Handbook of Clinical Neurology, Vol. 207 (3rd series)
Coma, Stupor, and Related Disorders of Consciousness
P.W. Kaplan and R.G. Geocadin, Editors
https://doi.org/10.1016/B978-0-443-13408-1.00007-5

Chapter 12

Non-pharmacologic interventions in disorders of consciousness

MARIE M. VITELLO[1,2], STEVEN LAUREYS[1,2], AURORE THIBAUT[1,2,†], AND OLIVIA GOSSERIES[1,2*,†]

[1]*Coma Science Group, GIGA-Consciousness, University of Liège, Liège, Belgium*

[2]*Department of Neurology, Centre du Cerveau (2), University Hospital of Liège, Liège, Belgium*

Abstract

Severely brain-injured patients with disorders of consciousness pose significant challenges in terms of management, particularly due to the limited therapeutic options available. Despite the potential for some patients to benefit from interventions even years after the injury, clinicians often lack clear and reliable treatment strategies to promote patient recovery. In response to this clinical need, the field of neuromodulation has emerged as a promising alternative to traditional pharmacologic therapies.

Both invasive and noninvasive brain stimulation techniques offer diverse possibilities for restoring physiologic neural activity and enhancing functional network integrity in these complex neurological disorders. This chapter offers a comprehensive overview of current neuromodulation techniques, exploring their potential applications and analyzing the existing evidence for their efficacy. Specifically, we describe transcranial electrical stimulation, transcranial magnetic stimulation, deep brain stimulation, low-intensity focused ultrasound, vagal nerve stimulation (including transcutaneous methods), spinal cord stimulation, and median nerve stimulation. While certain approaches show promise for patients with disorders of consciousness, there remains a pressing need for large-scale interventional clinical trials that will play an essential role for elucidating the underlying mechanisms of recovery and for refining stimulation parameters. This, together with the development of tailored individual interventions will move the field forward and optimize therapeutic outcomes.

MANAGEMENT STRATEGIES TO PROMOTE RECOVERY AFTER COMA: WHERE WE STAND[1]

Introduction to disorders of consciousness and clinical management strategies

Many approaches have attempted to define consciousness in its most basic state. From a psychologic perspective, consciousness is a highly unified experience of dynamically graded quantitative and complex components that are flexible and changing over time (James, 1890, 1894). It arises at the meeting point between the brain arousal level and the awareness that provides the content of consciousness and thoughts (Giacino et al., 2014). From a neurobiologic perspective, consciousness is the result of dynamic downhill and uphill brain interactions that involve cortical (e.g., frontoparietal areas) and subcortical structures (e.g., thalamus, striatum), resulting in core thalamocortical connections (Tononi and Edelman, 1998). Following severe brain injuries, however, patients can lose such innate component and enter the scope of disorders of consciousness (DoC) due to widespread dysfunction of neuronal connectivity (Graham et al., 2005). According to their levels of

[1]Abbreviations used in the chapter are listed at the end of the chapter before References section.

*Correspondence to: Dr. Olivia Gosseries, Coma Science Group, GIGA-Consciousness, University of Liège, Liège, Belgium. Email: ogosseries@uliege.be
[†]These authors contributed equally to this work.

arousal and awareness, patients with DoC can be diagnosed in different clinical entities, among which the first step is usually coma. Coma is defined as an acute condition in which a total absence of wakefulness and signs of consciousness is observed. Clinically, it means that the patient remains eyes-closed at all times, despite numerous attempts to induce wakefulness, while reflex behaviors only can still be observed at the bedside (Plum and Posner, 1972). The unresponsive wakefulness syndrome (UWS, also termed "vegetative state"), though similar to coma, is associated with the same behavioral picture but with the return of eye opening. When reproducible behaviors that can be clearly distinguished from reflexes can be observed again, the patient is thought to be in a minimally conscious state (MCS) (Giacino et al., 2002). Additionally, among the latter, one can also distinguish MCS minus (MCS−) from MCS plus (MCS+), depending on the absence or preservation of language-related behaviors, respectively (Bruno et al., 2011). Finally, when the patient is functionally able to communicate or use objects again, (s)he has emerged from the MCS (eMCS), and from a more general point of view, from DoC (Giacino et al., 2002). However, one must acknowledge that patients who have recovered from coma and/or subsequent DoC may remain severely disabled for several months, years, or even decades. Although this seems clear in theory, in standard clinical practice, things are way less obvious. Indeed, patients with severe brain injuries and DoC represent a challenging population with respect to diagnosis, prognosis, and treatment options. The past decade has thus worked on the refinement of diagnostic procedures that led to a better consensus among the specialists. For instance, it is now clearly established that a reliable DoC diagnosis should be provided through repeated multimodal assessments, including behavioral, neurophysiologic, and neuroimaging tools (Wannez et al., 2017; Kondziella et al., 2020), which is also recommended for the differential diagnosis of impaired consciousness and aphasia (Majerus et al., 2009). Joint efforts have also been made from a pluridisciplinary perspective as new diagnostic procedures have also been developed for the assessment of pain in postcoma patients (Chatelle et al., 2012), which was demonstrated to be associated with higher levels of spasticity in some behavioral work (Thibaut et al., 2015a), while other scales are currently under validation, such as the Swallowing Assessment in DoC for the diagnosis of dysphagia (Mélotte et al., 2021). However, although diagnosis issues have been largely worked on over the past years, therapeutic options still remain under-documented as there are currently no recommended evidence-based guidelines for DoC treatment (Giacino et al., 2018a,b; Kondziella et al., 2020).

At present, the therapeutic management of patients with DoC is a key issue that has been addressed in 2012 with the first pharmacologic large sample clinical trial testing the effects of amantadine on consciousness recovery following severe traumatic brain injury (Giacino et al., 2012). This trial truly acted as a gateway to therapeutic research for postcoma patients as many interventions have been investigated since. Among other alternative drugs, neurostimulants (e.g., amantadine, bromocriptine, levodopa) (Herrold et al., 2014) as well as nonbenzodiazepine (i.e., zolpidem) (Thonnard et al., 2013; Whyte et al., 2014; Machado et al., 2018) and benzodiazepine GABA agonists (e.g., midazolam) (Carboncini et al., 2014) have also been investigated to induce functional recovery in patients. However, up to now, only amantadine has provided class II evidence for treatment efficacy (Thibaut et al., 2019).

