Neuromodulation for severe brain injury; time for a paradigm shift?

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Neuromodulation represents a promising approach to promote neural plasticity following a brain injury, especially for non-communicative patients with persistent disorders of consciousness. However, to date, the outcomes are limited and inconsistent, driving researchers to explore alternative strategies to improve brain stimulation efficacy.

Patients with prolonged disorders of consciousness (DoCs) following severe brain injury represent a challenging population with respect to diagnosis, prognosis and treatment. Given the inability of these individuals to communicate and interact, rehabilitative strategies remain extremely limited. Neuromodulation for patients with severe brain injury and DoCs has been investigated for over a decade, and recent clinical trials indicate that neuromodulation techniques, such as non-invasive brain stimulation (NIBS) interventions, represent a promising path for this population[1]. However, the therapeutic outcomes are still limited and inconsistent, which could partially be explained by our incomplete understanding of how these techniques influence consciousness-related networks, and by the wide array of stimulation parameters that can be tested.

In this Comment article, we explore what we can learn from previous clinical trials and which directions we should take to refine clinical research in this field. We focus on transcranial current stimulation (tCS) — a technique that predominates in the current literature, partly owing to its ease of use and safety.

Towards a precision medicine approach

To date, most randomized controlled trials (RCTs) of tCS have used one-size-fits-all approaches, and we believe that time has come to improve therapeutic targeting and move forward with individualized approaches. Most scientists in the field of NIBS acknowledge the need to develop patient-tailored electrode montages based on individual structural alterations in the brain. However, individualization of the neuromodulation approach represents a challenge even for mild and moderate brain injuries and is drastically more complex for patients with DoCs given the heterogeneity (structural versus functional, cortical versus subcortical and initial versus secondary) and extent of their brain lesions.

In this context, approaches to integrate cortical lesions into optimized montages have been suggested, as such structural alterations will affect the current flow distribution across brain regions[2]. This methodology, however, requires computational skills and access to T1 structural imaging, which could hamper its applicability. Despite some limitations, such advanced methods represent a promising path to increase the effect sizes in RCTs and thereby enhance the clinical impact of tCS, which is probably underestimated because only a subset of patients respond to the treatment. Currently, we are unable to identify which patients are most likely to benefit from tCS.

Uncertainties also persist regarding the optimal timing of stimulation, considering fluctuations in brain state and overt behavioural output[3]. For patients in minimally conscious state, an EEG-based strategy to monitor fluctuations in vigilance and deliver transcranial

direct current stimulation (tDCS) accordingly has been proposed but remains to be validated[4]. In addition, NIBS methods such as transcranial alternating current stimulation, which synchronizes neuronal oscillations to particular frequencies through neural entrainment, seem promising[5], although the specific frequencies to target in the context of DoCs remain elusive.

Should we always target recovery of consciousness?

So far, the focus of therapeutic options for patients with DoCs has been to rewire consciousness-related networks. However, it is now widely admitted that a substantial proportion (15–20%) of patients with DoCs have some covert awareness and have greater awareness than can be observed clinically[6]. Several factors, such as motor disorders, language impairment, vigilance fluctuation, possible depression or akinetic mutism, could prevent patients from overtly expressing signs of consciousness. The outcome measures that are currently used in RCTs largely rely on overt behaviours, which might be suboptimal to detect infraclinical changes in patients with covert awareness.

tDCS ranks among the most commonly used NIBS techniques in the DoC literature, with the left dorsolateral prefrontal cortex (DLPFC) often being the target of choice. DLPFC-tDCS studies report reproducible efficacy in terms of behavioural improvements as assessed with the Coma Recovery Scale-revised[1,7]. Nonetheless, the median improvement of these scores might be considered as trivial, and assessments of clinically meaningful difference are still lacking in the DoC field[8].

In the current literature, most patients who responded to tDCS were minimally conscious, and tDCS failed to initiate signs of consciousness in unresponsive patients[7]. Knowing that a non-negligible proportion of unresponsive patients can have covert awareness, current tDCS protocols seem to be ineffective in terms of allowing patients to purposefully demonstrate behavioural signs of consciousness, highlighting the need to

develop adapted and optimized protocols to increase behavioural output. In this context, rather than enhancing recovery of consciousness, tDCS might prove useful for refining a patient's diagnosis.

A potential area of interest that seems to have been neglected in current therapeutic strategies for people with DoCs is the motor system — only a few studies with small sample sizes have attempted to target this system. Theoretically, the use of neuromodulation to stimulate motor pathways could improve behavioural responsiveness, thereby enabling patients to demonstrate signs of consciousness rather than increasing their levels of consciousness per se.

To complement this approach, focused ultrasound (FUS) could be used to stimulate subcortical regions, such as the thalamus, in an non-invasive manner[9]. The combination of cortical (tCS) and central approaches (FUS) could provide a holistic strategy to promote recovery of both motor and consciousness-related networks.

Conclusions and recommendations

Over the past decade, considerable advances have been made in therapies aimed at improving recovery of patients with DoCs, with drastically improved prospects of recovery at chronic stages. Neuromodulation is a promising approach to further improve outcomes in these patients, but the therapeutic effects have been limited and inconsistent to date.

To foster a paradigm shift and refine future research, we propose several recommendations. First, the neuromodulation approaches should be individualized on the basis of patients' brain lesions — an approach that is both necessary and challenging given the heterogeneity brain injuries and their resulting phenotypes. Second, efforts should be made to better consider confounding factors, such as motor or language deficits and depression, and shifting the emphasis from increasing consciousness towards improving

behavioural responsiveness, especially in the context of covert awareness. Third, as in the case of other rare conditions, multidisciplinary worldwide collaborations need to be supported. Initiatives such as the European Academy of Neurology Coma Panel, the International Brain Injury Association Disorders of Consciousness Special Interest Group and the Curing Coma Campaign provide unique opportunities to gather international expertise and offer common frameworks to collect data homogeneously (for example, developing common data elements[10]) and combine the findings. Last, we should embrace the ultimate goal of getting evidence into practice to ensure benefits for the target populations in their daily lives. Combining our strengths to better benefit the community should always be our main priority.

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Competing interests

The authors declare no competing interests.