

Neurofeedback and Neuromodulation

Subjects: [Engineering, Biomedical](#) | [Physics, Applied](#) | [Clinical Neurology](#)

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Neurofeedback is a non-invasive therapeutic approach that has gained traction in recent years, showing promising results for various neurological and psychiatric conditions. It involves real-time monitoring of brain activity, allowing individuals to gain control over their own brainwaves and improve cognitive performance or alleviate symptoms. The use of electroencephalography (EEG), such as brain–computer interface (BCI), transcranial direct current stimulation (tDCS), and transcranial magnetic stimulation (TMS), has been instrumental in developing neurofeedback techniques.

neurofeedback

transcranial magnetic stimulation

brain–computer interface

disorders of consciousness

transcranial direct current stimulation

1. Introduction

Electroencephalography (EEG) neurofeedback (NF) couples the observation of brain activity with feedback that can reinforce neural circuits important to cognitive and motor function ^[1]. By providing feedback on specific brainwave or connectivity patterns, individuals can learn to modulate their brain activity in a targeted manner that promotes plasticity and functional reorganization in the brain. This also involves the ability to modulate and control subconscious neural activity ^[1]. While EEG is a powerful technique, its use in DoC patients could be complicated by the presence of motion or sweating artifacts, making it difficult to obtain a clear signal.

2. Brain–Computer Interface

A BCI based on EEG is a technique that allows for brain activity to be directly translated into motor actions and can provide a means of communication and control for patients with DoC who are unable to move or speak. BCI technology allows for direct communication between the brain and a computer or other devices without the need for physical movement or speech ^[2]. BCI works by detecting and translating the electrical signals generated by the brain into commands that allow patients to communicate yes/no answers to questions, select items on a screen, or even control devices such as wheelchairs or robotic arms ^[2]. Observing and eventually modulating specific patterns of brain activity through self-regulation is essential for developing and implementing BCIs for therapeutic purposes. Long-term neuroplasticity can be induced by training the brain to perform specific tasks, promoting the overall improvement of brain functions ^[3]. Several studies highlighted the potential of using BCI in DoC patients. Coyle et al. reported that by EEG evaluation, patients with minimal consciousness could potentially use the BCI communication system, even if they cannot voluntarily control their movements. The recognition of consciousness

in this study was derived from unique sensorimotor patterns for each imagined motor task [4]. In another work, Li and colleagues [5] investigate the application of a combined BCI for identifying number processing and mental arithmetic in patients' DoC. The combined BCI integrates multiple types of brain signals or different BCI paradigms to improve the performance, reliability, and robustness of the interface [6]. In this case, the BCI system was combined with P300 and steady-state visual evoked potentials (SSVEPs) to guide three MCS, six UWS/VS, and two patients who emerged from MCS patients through three tasks: recognizing numbers; comparing numbers; and performing mental arithmetic (addition and subtraction). Interestingly, two of the six patients diagnosed as UWS/VS performed with accuracies significantly greater than the chance level, emphasizing the potential to use the combined BCI system in identifying and evaluating covert cognitive abilities in the DoC [5].

In another study involving DoC patients, Xiao and colleagues applied BCI in the evaluation of the visual fixation [7]. Despite not demonstrating visual fixation as evaluated by the CRS-R, 1 of the 15 patients in this study demonstrated a significant online accuracy in the BCI assessment. Another promising approach to assess DoC patients was used by Pan and Colleagues [8] to identify cases of cognitive motor dissociation (CMD) with BCI. CMD is a condition where patients show no observable responses to commands despite demonstrating an appropriate response through neuroimaging. This study assessed 45 UWS/VS and 33 MCS patients who were asked to execute a cognitive task (such as recognizing and selecting a photograph). CMD was observed in 18 UWS/VS and 16 MCS patients, indicating the strong diagnostic potential of BCI as opposed to traditional scales that rely solely on behavior.

Another work by Xie and colleagues [9] employed a gaze-independent audiovisual BCI system, which was used to assess the capacity of eight DoC patients to pay attention to congruent and incongruent visual stimuli presented sequentially. These stimuli typically evoke event-related potentials (ERPs), which were used as indicators of capability in this study. Notably, three patients demonstrated the ability to follow commands and recognize numbers, emphasizing the ability of this system to detect awareness levels in patients with DoC.