Along with this, brain stimulation approaches have also been developed. While pharmacology and brain stimulation therapies are both intended to modulate the brain's neural activity, pharmacotherapy involves neuromodulation effects through a direct chemical action on the neurons' receptors when the latter was designed to stimulate brain areas through electromagnetic or mechanical stimulations, thought to have similar neuromodulatory actions. This chapter focuses on eight brain stimulation techniques: transcranial electrical stimulations, transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), low-intensity focused ultrasound (LIFU), vagal nerve stimulation (VNS) and its transcutaneous alternative (tVNS), spinal cord stimulation (SCS), and median nerve stimulation (MNS). In the following sections, we will provide insights regarding their characteristics, supposed mechanisms of action, and effects on patients' clinical state. We will also discuss their potential as clinically relevant tools in standard practice.

Pathophysiologic models for severe brain injuries and recovery

Although there is consensus regarding the general networks associated with consciousness, the refined understanding of the neural correlates of consciousness remains primitive. From its widespread connections, it is no surprise that consciousness is closely related to other neural processes that can either be a consequence of it or modulate it, such as attention or memory-dependent processes (Aru et al., 2012). Therefore, the attempt to narrow down the minimal neural mechanisms sufficient to induce conscious experience only is a challenge that has been addressed numerous times. Over the years, many have suggested and supported theoretical frameworks describing the crucial role of frontal areas (i.e., prefrontal cortex) in consciousness and information processing (Dehaene and Naccache, 2001). Despite controversial evidence that challenged its true involvement in arousal and awareness networks, many are those who remain confident that anterior regions act as the hotspot of consciousness (Odegaard et al., 2017). In contrast, it has been argued that the posterior cortex (i.e., parietal, temporal, and occipital regions) may constitute the consciousness critical zone (Tononi, 2012), especially with regard to the content of consciousness itself (Boly et al., 2017).

Independently from these hypotheses, the anatomopathologic study of severe brain injuries from mixed etiologies permitted to build a robust theoretical framework accounting for the core role of the anterior forebrain in consciousness degradation, that is, the frontoparietal mesocircuit model (Schiff, 2010). If multifocal brain injuries are usually not enough to produce extensive neuronal death across the whole brain, what mechanisms underpin such severe disorders? Early autopsy studies on severe brain damage resulting in consciousness impairment revealed widespread bilateral thalamic cell death as a common feature in patients (Adams et al., 2000). In addition to such neuronal loss, both decreases in excitatory afferent drives from the central thalamus and top-down regulation from the frontocortical areas to the striatum seem to lead to a sharp cutback of the medium spiny neurons activity that requires high level of excitatory inputs to maintain its firing rate (Grillner et al., 2005). Lacking active inhibition from the striatum, the internal globus pallidus in turn over-inhibits the central thalamic neurons, thus promoting the forebrain circuit dysfunction and failing to maintain thalamic connections with the cortical frontoparietal areas (Fridman et al., 2014). In broader terms, this system failure actively maintains functional disturbances within the thalamocortical, thalamostriatal, and cortico-striato-palidal connectivity, leading to a broad decrease in the neuronal activity supplying consciousness networks (Schiff, 2010).

While this neuroanatomic model accounts for the pathologic brain activity underlying DoC, it also provides insights regarding recovery processes and potential treatment mechanisms of action. Indeed, the mesocircuit model often acts as a theoretical framework in the attempt to restore normal or near-normal function within the therapeutic research field (Schiff, 2016; Thibaut et al., 2019).

In that context, it has become widely accepted that some specific techniques and settings can induce excitability changes at the system level that are likely to reflect synaptic modulation. For instance, high-frequency repetitive TMS (rTMS) and anodal transcranial direct current stimulation (tDCS) have been proven to induce long-term potentiation-like plasticity effects while their opposite counterparts (i.e., low-frequency rTMS and cathodal tDCS) would reduce the cortex excitability (Ziemann et al., 2008). Such evidence has led to investigations regarding the potential use of brain stimulations for therapeutic purposes. The principle is simple and would be the following: increase the cortex excitability in pathologically hypoexcitable brain regions (e.g., traumatic brain injury) or decrease it in hyperexcitable brain areas (e.g., epilepsy) (Ziemann et al., 2008; Terranova et al., 2019). If we refer to the mesocircuit model, to restore the thalamic connections in DoC patients, several options are thus available, as shown in Fig. 12.1. On the one hand, due to the ascending-descending connection pattern of the mesocircuit model, one could first attempt to increase the cortex excitability to further reach the subcortical structures, as a top-down approach. On the other hand, one could also choose a complementary option and opt for a bottom-up approach, reaching the subcortical areas first to reinstate their intraconnectivity and subsequent interconnectivity with the central thalamus and cortical areas. Finally, one could also try to reach for the thalamus directly, as a central approach.

Overall, single-session brain stimulations are showing limited long-term potentiation effects on the brain. Their neuromodulating effects are usually short-lasting (i.e., between 30 min and a few hours) (Cirillo et al., 2017), especially as compared to the in vivo animal models from which they derive, where the aftereffects can last for hours or days (Rohan et al., 2015). It is of course critical to make general statements about brain stimulations since there are various techniques with each having technical specificities. However, their effects are usually highly prone to variability both at the intra and inter-subject levels (Ziemann and Siebner, 2015).

Depending on the therapeutic application, one can expect many different types of outcomes from brain stimulation interventions. Following the treatment of DoC patients, the detection of signs of recovery usually starts with a front-line clinical examination. The reemergence of consciousness can be detected at the bedside using scoring systems. Among them, the Coma Recovery Scale-Revised (CRS-R) was for many years the most comprehensive, recommended evidence-based behavioral assessment for identifying signs of consciousness in DoC patients (Giacino et al., 2004; Kondziella et al., 2020). However, because of its extensiveness, this scale can be challenging to administer, especially in intensive daily care routine. Thus, a shorter version of this scale was recently developed and validated to assess DoC patients more easily, in an equally rigorous

