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Cortical connectivity modulation induced by cerebellar oscillatory transcranial direct current stimulation in patients with chronic disorders of consciousness: A marker of covert cognition?

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HIGHLIGHTS

- Fronto-parietal network (FPN) functional connectivity was shaped by means of oscillating transcranial direct current stimulation.
- Our approach highlighted a potential to cognition in patients with chronic disorders of consciousness.
- Cerebellar stimulation improved the awareness level in minimally conscious state patients.

ABSTRACT

Objective: Although some patients suffering from unresponsive wakefulness syndrome (UWS) may retain some capacity for covert cognition, it is difficult to directly demonstrate this property by means of tasks needing patient active cooperation and preserved top-down attention processes. Instead, specific passive paradigms may allow identifying a residual θ and γ band functional connectivity within fronto-parietal networks (FPN), which may sustain covert cognitive processes.
Methods: We attempted to highlight such networks in a sample of minimally conscious state (MCS) and UWS patients by means of a cerebellar 5 Hz oscillatory transcranial direct current stimulation (otDCS), in order to modulate the FPN functional connectivity.
Results: We found a FPN θ and γ power modulation and coherence increase, which were paralleled by a transient coma recovery scale-revised score amelioration, only in MCS individuals.
Conclusions: Our data show a functional link between the FPN coherent θ and γ oscillations and the cerebellar-cerebral output. Moreover, our data highlighted a residual FPN functional connectivity, which is a fundamental prerequisite for objectifying every aware processes and the potential to cognitive processes (covert cognition).
Significance: Our otDCS cerebellar-cerebral connectivity modulation may be a useful approach in improving chronic disorders of consciousness differential diagnosis and ameliorating the level of consciousness.

1. Introduction

Patients suffering from chronic disorders of consciousness (DOC) show a dissociation between the two main components of consciousness, i.e. wakefulness and awareness. In particular, unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS) patients are awake but exhibit no or limited and fluctuant behavioral signs of awareness and mentation, respectively (Laureys, 2005). Although there are no univocal brain regions supporting awareness and cognition, it has been proposed that the level of awareness impairment may depend on the severity of connectivity deterioration within complex cortico-cortical and thalamo-cortical network (Vanhaudenhuyse et al., 2010; Crone et al., 2011; Rosanova et al., 2012; Fernández-Espejo et al., 2012; Thibaut et al., 2012; Laureys et al., 1999; Tshibanda et al., 2009). In particular, a complex fronto-parietal network (FPN) has been proposed to oversee the adaptive behavioral control according to cognitive demands (Cocchi et al., 2013, Cole et al., 2013;

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Dosenbach et al., 2008; Harding et al., 2015; Corbetta and Shulman, 2002). Noteworthy, many other areas outside the FPN may contribute to awareness and cognition, including subcortical areas (Di Perri et al., 2013; Zeng et al., 2013). In fact, a deep subcortical hyper-connectivity, particularly involving the ventral tegmental area, hippocampus, and cerebellum (paralleled by a FPN and thalamo-cortical disconnectivity) has been found to be significantly correlated to awareness impairment in DOC patients (Di Perri et al., 2013). Cerebellum has been suggested to be involved in perception, cognition, and emotion processes, although it has not been shown to be essential for awareness generation and maintenance (D'Angelo and Casali, 2013).

Functional neuroimaging studies in human beings in resting state have found a temporal coherence within FPN (i.e. a functional connectivity) concerning some brain oscillatory activities (Cole and Schneider, 2007; Power et al., 2011), which promptly change in response to behavioral demands, thus being a marker of cognitive activity (Prado et al., 2011). Brain oscillations can be investigated by means of electroencephalography (EEG), which can furnish many data concerning the level of cortical information processing and integration, and the changes occurring during switching of awareness levels (Kotchoubey et al., 2005). In particular, the EEG coherence (which is a measure of the degree of association or coupling of frequency spectra between two different time series) provides an estimate of the functional association between two brain regions, and completes the data obtained by power spectrum analyses (Davey et al., 2000). In particular, a θ- and γ-band synchronization within FPN has been proposed to be a signature of the integration of multiple information into unitary percepts (Tallon-Baudry et al., 2001; Sehatpour et al., 2008; Palva et al., 2005) and, thus, of awareness presence and cognitive activity (Perry et al., 2010).

