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Short Commentary Open Access

# A Short Commentary on Non-invasive Brain Stimulation in Chronic Disorder of Consciousness Differential Diagnosis

**Antonino Naro*** **and Rocco Salvatore Calabrò**

*IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy*

*Corresponding author: Antonino Naro, IRCCS Centro Neurolesi "Bonino-Pulejo" S.S. 113, Contrada Casazza, 98124, Messina, Italy, Tel: +3909060128840; E-mail: g.naro11@alice.it

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**Abstract**

The diagnosis and awareness assessments in chronic disorders of consciousness (DOC) are biased, owing to their reliance on clinical behavioral measures. Indeed, objective tools should be employed with the goal of more precise awareness detection in these patients. To this end, brain stimulation techniques have been developed to demonstrate residual cortical-thalamocortical connectivity patterns sustaining fragment of awareness. This short commentary aims at illustrating the Non-Invasive Brain Stimulation (NIBS) techniques applied to DOC patients. NIBS are promising in helping clinicians to differentiate among DOC patients and to identify residual fragments of awareness within Vegetative State individuals, namely Functional Locked-In Syndrome.

**Keywords:** Chronic disorders of consciousness; Functional locked-in syndrome; Minimally conscious state; Non-invasive brain stimulation; Vegetative state

## Introduction

Chronic disorders of consciousness (DOC), including Minimally Conscious State (MCS) and Vegetative State (VS) [1], are characterized by a deterioration of awareness (i.e., an impairment of purposeful behavioral responsiveness) that arises from severe brain injuries producing multifocal neuronal cell death and inter-area disconnection [2,3]. In summary, awareness impairment depends on a disruption of the basic connectivity patterns within the entire cortical-thalamocortical system (according to the Schiff's mesocircuit model), which are associated with different levels of consciousness [4-6]. The metabolic activity and the functional connectivity of specific parts of such a system (e.g., the precuneus and thalamus) have been shown to correlate with the levels of expressed behaviors and recovery in DOC patients [4,7]. Nonetheless, the postulated correlation between thalamocortical connectivity and behavioral responsiveness is not always straightforward. In fact, some DOC patients, namely the individuals suffering from Functional Locked-In Syndrome, may have a covert awareness but be unable to show purposeful behaviors because of severe motor output impairment, despite the thalamocortical system is functionally preserved [8].

Non-Invasive Brain Stimulation (NIBS) may represent a possible approach to differentiate the patients with covert awareness from the VS individuals. NIBS comprise a wide repertoire of instruments, including transcranial magnetic -TMS- and electric stimulation, which can shape synaptic plasticity and neural network connectivity [9]. TMS induces electrical currents within the brain through the Faraday's principle of electromagnetic induction. TMS is used to evaluate the integrity of the corticospinal tract, spinal cord, and peripheral nerves. In addition, repetitively employed TMS can induce plastic changes in the brain, modulate the activity of distant, functionally connected brain regions, and organize neuronal networks [9]. Among transcranial electric stimulations, the transcranial direct current stimulation (tDCS) is far back used as a NIBS technique. tDCS consists of a flow of weak currents (1-2 mA) from an anode to a cathode, circumscribing a brain area target. The delivered electrical current modifies the resting membrane potential and the activity level of spontaneous excitatory neurons [10].

When dealing with DOC patients, NIBS should be aimed at restoring specific and non-specific neurotransmission patterns within cortical-thalamocortical networks and the Schiff's mesocircuit model, which may release the thalamocortical outflow from central thalamus to the cortical targets, thus improving the level of awareness [5,11]. Both TMS and tDCS have been thought to interfere with long long-term potentiation and long-term depression mechanisms of synaptic plasticity [12], thus shaping the neuronal firing, synaptic strength, neurotransmitter release, and neural network connections [9]. Therefore, NIBS on specific brain targets may allow highlighting the crucial role of neuronal circuit mechanisms underpinning conscious state control, and to demonstrate indirectly the functional preservation of broad thalamocortical networks potentially sustaining covert awareness [13]. Indeed, it has been shown in DOC samples that TMS and tDCS can unmask residual covert connectivity patterns in parallel to a behavioral responsiveness improvement [14,15]. Moreover, audiomotor and visuomotor stimulation could be promising tools to potentiate the functional connectivity within large-scale sensory-motor networks [16,17]. These new approaches exploring covert behaviors and functional connectivity may yield further insight into DOC pathophysiology and improve the differential diagnosis.

In conclusion, NIBS may play a major role in inducing neuroplasticity within residual brain networks potentially sustaining awareness, thus allowing differentiating DOC patients. Moreover, there is growing evidence that NIBS has a great potential for improving the awareness level [11], with a potentially strong impact on the current rehabilitation protocols of DOC patients.

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