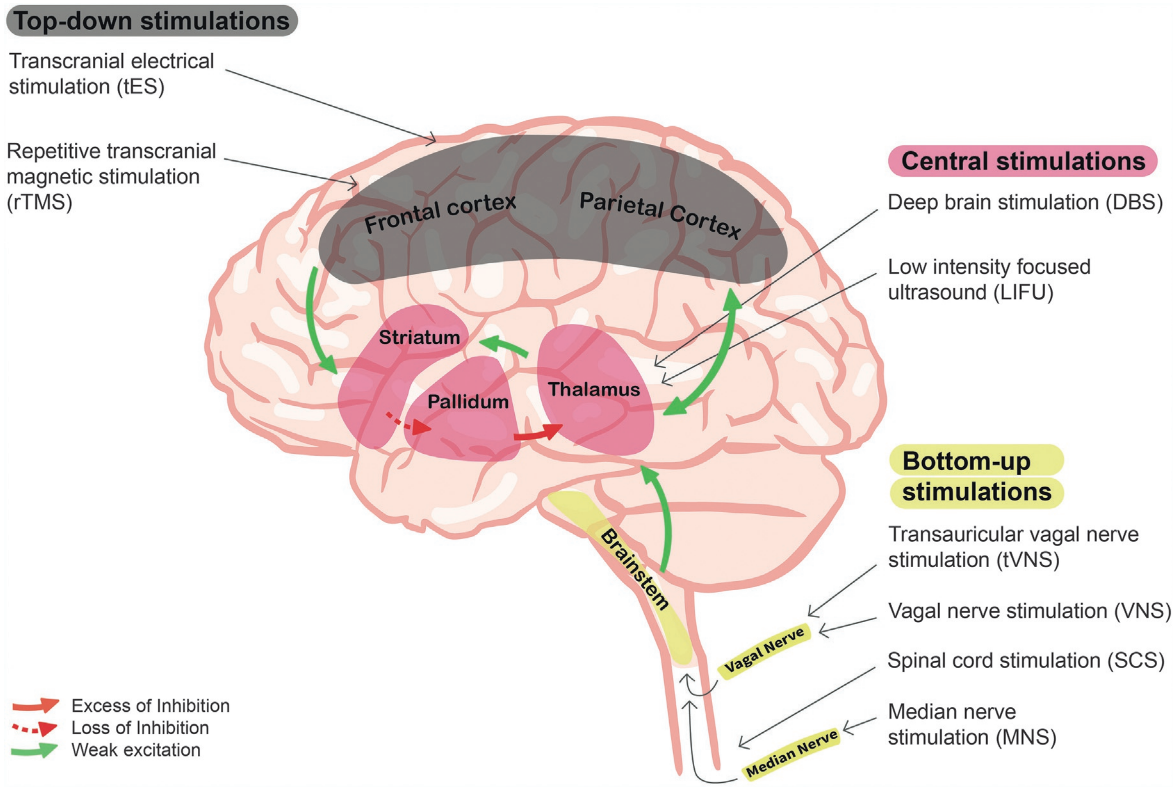

Fig. 12.1. Mechanisms of action of brain stimulation therapies following severe brain injuries within the mesocircuit model. The frontoparietal mesocircuit model explains the effects of brain stimulation techniques in severe brain injuries, such as top-down interventions (expected to act from the cortex to subcortical structures), central interventions (expected to reach deep brain nuclei), and bottom-up interventions (expected to act from subcortical to cortical structures). The model suggests that reduction of thalamocortical and thalamostriatal outflow following deafferentation and loss of neurons from the central thalamus withdraws important afferent drive to the medium spiny neurons of the striatum (*green lines*). Loss of active inhibition from the striatum (*dashed red line*) allows neurons of the internal globus pallidus (GPI) to tonically fire and provide active inhibition (*red line*) to their synaptic targets, including relay neurons of the already understimulated central thalamus, thus reducing thalamic activity and consequent thalamocortical connectivity. Brain stimulation therapies can modulate the activity and outflow of the frontoparietal network acting on different levels of the circuit, including top-down (e.g., transcranial electrical stimulation, repetitive transcranial magnetic stimulation), central (e.g., deep brain stimulation, low-intensity focused ultrasound), and bottom-up (e.g., vagal nerve stimulation, transcutaneous vagal nerve stimulation, spinal cord stimulation, median nerve stimulation) stimulations approaches.

way (Aubinet et al., 2021). The Simplified Evaluation of Consciousness Disorders therefore appears as a relevant alternative to be considered systematically as it is easy-to-use and provides fast and reliable diagnosis in severely brain-injured patients (Sanz et al., 2021). When performed accurately before and after the treatment phase, both the CRS-R and the Simplified Evaluation of Consciousness Disorders may allow the detection of the reinstatement of new signs of consciousness, that is, any low-level or high-level behavior that should not be attributed to reflexive processes only (e.g., withdrawal spinal reflex) or random fluctuation (Giacino et al., 2004; Fins and Bernat, 2018; Aubinet et al., 2021). Therapeutic effects of both non-pharmacologic and pharmacologic interventions are thus usually defined by the emergence of new signs of consciousness or a change in diagnosis based on the scales that have not been observed at baseline nor during the placebo intervention. Another alternative is to look for an increase in the scale's total score. However, since this score accounts for reflex behaviors, which are not related to consciousness, cautious interpretation or the use of an adapted CRS-R index (Annen et al., 2019) is needed when using the total score as an outcome measure. Moreover, in such patients, confounding factors (e.g., aphasia, motor impairment) may obscure the recovery tracking process. Therefore, protocols assessing the efficacy of potential brain stimulation treatments for consciousness recovery tend to include other robust measurements such as neurophysiologic and neuroimaging data.

Apart from the outcomes monitored at the bedside, consciousness recovery implies a shift in patterns of neuronal activity across the corticothalamic system that may be captured using electroencephalography (EEG), positron emission tomography (PET), or functional magnetic resonance imaging (fMRI) (Edlow et al., 2020). Recovery goes along with the restoration of excitatory neurotransmission across thalamocortical and thalamostriatal connections. Following treatment, one can thus expect the reemergence of certain EEG features, such as EEG background organization (Forgacs et al., 2014) as well as enhanced spectral connectivity and power spectrum (Chennu et al., 2017). These EEG metrics are supported by fMRI and fluorodeoxyglucose PET scan data, indicating the restoration of thalamocortical integrity as part of the neural recovery process (Forgacs et al., 2014).

Brain stimulations therapies

The field of experimental treatments is currently increasingly driven by a wide variety of brain stimulation therapies that have been developed and designed to treat an equally wide variety of neurologic and neuropsychiatric disorders. Before diving into this chapter's main focus, it seems important to clearly frame what can be understood as a brain stimulation technique. First, the various brain stimulation modalities share the common feature that is the aim to induce neuromodulatory processes in the brain by stimulating it, usually by targeting the nervous system (i.e., central or peripheral), either in an invasive or noninvasive way. Moreover, brain stimulation interventions do not involve the administration of any biologically active substance and do not imply protein binding as their first mechanism of action, which can allow to circumvent some of the issues related to basic pharmacologic action (e.g., side effects, interactions, drug tolerance). In the postcoma disorders research field, many techniques meet this definition. Thus, reviewing and detailing each and every technique that have been tried out to promote the recovery of patients with DoC may create an information overload, not necessarily relevant for possible future clinical application. For instance, although there is a growing interest for sensory stimulation programs such as music therapy (O'Kelly et al., 2013; Heine et al., 2015) or auditory-based training (Pape et al., 2012), this will not be the focus of this chapter. Indeed, to provide clinicians and researchers with a better understanding of the current state of the art regarding brain stimulation therapies for the treatment of DoC, their technical specificities, and their effectiveness, we will therefore only introduce the most documented techniques with the most robust evidence. However, for the sake of comprehensiveness, we will also briefly mention other alternative techniques that are fitting our definition. The next points will classify various brain stimulation procedures according to their level of action over the mesocircuit model. An overview of these interventions and underlying mechanisms of action over the circuit is displayed in Fig. 12.1.

