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Effect of High-Frequency Repetitive Transcranial Magnetic Stimulation on Brain Excitability in Severely Brain-Injured Patients in Minimally Conscious or Vegetative State

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) induces prolonged functional changes in the cerebral cortex in normal conditions and in altered states of consciousness. Its therapeutic effects have been variously documented.
Objective: The aim of this study was to investigate the reactivity of electroencephalography (EEG) and the clinical response in six severely brain-injured patients in an altered state of consciousness (minimally conscious state [MCS] or vegetative state [VS]). EEG rhythm and brain excitability were measured before and after a protocol of high-frequency rTMS.
Methods: All six patients underwent clinical and neurophysiological evaluation before rTMS and immediately thereafter. EEG data in resting state were acquired at the beginning of the exam (T_0), after rTMS (T_1), and 38 min after rTMS (T_2). From these data the power values were computed using Fast Fourier Transform.
Results: rTMS over the motor cortex induced long-lasting behavioral and neurophysiological modifications in only one patient in MCS. No significant clinical or EEG modifications were detected in any of the other patients, except for changes in motor threshold and motor evoked potential amplitude over the stimulated motor areas.
Conclusions: The main finding of the study is the correlation between EEG reactivity and clinical response after rTMS. Reappearance of fast activity and an increase in slow activity were noted in the one patient with transitory arousal, whereas no significant reliable changes were observed in the other patients showing no clinical reactivity.

Background

A persistent vegetative state (PVS) refers to a disorder of consciousness in which severely brain-injured patients remain in a state of wakefulness without detectable awareness. In this extended state of unconsciousness, accompanied by nearly normal cycles of sleeping and waking, the brainstem and thalamus are relatively spared, but cortical functional connectivity is limited or absent. The electroencephalogram (EEG) of PVS patients in a resting state is generally characterized by an increase of slow EEG oscillations (delta and theta rhythms) and a decrease of fast alpha oscillations [1]. In response to sensory inputs, Laureys et al. reported that an electrical stimulation of the median nerve could activate the primary somatosensory cortex, but not higher-order multimodal areas that appear disconnected in vegetative patients [2].

Persistently vegetative individuals have no signs of awareness of themselves or their environment. Some may progress to a permanent vegetative state (VS), generally 3 months after an anoxic brain event and 12 months after brain trauma, while others may progress to a minimally conscious state (MCS), in which integrated but undersustained cortical functions are retained [3,4]. If the disorder

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persists for longer than 12 months after severe traumatic brain injury, the state is generally considered to be immutable and no treatment has been shown to accelerate recovery or improve functional outcome [5,6]. Nonetheless, some studies have shown unexpected preservation of large-scale cerebral networks in MCS patients, a condition characterized by definite behavioral evidence of awareness of self or the environment [7–11].

Neurostimulation to restore cognitive and physical functions is an innovative and promising technique for treating patients with severe brain injury. Deep brain stimulation (DBS) has been proposed as an experimental therapeutic strategy that might produce consistent and sustained effects of maintaining excitatory activity within functionally disconnected forebrain neurons [12]. It is used in treating Parkinson's disease, essential tremor, or depression but it has not been tested in clinical trials. Besides its invasiveness associated with surgical risks and complications, another major barrier to its wider use is the syndromic heterogeneity and variance of subjects who might benefit from DBS. Furthermore, the selection of potential recipients of DBS is limited by the current inability to estimate cerebral function based on bedside examination [13].

Among currently available non-invasive painless stimulation techniques, single-pulse transcranial magnetic stimulation (TMS) has been demonstrated to be effective for assessing motor cortex excitability and the integrity of conduction along the central and peripheral motor pathways. Similarly, repetitive transcranial magnetic stimulation (rTMS) has been shown to induce prolonged functional changes in cerebral cortex in normal conditions and therapeutic effects in different diseases [14–17]. Several studies suggest that the thalamocortical system can be engaged in rapid causal interactions [18–22]. One way to study this phenomenon is to perturb directly a subset of cortical neurons with TMS and monitor the brain's reaction using electroencephalography (EEG) [23–27].