The possibility for DoC patients to follow commands was also studied by Lulé et al. [10], who used EEG-based BCI in a group of 18 DoC patients. Command-following was detected in one patient with MCS and another patient with locked-in syndrome (LIS).

While the performance of BCIs in assessing the consciousness level of DoC patients appears promising, their effectiveness varies widely depending on the type of BCI and paradigm used. Several studies used P300-based BCIs [11][12][13], which were shown to be effective when assessing consciousness in DoC patients, even when no behavioral responses were observed. Other studies investigated the use of vibrotactile BCIs to detect consciousness [14][15][16][17], which showed promising results as some patients demonstrated neurophysiological signs of command following in the absence of behavioral responses. The results with Hybrid BCIs, which combine multiple EEG markers such as P300 and SSVEPs [8][18], indicated the potential benefits of a multimodal approach to the assessment of consciousness in DoC patients. On the other hand, BCIs based on sensorimotor rhythms showed limited success in assessing consciousness in these patients, highlighting the need for more research in this domain [4][19].

3. Transcranial Magnetic Stimulation

TMS, a non-invasive technique for brain stimulation, was initially introduced by Barker and colleagues in 1985 [20]. It is considered safe when used in accordance with the safety and application guidelines approved by the International Federation of Clinical Neurophysiology [21]. This technique is based on Faraday's principle of electromagnetic induction [22].

In TMS, a high-intensity electric current, which changes rapidly (known as the TMS pulse), is directed through conducting wire loops enclosed in a protective casing and positioned against a specific area on the scalp. This alteration in the electrical current generates a strong, fluctuating magnetic field that can easily pass through the skull and stimulate a secondary electric current (moving in the opposite direction to the initial current) within the brain's excitable tissues [23][24].

When this induced current is applied with adequate intensity to the cortex, it causes depolarization of cortical neuronal groups directly beneath the coil and in nearby and distant brain regions, leading to neurophysiological and behavioral outcomes [25][26]. This means that TMS, particularly when combined with EEG, can be a powerful tool for evaluating and modulating cortical excitability, plasticity, and functional connectivity. It allows for mapping specific brain regions' roles in cognitive processes and investigating learning mechanisms. Moreover, the application of TMS can lead to a range of behavioral effects, including improved motor skill learning, altered cognitive control and decision-making, memory, language, and visuospatial abilities [25][26].

To stimulate activity in the human brain, the initial current usually needs to be around 4–8 kA with a rate of change peaking at 100–200 μ s, which induces an electric current perpendicular to the coil's surface and in the range of 7–15 mA/cm² [27].

The strength of the induced current is directly proportional to the original current and decreases with distance due to factors such as bone, air, tissues, subdural and subarachnoid cerebrospinal fluid, and changes in the cortical structure [28].

Single-pulse Transcranial Magnetic Stimulation (spTMS) protocols involve the discharge of individual pulses, typically separated by intervals of 4–8 s. When a TMS pulse is applied to the primary motor cortex (M1), it can activate the corticospinal tract and related neural circuits, resulting in a muscle twitch in the area represented by the stimulated brain region [29].

This muscle twitch's electrical activity can be recorded as a motor-evoked potential (MEP) through a surface electromyography (EMG) [30].

Higher cognitive functions, such as attention, memory, and language, can also be examined by applying TMS pulses to higher cortices and associated networks. This can temporarily disrupt physiological processes and/or behavioral activities supported by the stimulated brain regions [31][32]. The motor cortex is often the most targeted region in TMS studies because of its objective and easily obtainable neurophysiological output.

The TMS-induced MEP is often characterized by its amplitude and latency relative to the onset of spTMS, reflecting the functional integrity of the corticospinal tract. The MEP's magnitude provides a measure of motor cortical excitability, which, in reality, reflects the balance between cortical excitation and inhibition, two opposing forces that control the activity in the cortex [33]. The MEP's latency provides a measure of conduction time along central corticospinal motor pathways.

For all of its potential applications, TMS has been investigated as a potential tool for promoting recovery and neuroplasticity following brain injuries [34] and was used in DoC patients.

