day, 5 days per week, for 2 weeks. An anodal electrode was placed over the left primary sensorimotor cortex or the left dorsolateral prefrontal cortex, with cathodal stimulation over the right eyebrow. One patient in an MCS received a second round of 10 tDCS sessions 3 months after initial participation.

Main Outcome Measure: JFK Coma Recovery Scale-Revised.

Results: All patients in an MCS showed clinical improvement immediately after treatment. The patient who received a second round of tDCS 3 months after initial participation showed further improvement and emergence into consciousness after stimulation, with no change between treatments. One patient who was in an MCS for <1 year before treatment (postoperative infarct) showed further improvement and emergence into consciousness at 12-month follow-up. No patient showed improvement before stimulation. No patient in a PVS/UWS showed immediate improvement after stimulation, but 1 patient who was in a PVS/UWS for 6 years before treatment showed improvement and change of status to an MCS at 12-month follow-up.

Conclusions: tDCS seems promising for the rehabilitation of patients with severe disorders of consciousness. Severity and duration of pathology may be related to the degree of tDCS' beneficial effects.

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Comatose patients who survive brain trauma because of the ongoing improvements of intensive care medicine either begin to recover consciousness within several days or weeks, or enter an unresponsive wakefulness syndrome (UWS), previously known as a vegetative state (VS).[1] VS/UWS is characterized by wakefulness without awareness.[2] Unlike a coma that does not become chronic, a VS/UWS may progress to a long-lasting condition, usually with irreversible results.[3] The term persistent vegetative state (PVS) was introduced by the Multi-Society Task Force[4] to classify the irreversibility of the condition beyond 12 months after traumatic brain injury (TBI) and beyond 3 months after non-TBI. Nevertheless, even after these delays, some patients may exceptionally recover consciousness.[5,6] A distinct condition that can emerge after a coma was defined by Giacino et al[7] as the minimally

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conscious state (MCS), where consciousness is severely altered, but definite—although minimal—behavioral evidence of self- or environmental awareness is demonstrated. Recently, this term has been subcategorized into minimally conscious state minus (MCS−) and minimally conscious state plus (MCS+) based on the level of nonreflexive responsiveness of these patients, and this subcategorization has been validated with [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) showing distinct patterns of cerebral metabolism across the 2 categories (MCS− and MCS+).[8] MCS− is characterized by noncommunicative responses to meaningful stimuli (eg, visual pursuit, localization of noxious stimulation, and/or smiling/crying in contingent relation with external stimuli), whereas MCS+ is characterized by command following.

Patients who are in a PVS/UWS or MCS typically receive peripheral treatment (eg, physical therapy, speech therapy) in addition to any drugs administered for controlling seizures; they usually breathe through a tracheostomy and are fed through a gastrostomy. No central nervous system treatment is available for these conditions, apart from the surgical insertion of an intrathecal baclofen pump, a device to inject baclofen (a gamma-aminobutyric acid agonist) directly into the cerebrospinal fluid in order to reduce spasticity.[9] It has been reported that a small number of patients who were in a PVS/UWS for <12 months recovered after insertion of an intrathecal baclofen pump.[10] Moreover, there are 2 reports of thalamic deep brain stimulation in patients with PVS/UWS or MCS showing neurobehavioral gains.[11,12]

Transcranial direct current stimulation (tDCS) uses the administration of a relatively weak constant electrical current flow via scalp electrodes into the cerebral cortex. The technique has been studied since the 1960s with animals and humans, when it was concluded that anodal polarity enhanced neuronal activity, whereas cathodal polarity reduced neuronal activity.[13-15] Although tDCS does not induce neuronal action potentials, it affects the resting potential of the neuronal membrane.[16] Anodal (positive) tDCS has excitatory effects, whereas cathodal (negative) tDCS has inhibitory effects on the underlying cortex.[17,18] There are no known side effects of tDCS when applied as in the present study. Some studies[19,20] have reported skin lesions at the area under the electrode when tap water was used instead of saline solution in order to minimize skin discomfort.