Top-down approaches

Among the top-down neurostimulation research, *tES* and *TMS* are the most explored techniques in the DoC therapeutic field. tES is a generic term that encompasses all noninvasive stimulation techniques that pass an electrical current through an individual's scalp to reach the superficial portions of the brain cortex (Reed and Cohen Kadosh, 2018). Traditionally, two conductive electrodes are used when employing tES, with one being the anode (i.e., positive, active electrode), and the other the cathode (i.e., negative, return electrode), the current passing from one electrode to the other, either continuously (direct current) or alternatively (alternating current or random noise). They conventionally consist of saline-soaked sponges containing rubber electrodes. The positioning of the two electrodes on the scalp depends on the target brain area: while the anode is usually placed over the region to be modulated, the cathode is often placed on a neutral area such as the contralateral supraorbital region (Guleyupoglu et al., 2013). tES delivers low-intensity current that is maintained at the neural subthreshold level, meaning that it affects cortical excitability but does not elicit firing by itself, as opposed to suprathreshold-based techniques, such as TMS (Radman et al., 2009). As a result, the neurons' firing threshold thus decreases (following depolarizing stimulation) or increases (following hyperpolarizing stimulation) and the stimulated region becomes, respectively, more or less excitable. One key aspect of this type of technique is that it is safe, inexpensive, and easy-to-use and thus can be easily implemented in clinical settings, even in the acute stages of the disease in more fragile patients. However, by its very own technical principle, the general downside of tES is that approximately 75% of scalp-applied currents are amortized in soft tissues and skull, with only a small portion of the current reaching the brain and being conducted through the cortex (Vöröslakos et al., 2018).

Pragmatically, tES comprises a number of techniques that essentially differ from their current patterns. For instance, *transcranial pulsed current stimulation, transcranial alternative current stimulation,* and *transcranial random noise stimulation* are all tES techniques that have been tested on DoC patients, but while the first two involve pulsatile current injections at a set frequency and amplitude with respective square and sinusoidal shapes, the latter delivers a weak alternating current oscillating at random frequencies and with random amplitude. While these techniques are similarly applied (i.e., electrodes placed over the scalp), the current features differ, and these methods are thus believed to interact differently with the neural tissue.

Still, the most popular and documented tES technique is tDCS, all pathologic contexts taken together. tDCS simply delivers a continuous current with a set amplitude. Since the first clinical trial that employed this technique to promote recovery in postcoma patients, a long way has been made. Many stimulation sites, as well as stimulation protocols have been investigated showing contrasting evidence and effects (Huang et al., 2017; Martens et al., 2019, 2020; Barra et al., 2022). Overall, it seems like the stimulation of the prefrontal cortex, more specifically the left dorsolateral prefrontal cortex, has demonstrated the most convincing results in patients with DoC compared with other target locations such as the precuneus, the motor cortex, or the orbito-frontal cortex (Thibaut et al., 2019). Nevertheless, to assert such a statement with high level of conviction, it would be necessary to develop high-quality studies devoted to directly investigate locations' effectiveness comparison. At the behavioral level, improvements following prefrontal tDCS interventions have been documented; however, the magnitude of their effects remains small to medium (Thibaut et al., 2019) and most often involve changes observed at the patient individual level rather than at the group level. For instance, in 2014, Thibaut et al. reported behavioral CRS-R improvements following a single session of 2 mA 20 min frontal tDCS in MCS patients, with 43% of them having recovered at least one sign of consciousness. Such improvements were not observed for unresponsive patients nor in the sham group, suggesting that only a portion of the DoC population may benefit from tDCS and more largely, tES interventions.

Although researchers and clinicians working with patients with DoC may be faced with a lack of behavioral response following tES treatments, one must acknowledge that neurophysiologic improvements sometimes appear preliminary to any clinical changes or even in their absence (Carrière et al., 2020). Following tES intervention, the clinician could first expect a modulatory effect of the stimulation on the delta frequency band (i.e., decreased power) (Bagnato et al., 2017). Therapeutic tES was also demonstrated to increase the power of both alpha (Cavinato et al., 2019; Carrière et al., 2020) and theta (Naro et al., 2016; Bai et al., 2017a; Carrière et al., 2020) bands, which are thought to parallel recovery. On the other hand, it can also affect the neural connectivity within the alpha band (Thibaut et al., 2018) and coherence within the frontoparietal network (Bai et al., 2017a, 2018; Cavinato et al., 2019). From another point of view, a difference in the theta band network connectivity between responders and nonresponders was also demonstrated, with responders presenting more robust theta networks. Thus, preserved connectivity in the theta band was suggested to have a linear relationship with clinical responsiveness to tDCS (Thibaut et al., 2018). Finally, it is important to keep in mind that if such EEG improvement patterns have been found to often go along with clinical evidence of consciousness recovery (Bagnato et al., 2017; Cavinato et al., 2019), as mentioned earlier, it is not always the case as some patients might not display any behavioral improvement despite EEG changes. To explain such phenomenon, it was suggested that while tES and especially single sessions of tDCS interventions might have an effective decreasing effect on the slow-wave activity component of bistability, it may not have enough power to directly affect high-frequency activity, which may be mandatory to recover neural function and subsequent expressed consciousness (Mensen et al., 2020).

We spoke earlier about how tES was designed to deliver low-intensity current under the threshold potential of neurons. Although the currents applied do not usually elicit action potentials, they modify the transmembrane neuronal potential and thus modulate the cortex excitability level by increasing or decreasing the firing likelihood of neurons (depending on the stimulation parameters). There are, however, other techniques that deliver an electric field of sufficient magnitude to effectively induce direct neuronal responses (action potentials) and/or subsequent synaptic responses (excitatory postsynaptic potentials) (Lopez et al., 1991; Radman et al., 2009).