TBI can lead to a range of neurological symptoms, such as chronic pain [35], disturbances in mood [36] and sleep [37], and an increased risk of seizures and post-traumatic epilepsy [38]. These symptoms may be explained by a decrease in cortical inhibition, which results from a reduction in GABA-mediated synaptic inhibition and a decrease in GABA-synthesising enzymes at the cortical inhibitory synapses [39][40].

Research indicates that the impairment of cortical inhibition circuits in the motor regions of DoC patients can be assessed using TMS-EMG. A study conducted by Lapitskaya et al., which employed TMS-EMG on a group of 24 UWS/VS patients, 23 MCS patients, and 14 healthy controls, found that cortical motor regions for DoC patients were stimulated in an abnormal manner [41]; compared to the healthy control group, the patients exhibited higher Resting Motor Thresholds and lower average amplitudes of maximal peak-to-peak M-wave, MEP, Sensory Evoked Potential, and Short-latency Afferent Inhibition.

In another study, Bagnato and colleagues used paired-pulse TMS to detect significant alterations in the transmissions of inhibitory and excitatory neurons in UWS/VS patients [42]. Paired-pulse TMS (ppTMS) refers to the delivery of two magnetic pulses in rapid succession to the brain. The two pulses can be delivered with fixed or adaptive stimulus parameters to examine cortical excitability in the human motor cortex and probe intra-cortical and inter-cortical connections [43]. When compared to the healthy control group, the phenomena of Intracortical Inhibition (ICI) and Intracortical Facilitation in UWS/VS patients were significantly diminished [42].

However, studies using different ppTMS measures of ICI have reported mixed results, including facilitation, suppression, and no effect on MEPs following mild TBI [44].

In contrast to ppTMS, which involves delivering two magnetic pulses in rapid succession to the brain, other protocols utilize repetitive Transcranial Magnetic Stimulation (rTMS). These protocols involve delivering multiple pulses or bursts of stimulation at a fixed frequency ranging from 0.5 to 20 Hz. The duration of rTMS can vary from a few seconds to 30–40 min. This technique allows for the modulation of cortical excitability even beyond the stimulation period and can be applied to both motor and non-motor regions of the brain. As a result, it induces effects on brain activity that can be observed locally as well as in distant areas [45][46].

While high-frequency (≥ 5 Hz) rTMS protocols were found to generally increase cortical excitability as observed by MEPs [47], low-frequency (≤ 1 Hz) rTMS protocols were found to decrease it [47]. However, the impact of rTMS can

also depend on the state of the cortex at the time of stimulation, which can be leveraged to enhance the specificity of the rTMS-induced effects [\[48\]](#).

Using rTMS, it is possible to depolarize neurons, alter the state of the cortex, and either excite or suppress the functionality of the local cerebral cortex between the stimulation coil and remote areas. As such, rTMS can be employed to amplify specific cognitive processes or modulate the activity of particular regions of the brain [\[49\]](#).

A study found that 60% of DoC patients began to show signs of visual tracking, emotional response, and even indicative action after receiving 5 Hz rTMS intervention, which corresponded to significant increases in the Glasgow Coma Scale and the CRS-R [\[50\]](#).

rTMS was also found to have a positive impact on the behavioral and resting-state functional connectivity of individuals with disorders of consciousness. The DoC patients who underwent 20 Hz rTMS treatment showed significant improvements in consciousness level, response to commands, and motor function compared to those receiving sham treatment. Moreover, resting-state fMRI analysis indicated that rTMS led to changes in functional connectivity patterns within the brain [\[51\]](#).

Another study involved 10 UWS/VS patients who received 10 Hz rTMS over the left dorsolateral prefrontal cortex (DLPFC). The findings indicated several positive outcomes from the procedure, including increased arousal and responsiveness, improved cognitive functions such as attention and working memory, and enhanced motor responses [\[52\]](#).

The effects of 10 Hz rTMS were also investigated by Xia and colleagues, who stimulated the left DLPFC and conducted quantitative EEG analysis in 18 chronic DoC patients. They found decreased low-frequency band power and increased high-frequency band power in the patient group, especially for those diagnosed with MCS, suggesting that quantitative EEG can be useful for assessing the effect of rTMS in DoC patients [\[53\]](#).