To date, few studies have focused on the use of TMS in patients with impaired consciousness [28,29]. Recent advances in EEG-TMS co-registration have shed new light on EEG reactivity in humans [30–32]. For instance, Babiloni et al. demonstrated a relationship between alpha EEG rhythm and conscious awareness [33]. They showed that the parietal and occipital source power of alpha rhythm was high in the normal subjects, low in the PVS patients who recovered some level of consciousness at 3 months follow-up, and practically null in the PVS patients who did not recover. Their findings suggest that the sources of alpha rhythm are related to the outcome of PVS patients at 3 months follow-up. Corroborating this hypothesis, our recent study reported the reactivity of a single MCS patient after brain stimulation, in which an increase in the alpha band was correlated with functional improvement [34]. Also Louise-Bender Pape et al. reported results of a 10 Hz rTMS protocol applied to a MCS patient. They highlighted the therapeutic effect of rTMS concluding that thirty application of rTMS protocol may promote clinically significant neurobehavioral recovery in chronic severe traumatic brain injury [29].

Generally, in behaviorally awake but unresponsive VS patients, TMS triggers a simple, local slow response that indicates a breakdown in effective connectivity, similar to that observed in unconscious sleeping or anaesthetized patients [35–37]. In contrast, in MCS patients, who show fluctuating signs of non-reflexive behavior, TMS seems to trigger complex activations that sequentially involve distant cortical areas ipsilateral and contralateral to the site of stimulation.

Evidence from electrophysiological studies of stimulation over a healthy primary motor cortex (M1) suggests that there is a progressive increase in the excitability of local circuits during rTMS, but not only. Remote changes in cortical and subcortical activity, including associative regions such as the thalamus, caudate nucleus, and putamen, may be involved in stimulation. The nature of the remote effect of TMS is not well understood. The presumed net facilitatory effect on neural activity in remote regions may be produced by trans-synaptic or direct activation of cortico-cortical, or cortico-subcortical neurons [38].

Hypothesis

On this basis, we hypothesized that rTMS could be a useful means to investigate behavioral responsiveness in MCS patients, with possible implications for non-invasive therapy, since the majority of such patients show a consistent presence of residual network properties underlying the expression of fragmentary behavioral patterns [2,19].

The aim of this study was to investigate EEG reactivity and clinical response in 6 severely brain-injured patients in a state of altered consciousness. EEG rhythms and brain excitability were measured before and after a protocol of high-frequency rTMS.

Methods

Patients

Six patients (5 men, 1 woman; mean age, 48 years, ±standard deviation [SD] 19.4 years) in VS or MCS, admitted to the Neurorehabilitation Center of San Camillo Hospital, Venice, between April and July 2008 or resident in an adjacent nursing home during the same period, met the study inclusion criteria: absence of contraindications to TMS; stability of vital parameters; and >12 months since injury event [4,39]. The clinical characteristics of the enrolled patients are shown in Table 1.

Clinical features were assessed with the Disability Rating Scale (DRS) and the JFK Coma Recovery Scale (JFK CRS-R) [40,41]. The JFK CRS-R scale consists of 23 items in six subscales addressing auditory, visual, motor, oromotor, communication and arousal functions. The CRS-R subscales comprise hierarchically arranged items associated with brainstem, subcortical and cortical processes. The lowest item on each subscale represents reflexive activity, while the highest item represents cognitively mediated behaviors.

Table 1
Clinical profiles.

Case	Age	Gender	Clinical diagnosis	Etiology	MRI findings	Months since injury	DRS
1	70	M	MCS	Hemorrhagic	Right thalamic and intraventricular hemorrhage	48	27
2	37	F	VS	Traumatic	Subdural hematoma and diffuse cortical lesions	34	26
3	67	M	VS	Hemorrhagic	Multifocal bifrontal lesions	31	29
4	29	M	MCS	Traumatic	Multifocal bifrontal lesions	94	24
5	38	M	MCS	Traumatic	Pontomesencephalic lesion	36	23
6	27	M	VS	Hemorrhagic	Right centroparietal hematoma	12	28

DRS = Disability Rating Scale.