TMS relies on principles of electromagnetic induction to stimulate the neural tissue in a noninvasive way. TMS stimulations can be delivered through single pulses, pairs of pulses, or as trains of repeated pulses with a set desired frequency (Kobayashi and Pascual-Leone, 2003). Single-pulse TMS is a useful technique that can elicit measurable effects and create transient functional lesions, thus allowing to study certain cognitive systems or pathways such as corticospinal excitability. For instance, when applied to the occipital cortex, single-pulse TMS can induce phosphenes (Ray et al., 1998; Samaha et al., 2017) or reversible scotomas (Amassian et al., 1989). Along the same lines, if applied over the primary motor cortex, a single TMS pulse may induce a quantifiable motor output in the form of a contralateral muscle twitch (Merton and Morton, 1980) or suppression of voluntary movement (Davey et al., 1994). However, while single-pulse TMS does not appear to produce any long-lasting effects beyond the few seconds following the stimulation, trains of repeated pulses can modulate cortical excitability in a more persistent way, that outlasts the stimulation period (Pascual-Leone et al., 1998). Repeated TMS thus stands as the preferred tool for therapeutic uses.

rTMS is particularly relevant in clinical research as it allows for very good sham-controlled conditions, due to the manufacturing of undistinguishable sham coils. Moreover, it is fairly safe and side effects are usually limited to transient headaches or discomfort. However, rTMS is not suitable for all patients as metallic implants (ferromagnetic or otherwise) are subject to potential heating and mechanical displacement or dysregulation induced by the magnetic forces elicited by the TMS-generated fast alternating magnetic fields (Golestanirad et al., 2012). Extra caution is thus recommended in severely brain-injured patients as they often wear cerebral shunts, especially in the acute to subacute stages of the condition. Moreover, while low-frequency rTMS can be effective in reducing seizure frequency in drug-resistant epilepsy (Mishra et al., 2019), the use of high-frequency rTMS is strongly discouraged in patients with a known low epileptogenic threshold.

In other contexts, high-frequency rTMS is already established as a validated treatment in standard clinical practice for various conditions, such as major depressive disorders, neuropathic pain, and postmotor stroke (Lefaucheur et al., 2020). In DoC, however, evidence of such therapeutic benefit to patients is not that obvious. To date, most studies of robust design investigating the therapeutic use of high-frequency (>5 Hz) rTMS have focused on targeting the primary motor cortex (M1) of postcoma patients to elicit recovery. Unfortunately, this target location has not reported any clinical improvement at the group level (Cincotta et al., 2015; He et al., 2018; Liu et al., 2018). The barely same results can be observed at the individual level, with only two patients from these three studies having shown clinical benefit following treatment as measured by the CRS-R (He et al., 2018; Liu et al., 2018). Faced with this clinical failure, other brain regions have since been investigated. Two randomized controlled trials (RCT) recently reported significant increases in the behavioral total scores of DoC patients following high-frequency rTMS, respectively, using 20 sessions of 20 Hz rTMS over 4 weeks (Fan et al., 2022) and 10 sessions of 10 Hz rTMS over 2 weeks (He et al., 2021), targeting the left prefrontal regions, as opposed to patients in the sham group who did not display any clinical improvement. As for uncontrolled studies targeting the prefrontal cortex, they all seem to go in line with these results and reported clinical improvements after rTMS treatment phase. However, they should not be considered reliable evidence for treatment efficacy due to poor study robustness (Naro et al., 2015; Xia et al., 2017a; Ge et al., 2021).

Clinical results are here corroborated by neurophysiologic data. While the stimulation of M1 is not associated with any significant change in the patients' EEG activity (Cincotta et al., 2015; He et al., 2018) or connectivity patterns (Liu et al., 2018), clinical improvements following prefrontal rTMS may be associated with a significant power decrease in low-frequency bands (i.e., theta and delta bands) and increase in higher frequency bands (i.e., beta and gamma bands), especially in MCS patients (Xia et al., 2017b). At the single case level, consciousness recovery can also be found to be observed along with an enhanced functional connectivity in the fronto-temporo-parietal network (Liu et al., 2018), as well as increased cortical excitability and a partially restored cortico-cortical connection pattern (Naro et al., 2015).

Central approaches

Another way of reinstating the thalamocortical connectivity that is impaired in DoC patients would be by targeting directly the thalamus instead of going by the cortical areas first. To address this, central approaches have been developed to stimulate those key deep brain nuclei that were usually under-targeted because of difficult anatomic position in the brain. Thus, both thalamic *DBS* and *LIFU* are thought to directly act over the thalamus, respectively, presenting invasive and noninvasive alternatives. More specifically, in order to restore function at the circuit level following brain injury, central interventions should target the neurons from the anterior intralaminar nuclei within the central thalamus given their core contribution to arousal regulation and their strategic anatomic position across cerebral networks (Schiff, 2008, 2010).

DBS is an invasive surgical procedure that has provided remarkable clinical improvements in some patients with a broad range of neurologic—often treatment-resistant—conditions, such as Parkinson disease, obsessive-compulsive disorder, or Tourette's syndrome (Perlmutter and Mink, 2006). It consists of the implantation of electrodes into deep brain structures, here, the thalamus, to modulate its electrical activity through high-frequency (i.e., ~100 Hz) stimulations. Although DBS offers the advantage of directly acting upon the pathologic neural circuit with high focal precision, it has major drawbacks. First, as a serious neurosurgical procedure, DBS is associated with considerable risks (e.g., postoperative infection) and financial costs. Moreover, from an evidence-based scientific perspective, DBS does not allow for robust randomized double-blind studies that is for obvious ethical reasons. Therefore, to date, no sham-controlled trial has been published on DBS in patients with DoC. This treatment option thus suffers from a lack of study protocols that would allow to test the generalizable effects of DBS beyond case reports or small sample open-label studies.

In 2007, Schiff et al. showed over a double-blind alternating crossover design study that bilateral DBS of the central thalamus could significantly improve the clinical state of a patient who had remained in MCS for 6 years after a severe traumatic event. The patient showed significant consciousness improvements in motor function and arousal level, as well as communication ability. This achievement, which demonstrated that DBS could promote late functional recovery, further drew attention to this brain stimulation technique as a treatment option for DoC. Among the following results worth mentioning, two studies reported clinical improvements following DBS procedure of the thalamic reticular nuclei in 7 patients out of 17, with 3 MCS patients regaining functional communication and ability to interact, as well as walking abilities for 2 of them. One chronic unresponsive patient also recovered signs of consciousness (i.e., command following) (Chudy et al., 2018). Nevertheless, it is to be noted that over these two samples, 59% of the patients did not substantially benefit from the surgery (Magrassi et al., 2016; Chudy et al., 2018). Moreover, out of the seven patients who responded to the treatment, three of them only displayed slight behavioral score improvements, up to 3 points on the CRS-R, but no shift in diagnosis. Finally, one last open-label crossover study adds on to these uncertain findings as it failed to demonstrate that the effect of DBS-on periods was stronger than the effect of the DBS-off periods in five postcoma patients (Lemaire et al., 2018). Apart from clinical improvements, it appears that neurophysiologic outcomes could also be expected in responders to DBS as after 1 month of stimulation EEG power spectrum increases in the theta and gamma frequencies were reported in some patients (Magrassi et al., 2016). Given these results, the use of DBS to improve patients' recovery seems to be limited to a small proportion of postcoma patients. Moreover, as all studies reporting clinical effects of DBS were uncontrolled trials, clinicians, and researchers cannot exclude possible experimenter bias or spontaneous recovery when assessing patients after the intervention. Thus, before considering DBS as a possible treatment option for this challenging population, some serious ethical considerations must be taken into account by clinicians regarding the risk-to-benefit ratio.