To study the therapeutic efficacy of rTMS, a randomized, double-blind, sham-controlled trial was conducted in 40 DoC patients with the administration of 20 Hz active-rTMS or sham-rTMS. It was found that compared to those treated by sham-rTMS, some patients showed significantly improved markers of consciousness. However, rTMS did not significantly enhance the awakening ratio [\[54\]](#).

Manganotti et al. explored 20 Hz rTMS impact on six MCS and UWS/VS patients observing significant behavioral and neurophysiological changes in only one MCS patient, correlating EEG reactivity and clinical response after rTMS [\[55\]](#). Nonetheless, some research indicates that 20 Hz rTMS at M1 has no therapeutic impact on both MCS [\[51\]](#) and patients with UWS/VS [\[56\]](#), leaving the effectiveness of this approach unclear.

A recent study protocol has been proposed that will involve 30 DoC and investigate the potential use of 10 Hz rTMS in aiding the recovery of consciousness. The key goal is to apply stimulation over individualized target areas for each patient, which will be based on different areas of injury; this work presents an important step, as previous works focused on non-specific target areas for stimulation with low effectiveness for DoC patients [\[57\]](#).

In a study that involved 14 UWS/VS, 7 MCS, and healthy subjects, significant changes were found in TMS-evoked potentials and TMS-evoked connectivity in the healthy and MCS groups, but no significant changes were found in UWS/VS patients. These findings suggest that rTMS can effectively modulate effective connectivity in MCS patients [\[58\]](#).

Using TMS in conjunction with EEG offers an immediate approach to identifying the brain's state and observing the dynamics of a wide range of cortical regions [\[56\]](#). This non-intrusive method allows for the assessment of brain excitability, instant connectivity, and ephemeral brain states. When applied to the cerebral cortex, TMS elicits synaptic activity that can be viewed and quantified through EEG, a phenomenon known as TMS-evoked potentials (TEPs) [\[59\]](#).

Consciousness is supported by cortex–cortex and corticothalamic–cortex connections that also involve distant brain regions [\[60\]](#). Since TMS-EEG allows for the assessment of effective connectivity, it was possible to differentiate between states of reduced awareness (e.g., sleep and anesthesia) and higher levels of consciousness (being awake or experiencing dreams) [\[61\]](#).

Previous findings showed that the breakdown of communication within the cerebral cortex during sleep may be necessary for consciousness. It was shown that in wakeful participants, TMS caused neural activity to spread across specific brain regions. However, during non-REM sleep, the TMS stimulus only generated neural activity at the stimulated site [\[62\]](#). When studying this concept in DoC patients, Ragazzoni and colleagues found that in UWS/VS patients, TMS elicits a localized EEG response, indicating disrupted effective connectivity. In MCS patients, TMS often induces a more complex EEG activation pattern, but not at the same level as that of healthy individuals [\[63\]](#).

These studies emphasize the importance of the perturbational complexity index (PCI) as a marker of consciousness in TMS studies. Since consciousness relies on the brain's ability to support complex activity patterns that are both integrated and information-rich, a measure that can capture this complexity is needed to measure the conscious level. When TMS is used to perturb the cortex, PCI measures the algorithmic complexity of the resulting electrocortical responses, which renders it a promising measure. Extensive testing on diverse subject populations, including healthy individuals in different conscious states and patients recovering from a coma, has shown that PCI can reliably discriminate levels of awareness. This measure may pose a solution to the challenge of subjectivity in assessing consciousness, as it provides an objective tool that can be employed at the bedside of patients with acquired brain injuries [\[64\]](#).

Casarotto and colleagues found that PCI was able to effectively stratify unresponsive DoC patients into different subgroups. EEG analysis of healthy subjects, MCS, and UWS/VS patients showed decreasing PCI values with increasing DoC severity [\[65\]](#).

In a study on DoC patients using 10 Hz rTMS applied to the DLPFC, a significant increase in the level of consciousness was observed, which was indicated by the CRS-R assessment, TEP, and PCI. These findings

highlight the concurrent use of TMS-EEG and PCI as efficient tools for assessing the therapeutic effectiveness of rTMS in DoC patients [66].