The non-invasive perturbation of brain oscillatory activity and of FPN functional connectivity have been demonstrated as extremely useful in order to better understand cognitive process (e.g. Fröhlich et al., 2015; Chen et al., 2013), with particular regard to the covert ones, i.e. those not resulting in discernible motor or verbal responses (Cruse et al., 2012; Nachev and Hacker, 2010). DOC patients mostly have a deterioration of large-scale brain connectivity and top-down attentional processes, with a consequent behavioral impairment (Chennu et al., 2013). Notably, large scale connectivity is a fundamental, but insufficient, component in order to perform purposeful behaviors that can be quantified through appropriate clinical scales, including the JFK Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004). In fact, the preservation of top-down attention (Monti et al., 2010) is also necessary to have such behaviors. Nonetheless, a residual large-scale connectivity may still sustain covert cognitive patterns that are not discernible through clinical scales or active paradigms (both requiring top-down attention), but only by means of passive neurophysiological or neuroimaging approaches. In this regard, particular types of transcranial currents may allow perturbing brain oscillatory activity, including the low-frequency oscillatory transcranial direct current stimulation (otDCS) (Groppa et al., 2010; Marshall and Binder, 2013). Moreover, several non-invasive neurostimulation approaches, including transcranial magnetic stimulation and transcranial electric stimulation, have been employed in shaping the cerebellar-cerebral pathways (Tomlinson et al., 2013).

Interestingly, it has been proposed that cerebellum may modulate θ- and γ-band oscillations within the FPN, especially when involved in cognitive tasks (Popa et al., 2013; Schwarz, 2010; Guggisberg et al., 2008). Such role could be sustained by several cerebello-cortical networks targeting different areas, including prefrontal cortex and basal ganglia, beyond the primary motor area (M1) (Middleton and Strick, 1998, 2000; Hoover and Strick, 1999; Kelly and Strick, 2003). Induced currents within cerebellum are thought to excite or depress Purkinje cells (PC) in a polarity- and frequency-dependent manner, thus affecting the cortical excitability through a synaptic relay probably involving the ventro-lateral thalamus (Nitsche and Paulus, 2011).

Therefore, aim of our study was to investigate the usefulness, safety, and feasibility of a 5 Hz-otDCS protocol applied over the cerebellum in perturbing the FPN connectivity, with regard to θ- and γ-rhythm, in a DOC sample and in a control group of healthy volunteers (HC). We hypothesized that the otDCS could modulate the FPN connectivity in HC, in reason of a link between FPN oscillations and cerebral-cerebellar connectivity, and bring to light a residual FPN connectivity in DOC patients, thus supporting the clinical differential diagnosis between MCS and UWS.

2. Methods

2.1. Subjects

Fourteen DOC patients (10 MCS and 10 UWS) and 10 HC participated to this study. Patients were selected according to the criteria for vegetative state and MCS diagnosis (The multi-society task force on PVS medical aspects of the persistent vegetative state, 1994; Giacino et al., 2002). The exclusion criteria were: pre-existing severe neurological or systemic diseases; critical conditions, such as inability to breathe independently, hemodynamic instability; administration of other modifying cortical-excitability drugs than L-Dopa and baclofen (Table 1); presence of epileptic history, pace-maker, aneurysms clips, neurostimulator, brain/subdural electrodes or other electric/electromechanical devices; EEG burst-suppression pattern. DOC level was assessed through the coma recovery scale-revised (CRS-R) (Giacino et al., 2004), which was daily performed for one month, independently by two DOC diagnosis-skilled neurologists. Detailed demographic and clinical characteristics are reported in Table 1. The Local Ethics Committee approved the present study and written informed consent was obtained from either HC or the legal guardian of each patient.

2.2. Experimental design

The experimental procedure was carried out at bed and on a comfortable reclining chair, respectively in patients and HC. First, we applied the CRS-R arousal protocol in DOC patients, thus administered the CRS-R, and then registered the baseline EEG. Thereafter, we applied a real_ and a sham_otDCS. The two protocols were delivered in random order, one day apart from each other. Both HC participants and the experimenters who analyzed data were blinded to stimulation procedure. We measured the effects of otDCS on EEG immediately after the end of the conditioning protocol ($post_0$), and after 30 ($post_{30}$) and 60 min ($post_{60}$). Fig. 1 summarizes the experimental paradigm.

2.3. CRS-R

CRS-R is a reliable and standardized tool, which integrates behavioral and clinical assessments, and includes the current diagnostic criteria for coma, UWS and MCS, allowing the patient to be assigned to the most appropriate diagnostic category. It consists of 29 hierarchically organized items divided into 6 subscales addressing auditory, visual, motor, oro-motor, communication, and arousal processes. The total score ranges from zero to 23. A score of $\leqslant$2 on the auditory, motor, and oro-motor/verbal subscales and $\leqslant$1 on the visual subscale, and of zero on the communication subscale is consistent with the diagnosis of UWS. Thus, the CRS-R