Low-intensity focused ultrasound is a neuromodulation technique that involves low-energy sound waves to modulate brain activity. Compared to DBS, LIFU is theoretically supposed to directly target and stimulate subcortical deep brain structures, such as the thalamus in a noninvasive way. Such ability to reach key deep brain structures without any surgical procedure makes LIFU a very interesting and safe tool to use for clinicians and researchers. Technically, typical LIFU ultrasound waves are thought to induce reversible and undamaging mechanical agitation over the cell membrane, which in turn elicits polarity changes that modulate the neural excitability and thus chances of neuronal firing (Fomenko et al., 2018). To date, LIFU has not been tested through RCT in postcoma patients yet. However, a few data are available from uncontrolled studies. One patient with acute DoC (i.e., 19 days postinjury) was treated with a single session of 10 thalamic stimulations (Monti et al., 2016). At the clinical level, this patient exhibited behavioral improvements on the CRS-R total score and recovered full language-related abilities together with locomotor skills 5 days following the LIFU intervention. Such a case report is certainly encouraging but does not provide control for spontaneous recovery. Thus, since this patient was in the acute phase of DoC (i.e., <28 days postinjury), one cannot exclude that such fast clinical improvement was actually independent from the treatment procedure, standing as a great example of spontaneous recovery. More recently, the same protocol was applied to three patients with prolonged DoC (i.e., >28 days postinjury). Compared to baseline, two out of three patients displayed significant increases in behavioral consciousness levels following LIFU intervention (Cain et al., 2021). However, similar limitations apply here, and no robust conclusion can be extracted from these two studies, except with regard to the safety and feasibility of LIFU protocols.

Bottom-up approaches

In the DoC therapeutic field, other neuromodulation strategies are thought to promote patient's recovery through an uphill ascending action on the frontoparietal circuit.

This is the case of both invasive *VNS* and its noninvasive counterpart, *tVNS*. VNS is designed to deliver electrical impulses to the tenth pair of cranial nerves. It involves a surgical procedure where a battery-powered pulse generator is usually implanted in the upper left chest, below the collarbone, with an electrode wrapped around the cervical branch of the vagus nerve. To date, it is mainly used in clinical practice for the treatment of pharmaco-resistant depression as well as refractory epilepsy (Johnson and Wilson, 2018). There is not much evidence for the clinical relevance of this technique as a therapeutic alternative for DoC patients; however, some effects have been documented. A VNS device was implanted in a patient with a prolonged unresponsive state, who did not show any sign of recovery for 15 years. Some observable clinical changes (e.g., new signs of contingent behaviors and localization to sound) were recorded 1 month following the stimulation onset but did not allow for a change of diagnosis. Neurophysiologic outcomes showed increased power EEG patterns in the theta band as well as enhanced connectivity patterns within the parietal, temporal, and occipital brain regions (Corazzol et al., 2017; Hoshide and Jandial, 2018). Although this clearly does not provide sufficient evidence for treatment efficacy, it informs on the applicability of the technique for further applications in patients with DoC and VNS potential for consciousness restoration.

Despite VNS being minimally invasive as compared to other possible procedures such as DBS, it is still associated with risks due to the thorny implantation site requiring dissection of the vagal nerve from the carotid artery. Moreover, as with all surgical procedures, this intervention is quite expensive and thus cannot be considered an accessible first-line treatment option to every patient. To overcome such limitations, the clinical relevance of tVNS has been investigated in recent years as this technique is believed to produce similar therapeutic effects of those of regular VNS (Stefan et al., 2012; Hein et al., 2013). In tVNS, however, no device is implanted as the electrical current is delivered over the patient's outer ear skin, either over the cymba conchae or the tragus due to anatomic considerations regarding the accessibility and distribution of the auricular branch of the vagus nerve in these locations (Peuker and Filler, 2002). The device is usually small, requires minimal qualification, and can be easily installed on the patient's ear. Mechanistically, both invasive VNS and tVNS are peripheral techniques thought to stimulate bottom-up connectivity by stimulating the thalamus and thus the thalamocortical connectivity through the vagal nerve connections with the lower brainstem areas (Briand et al., 2020). Up to now, tVNS interventions have reported promising results in patients with prolonged DoC, also reporting minimal to no undesirable effects (Yu et al., 2017; Hakon et al., 2020; Noé et al., 2020). Indeed, all feasibility trials and case report investigating the therapeutic effects of tVNS in postcoma patients have reported clinical improvements at the behavioral level (Yu et al., 2017; Hakon et al., 2020; Noé et al., 2020; Osińska et al., 2022). In the first therapeutic trial ever conducted with this technique, a patient in a UWS recovered signs of consciousness following a 4-week stimulation protocol (Yu et al., 2017). Such clinical results were confirmed later on in 2 uncontrolled studies that overall reported behavioral total score improvements in 9 out of 19 patients, with 7 of these patients being initially in MCS (Hakon et al., 2020; Noé et al., 2020). Moreover, these clinical changes led to a change of diagnosis in three patients, shifting from UWS to MCS and even to eMCS. Neurophysiologic data seem to also support such results as an increase of functional connectivity within the precuneus, thalamus, and the hypothalamus was observed through fMRI (Yu et al., 2017). Although encouraging, these insights must be interpreted with caution as apart from one small-sample pilot RCT (Yifei et al., 2022), no robust trial controlled for the effect of spontaneous recovery so far. Moreover, no general tVNS treatment protocol can be extracted from these pilot data as the published studies used different stimulation parameters (e.g., dose varying between 30 min and 4 h daily; protocol length varying from 4 to 8 weeks). However, one could say that tVNS literature seems to provide evidence that this intervention is feasible and safe for patients in prolonged and acute DoC and that stimulation might be beneficial to some of them through repeated sessions.