Another study utilized the fast perturbational complexity index (PCIs) to differentiate between healthy individuals, MCS, and UWS/VS patients based on transcranial magnetic stimulation-evoked potentials (TMS-TEP). PCIs demonstrated significant differences in specific frequency bands, providing a potential tool for quantifying consciousness levels and assessing diagnosis and prognosis in DoC patients [67].

In a study that combined rTMS with standard rehabilitation on the recovery of consciousness in patients with persistent vegetative state, it was found that the group receiving rTMS showed significant improvements in the CRS-R and EEG grading indices following 30 and 60 days of treatment compared to the control group [68].

Finally, a pilot study evaluated the impact of rTMS, amantadine, and their combination on neurobehavioral gains in four DoC patients 1–15 years after their traumatic brain injury. Changes were observed in resting-state functional connectivity for language, salience, and sensorimotor networks after the period of treatment. This finding suggested that the combination of treatments that rely on different mechanisms to modulate neural activity may aid neurobehavioral recovery in DoC patients [69].

A study aims to uncover the neural responses of DoC patients to rTMS. Participants included DoC patients and healthy subjects who received rTMS. Measurements before and after rTMS were made with TMS-EMG. Notable changes in TMS-evoked potentials were observed in healthy participants but not in DoC patients. However, TMS-evoked connectivity increased significantly in healthy and MCS patients and was positively correlated with CRS-R scores. No significant changes were observed in UWS/VS patients [58].

4. Transcranial Direct Current Stimulation

While TMS can be a useful neurofeedback technique for DoC patients, another promising technique is transcranial direct current stimulation (tDCS), which offers a simple approach for localized brain stimulation. In contrast with TMS, tDCS does not induce direct neuronal action potentials because the static fields generated by tDCS do not provide the rapid depolarization required to produce action potentials in neural membranes [70]. Therefore, for tDCS to be effective, it is typically administered together with motor training tasks. The highest effects of tDCS are observed when it is applied before or during the task [71].

tDCS traces its origins back to the late 19th century, shortly after the advent of electricity [72]. It is a non-invasive approach that delivers a weak direct current (usually 1–2 mA) to specific cortical regions beneath two opposing electrodes contained in saline-soaked sponges [73]. It was found that anodal polarity (positive electrode) enhances neuronal activity, while cathodal polarity (negative electrode) reduces neuronal activity [74].

In more recent years, interest in tDCS was renewed under the guidance of Dr. Walter Paulus and his team in Gottingen, Germany, with over a hundred scientific articles published in the last decade [75]. The effects of tDCS on

the brain are yet to be fully comprehended [70], but studies indicate that it can increase cortical excitability and improve memory in healthy individuals [76][77].

Depending on whether the area of focus is put into contact with an anode or cathode, researchers refer to the method as anodal or cathodal tDCS. The electrode placed in the target area is typically designated as the “active electrode”, while the other serves as the “reference electrode”. When both electrodes are positioned on conductive surfaces such as the scalp, a direct current passes between the anode and the cathode, resulting in distinct modifications in the excitability of the underlying cortical tissue. In this process, the cathode, which is negatively charged, serves as the exit point for the electric current. A smaller cathode can create a more concentrated delivery of charge to a specific brain region since more charge is aligned underneath the smaller exit point. Therefore, the size of the affected brain region can be influenced by modifying the size of the cathodal electrode (with a smaller size leading to more focused effects) [78] or by altering the size and position of the anodal electrode [79][80]. This stimulation technique can, therefore, be rather intricate as specific effects vary with different brain regions and the properties of the electrode used to deliver the current [81]. For instance, Accornero and colleagues noted that 10-min anodal tDCS decreased visual evoked response amplitudes, while 10-min cathodal tDCS increased them for a few minutes post-stimulation [82].

Regarding the duration of effects, changes induced by tDCS can persist for a considerable time post-treatment, although more precise estimates of durations continue to be investigated [83]. Nevertheless, alterations caused by tDCS can induce behavioral changes and even improve the neuroplasticity [84].

Numerous studies have demonstrated that this technique can alter perceptual, cognitive, and behavioral functions when applied to different brain regions. In addition, initial findings imply that tDCS could potentially have therapeutic benefits in the management of various brain disorders [70].