Studies with humans have shown tDCS effects in motor and cognitive performance,[21-28] sensory perception,[29] electrophysiological measures such as motor-evoked potentials[18,30-32] or event-related potentials,[33,34] electroencephalographic visual-evoked potentials or pain-evoked potentials,[35-37] and electroencephalographic amplitude[30,38] and brain responses measured by functional magnetic resonance imaging (fMRI)[39-41] or by FDG-PET.[42] Using proton magnetic resonance spectroscopy after 30 minutes of tDCS, Clark et al[43] found increased concentrations of glutamate and glutamine at the right parietal cortex underlying the anodal electrode. They used a noncephalic cathodal electrode, and there were no changes at the homologous (left) hemispheric area.

There is evidence of motor improvement after anodal stimulation of the primary motor cortex in patients with stroke. Hummel et al[44,45] found shortened reaction times, improved pinch force, and improved functional hand motor skills in the paretic hand of patients with a history of ischemic cerebral infarct (1y poststroke) after 20 minutes of 1mA anodal stimulation over the hand area of the affected hemisphere's primary motor cortex, via a 25cm^2 electrode, with the cathode over the contralateral orbit. Boggio et al[46] found improved functional hand motor skills in patients with chronic, subcortical stroke after 20 minutes of 1mA anodal stimulation over the hand area of the affected hemisphere's primary motor cortex, or with cathodal stimulation over the hand area of the unaffected hemisphere's primary motor cortex, with the alternative pole over the contralateral supraorbital area, via 35cm^2 electrodes. These researchers found cumulative effects after 5 consecutive days of cathodal stimulation over the hand area of the unaffected hemisphere's primary motor cortex. Moreover, studies have shown that anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC) leads to cognitive improvement in verbal fluency[26] and working memory[25,47] in healthy volunteers, and to significant reduction of depressive symptoms in patients with major depression.[48]

tDCS shows regional cerebral blood flow (rCBF) changes when compared with sham stimulation, but there is no clear effect of tDCS current polarity on rCBF. Studies with fMRI or positron emission tomography show increases in rCBF in areas close to the anodal electrode,[41] rCBF decreases in areas close to the cathodal electrode,[39] or rCBF increases in widespread areas, irrespective of current polarity.[42]

Although wakefulness (in this case arousal from coma) is controlled by subcortical brain areas located in the brain stem, hypothalamus, thalamus, and basal forebrain,[49-51] awareness is controlled in brain areas located in the cortex.[52] Internal (self-) awareness is controlled by midline cortical areas (precuneus, anterior and posterior cingulated cortex, mesiofrontal parahippocampal areas), whereas external (environmental) awareness is controlled by lateral frontoparietal cortical areas.[53]

In the current study, tDCS was applied in patients in a PVS/UWS or MCS. Based on the literature, 2 alternative electrode placements were used (F3 and C3 positions of the 10/20 international electroencephalography system), given their repeated success in eliciting behavioral, cognitive, and emotional results with anodal tDCS. The rationale was to either stimulate areas of the primary sensorimotor cortex to improve motor function, or activate the left DLPFC to improve cognitive function. Given that larger effects have been seen by (1) higher current, (2) prolonged session time, and (3) multiple sessions,[46] and because of the severity of the patients' condition, the maximum amount of stimulation that has been shown to be safe was used.

List of abbreviations:

CRS-R	**Coma Recovery Scale-Revised**
DLPFC	**dorsolateral prefrontal cortex**
FDG-PET	**[^{18}F]-fluorodeoxyglucose positron emission tomography**
fMRI	**functional magnetic resonance imaging**
MCS	**minimally conscious state**
MCS−	**minimally conscious state minus**
MCS+	**minimally conscious state plus**
PVS	**persistent vegetative state**
rCBF	**regional cerebral blood flow**
TBI	**traumatic brain injury**
tDCS	**transcranial direct current stimulation**
UWS	**unresponsive wakefulness syndrome**
VS	**vegetative state**

Methods

Ten patients (3 women) took part in the study. Three patients were classified as in an MCS and 7 as in a PVS/UWS, based on the JFK