Among central and peripheral nervous system stimulation techniques, *SCS* and *MNS*, have also been tested as treatments for severely brain-injured patients. SCS is an invasive technique that requires the surgical placement of a pulse generator connected to the nerve fibers of the spinal cord. In DoC management strategies, the rationale for performing SCS to promote consciousness recovery remains unclear. However, some have suggested a stimulation of the thalamic nuclei through an activation of the reticular formation, in the brainstem areas (Bai et al., 2017b). Probably for that reason, little evidence is available regarding the effects of SCS on patients with DoC and no RCT has been conducted so far. Still, a large-scale study was recently conducted to assess the clinical effects of SCS on 110 chronic DoC patients. Following the stimulation protocol, 31.8% of the patients showed positive clinical outcomes according to the CRS-R, most of them being MCS patients as diagnosed at baseline (Yang et al., 2022). However, this study was not controlled by a placebo group to ensure bias-free conclusions regarding treatment efficacy. Thus, experimenter bias cannot be excluded and might have led to an overestimation of the treatment effects. In another study, Yamamoto and colleagues also tested SCS in 31 postcoma patients (Yamamoto et al., 2017). Unfortunately, no clinical behavioral data can be derived from this trial since the investigators did not use any standardized scale to clearly establish baseline diagnosis or report any therapeutic effects. Finally, at the neurophysiologic level, SCS may be associated with delta and gamma power changes in MCS patients (Bai et al., 2017b). Moreover, for the clinicians, EEG complexity could indicate patients' brain responses to treatment as permutation entropy was shown to be modulated by SCS, with increased measures following a stimulation protocol (Wang et al., 2020).

In order to be seriously considered as a treatment option for severely brain-injured patients, the SCS research field urgently needs to provide accessible well-designed controlled studies using precisely defined clinical outcomes as well as validated assessment tools.

Finally, at the peripheral level, MNS can also be considered to induce an effect on the central nervous system through the ascending reticular activating system. When MNS is conducted, an electrode connected to a stimulator is placed over the volar surface of the forearm to reach the median nerve. However, this technique suffers from the same lack of robust scientific evidence as SCS. Further studies on this technique need to rely on recommended evidence-based measurements for primary clinical outcomes as no trial from this field used the Simplified evaluation of Consciousness Disorders nor the CRS-R but rather clinical tools providing weaker diagnostic information, such as the Glasgow Coma Scale (Cooper and Cooper, 2003; Lei et al., 2015; Feller et al., 2021). Therefore, the few studies published so far on MNS do not allow us to draw any conclusion about the efficacy of MNS intervention on the level of consciousness. However, one study on DoC reported a benefit of the intervention on the number of days in the intensive care unit in the active group as compared to the control group, which seems promising (Cooper and Cooper, 2003).

Eventually, one could also mention *thermal/caloric vestibular stimulation*, which is traditionally achieved by irrigating the external ear canal with warm or cool water; *and galvanic vestibular stimulation*, which is performed by applying small electrical currents to the vestibular labyrinth using electrodes. The change in afferent firing rate of the vestibular nerve is believed to induce a natural head movement, which, via basal forebrain/brainstem projections through central thalamus and hypothalamus, should elicit a variety of compensatory responses in the frontal–parietal and striatal networks. However, of the two techniques, only thermal stimulation has been yet tested in patients with DoC in only one single-case pilot study (Vanzan et al., 2017), not allowing for any clinical conclusion at this stage.

Overall, as shown in Fig. 12.2, it appears quite clearly that top-down interventions are the most documented techniques, providing the most well-designed studies of large cohorts of patients, thus permitting to draw a set of conclusions regarding their potential use as part of DoC patient's rehabilitation strategies. First, as a general statement, one could say that both tES and rTMS interventions are at the end of the feasibility stage and have shown encouraging results to promote postcoma patients' recovery with certain parameter settings. For both techniques, it seems that the frontal areas, and more specifically, the dorsolateral prefrontal cortex, should be chosen as the preferred stimulation site when trying to improve patient's recovery. However, more studies providing a direct thorough comparison of these potential stimulation sites should be conducted. Moreover, as compared to UWS, MCS patients might be more likely to benefit from top-down interventions, especially for tDCS, with a probability of positive treatment response rate of 25%–50%, while rTMS might be effective for both conditions, but with greater changes in MCS patients (O'Neal et al., 2021). Regarding central stimulations, one major consensus is also related to the stimulation site, as these techniques should target the central nuclei of the thalamus to provide the most conclusive results. From a clinical point of view, while DBS requires a careful clinical consideration of the procedure's risk-to-benefit ratio for each eligible patient due to the highly invasive procedure, LIFU could be considered

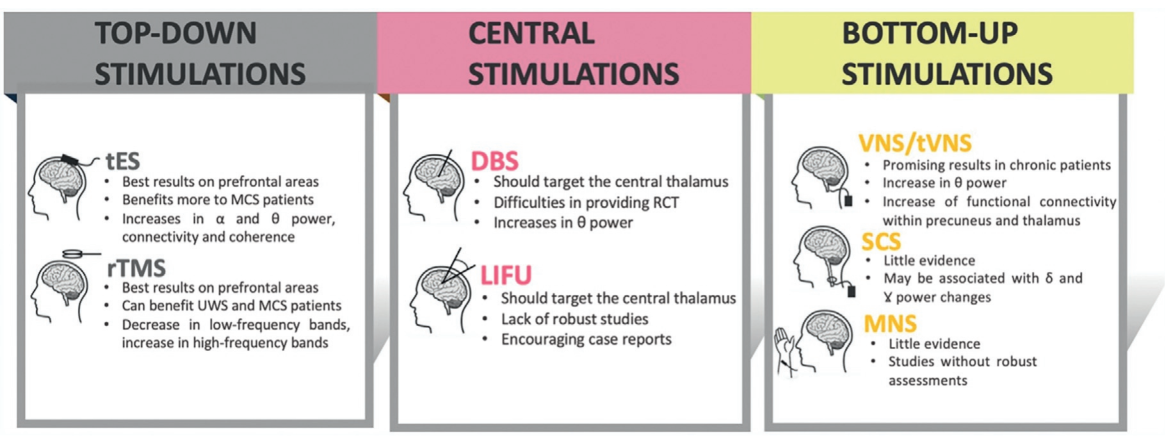

Fig. 12.2. Summary of the main evidence for each brain stimulation technique. *DBS*, deep brain stimulation; *LIFU*, low-intensity focused ultrasound; *MNS*, median nerve stimulation; *rTMS*, repeated transcranial magnetic stimulation; *SCS*, spinal cord stimulation; *tES*, transcranial electrical stimulation; *tVNS*, transcutaneous vagus nerve stimulation; *VNS*, vagus nerve stimulation.

an interesting option to safely reach deep brain nuclei in order to restore consciousness but would need way more work to be done before considering it for clinical purposes. Eventually, bottom-up stimulations follow the same lines as most of them, the class of clinical evidence for these techniques to be considered as a treatment for patients with DoC is currently at the pilot stage, although tVNS' efficacy seems very promising and is currently under investigation through robust designed studies. To ease progress at this stage, the future direction of research should involve performing large sample RCTs using comprehensive behavioral assessments (i.e., Simplified Evaluation of Consciousness Disorders, CRS-R) as well as at least one additional measurement (e.g., electrophysiologic or imaging assessments) allowing for more objective neurophysiologic indicators to be involved in the treatment's assessment, while also clarifying the therapeutic mechanisms underlying neuromodulation. Still, the path to an efficient application in clinical settings remains long.