In a study involving ten chronic stroke patients [85], each participant underwent two separate sessions. They received either anodal tDCS or sham tDCS in a randomized order. To evaluate the brain’s response following tDCS, the team used spTMS. They found that when patients received anodal tDCS, those with stronger connections in a specific brain network showed a greater increase in brain responsiveness. This network included regions near the site of stimulation in the affected hemisphere’s motor cortex, as well as areas close to the affected hemisphere’s parietal cortex and the fronto-temporal cortex in the opposite hemisphere. These connections were observed in a specific frequency range (8–13 Hz) known as the alpha band. Importantly, this relationship between brain network connectivity and increased brain responsiveness was not seen after the placebo (sham) stimulation.

Bai et al. [86] observed that tDCS can effectively influence cortical excitability in DoC patients, and the changes in excitability, both temporally and spatially, differ between MCS and UWS/VS patients. In their study, which compared to baseline and sham stimulation, MCS patients demonstrated increased overall cerebral excitability in the initial time windows (0–100 ms and 100–200 ms). On the other hand, UWS/VS patients showed an increase in overall cerebral excitability in the 0–100 ms interval, but a decrease was witnessed in the 300–400 ms interval. This difference was likely due to differences in the severity of brain injury, which reflects varying degrees of

connection integrity for different patients. These findings also suggest that the modulation effects of tDCS may be influenced by the underlying structural integrity of the cortical network in question [86].

Another study [87] explored the impact of tDCS applied to the left DLPFC on the behavior and brain activity of patients suffering from prolonged DoC. The authors adopted a double-blind, sham-controlled, crossover design in which thirteen patients with severe brain injuries were subjected to either an active or a sham tDCS session in a randomized order. Following the active tDCS session, an increase in relative power in both the alpha band in the central regions and the theta band in the frontal and posterior regions was observed. Behavioral enhancements were observed in three patients after the active tDCS session and in one patient after the sham session. The authors concluded that a single tDCS session could induce changes in brain activity in prolonged DoC patients, but these changes might not always be associated with notable behavioral advancements.

Another study focused on specific DoC pathology and investigated the potential of tDCS to enhance consciousness in patients diagnosed as UWS/VS and MCS [74]. The treatment included a week of sham tDCS and two weeks of real tDCS, both administered for 20 min daily for five days a week. Following treatment, all MCS patients demonstrated immediate clinical progress, while no such improvement was observed in UWS/VS patients. However, one UWS/VS patient, six years into the condition, exhibited improvement and transitioned to MCS at the one-year follow-up.

Aloi et al. evidenced that many patients with prolonged DoC maintain high cognitive function and awareness [88], a phenomenon called cognitive-motor dissociation [89]. However, detecting covert cognition in these patients does not improve their prognosis, as most remain in a state of low responsiveness. In their work, they evidenced that tDCS could present a promising prospective therapeutic tool for MCS patients when used over several sessions. However, current results are inconsistent due to small study populations, diverse methodologies regarding tDCS parameters and outcome measures, and challenges associated with electrode placement and the heterogeneity of brain damage observed in these patients [88].

Thibaut and colleagues [90] studied the impact of left DLPFC tDCS on consciousness in patients with severe brain injuries at least one week after the acute event. Using a double-blind, sham-controlled crossover design, they delivered anodal and sham tDCS to patients in MCS or UWS/VS. They observed significant treatment effects on CRS-R scores in MCS patients but not in UWS/VS patients. Interestingly, 43% of MCS patients and 8% of UWS/VS patients showed signs of increased consciousness post-tDCS, which were not observed for pre-tDCS or sham evaluations. However, these tDCS-induced changes did not affect long-term outcomes. The conclusion was that tDCS can temporarily enhance signs of consciousness in MCS patients, as reflected in CRS-R score changes.

In a study by Hermann and colleagues [91], 60 DoC patients were stimulated via the left DLPFC. Results showed a 20% improvement in clinical behavioral assessment. In the EEG analysis, the improvements were correlated with increased power and long-range cortico-cortical functional connectivity.

A retrospective study evaluated resting-state functional MRI of 16 MCS patients who received a single left DLPFC tDCS in a randomized trial. Results indicated that six tDCS responders showed increased intra-network connectivity, particularly with the left inferior frontal gyrus; differently, non-responders displayed increased connectivity between left DLPFC and midline cortical structures [\[92\]](#).

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