FROM RESEARCH TO PRACTICE: CHALLENGES FOR TRANSLATION TO CLINICAL SETTING

Several scientific evidence have illustrated that the use of non-pharmacologic interventions to promote consciousness recovery in severely brain-injured patients may be an efficient approach that elicits therapeutic effects. However, for these techniques to reach their full potential as real-life clinically relevant tools for therapy, some work still must be done (Edlow et al., 2021). This section identifies two key levers to move brain stimulation therapies from translational research to standard clinical practice: (1) identify the optimal stimulation parameters and reveal their precise mechanisms of action and (2) develop patient-fitted interventions based on endotype and phenotype.

Identify the optimal stimulation parameters and reveal their precise mechanisms of action

Electromagnetic and mechanical stimulations allow the choice of many parameter settings among pulse width, frequency, current intensity, and amplitude, which can be gathered into different stimulation train parameters of varying intervals. To a greater extent, even the optimal anatomic site of stimulation remains unknown with regard to each technique. Thus, the neurostimulation translational research field is currently moving forward based on a trial-and-error approach, most of the time based on anatomic network theories, combining different stimulation sites and settings until one combination produces convincing results. Moreover, even when a site seems to reach a consensus, the assessment of the anatomic accuracy of the target can be challenging, especially in severely brain-injured patients with preexisting structural distorted anatomy due to the lesions. This also causes some neurostimulation therapies to require extensive patient-specific design with regard to the above-mentioned impaired structural anatomy as well as the related specific network disconnections (Vogel et al., 2020).

The previous section has highlighted that among top-down approaches (i.e., tES, rTMS), the frontal sites appear to be the preferred targets that produce the most conclusive results. However, the scientific rationale attesting for the effectiveness of the dorsolateral prefrontal cortex remains unsure. Overall, it mainly relies on the mesocircuit hypothesis. Indeed, when targeting such a portion of the frontal cortex, it is expected that it could elicit the reinstatement of important cortical connections with the striatum, which are thought to reduce inhibition and deafferentation to the thalamus, which in turn, could promote thalamocortical connectivity (Schiff, 2010). However, this remains purely hypothetical as to date, no RCT has provided evidence regarding the actual underlying neural response pathway that can be observed following the stimulation of a specific site. However, it is to mention that in 2007, a study investigated the brain activations of healthy subjects in response to tVNS through fMRI, showing among others hyperactivation in the insula, precentral gyrus, and thalamus (Kraus et al., 2007). Ten years later, this analysis was reproduced in a postcoma patient and showed an increased activation of the thalamus and precuneus after tVNS intervention (Yu et al., 2017). Although this is not sufficient to affirm with certainty that these are the underlying activation mechanisms of tVNS that could explain consciousness restoration in DoC patients, it is nonetheless a step forward in the understanding of the impact of brain stimulation approaches. In the future, it would be highly beneficial to the field to actually challenge and verify (or disprove) the models they are based on by taking advantage of neuroimaging and neurophysiologic tools, as well as potential in vivo studies.

Once the technical parameters and brain target are all set, another milestone of non-pharmacologic interventions, and actually of every type of treatment, is the dose to be given to the patient. Indeed, while some one-shot interventions might produce clinical improvements in some patients, it has been shown that repeated sessions increase both the effect size and the number of responders (Thibaut et al., 2017), suggesting that some patients might need more than one session of stimulation to maximize the intervention's benefits or to get a benefit at all. Knowing this, it seems fair to wonder why therapeutic trials do not always involve repeated sessions. However, one must keep in mind that with longitudinal studies goes a higher need for resources. Moreover, DoC patients represent a critical population, with high risks of medical complications, possibly leading to study drop-out. As a consequence, increasing the length of an interventional protocol also increases the chances to get an incomplete dataset, thus requiring higher sample sizes to reach satisfactory study power, which is not an easy task to achieve considering the fact that DoC is a rare disease. Despite these challenges, it is important that the field provides more RCTs focusing on longer treatment phases to increase the positive clinical results' likelihood.

Finally, questions remain regarding the optimal time frame to initiate therapy. As most of the studies have focused on the treatment of chronic patients for the sake of convenience as well as for safety reasons (e.g., highly stabilized patients, lesser complications), therapeutic interventions in acute to subacute severely brain-injured patients may produce different results that need to be investigated. For instance, only considering chronic patients may induce a survival bias in studies. However, knowing when to stimulate to be as efficient as possible is not only about how long since the injury but also at what time of the day, or even at what time of the patient's own state. Indeed, the possibility of matching the moment of stimulation to the patient's brain state fluctuations is currently being explored. This has been proposed to be achieved in tDCS research by using an EEG-based device theoretically able to deliver electrical stimulation depending on the patient's current state of vigilance (Martens et al., 2021). Such a proposition is based on evidence showing that the vigilance level of MCS patients displays periodic average cycles of 70 min (Piarulli et al., 2016). This specific feature could potentially prevent the patients from being in an optimal neural state to get the full benefits of tDCS interventions. Thus, it appears that this aspect should be consistently taken into account when trying to set the best stimulation parameters to produce the best clinical benefit in real-life practice.

Develop patient-fitted interventions based on endotype and phenotype

As mentioned in the previous section, implementing individualized assessments of structural injury and connection network patterns may help to support the choice of an appropriate stimulation site. However, this is obviously not the only feature that would need to be adapted to patients' characteristics.

In RCT, researchers are forming groups of patients either receiving the active treatment or the placebo treatment (i.e., parallel designs), or both (i.e., crossover designs). To further allow for comparison, one of the main goals of the researchers is to ensure that the interventions provided to each of the patients within the same group are highly homogeneous, similar in every single respect. However, such reasoning is not clinically relevant and thus cannot be transferred to real-life patients' management. We discussed in the previous section that significant positive results are rarely observed in all patients following non-pharmacologic interventions. This suggests that not all patients can benefit from all types of interventions, thus supporting the clinical approach, which pays particular attention to each patients' specific characteristics in order to design a treatment plan. Indeed, it would be highly optimistic to believe that the neurostimulation therapeutic field could simply ignore patients' endotype and propose homogeneous protocols, erasing patients' heterogeneity. However, as long as the specific features of a technique's responders remain unknown, it seems challenging to propose such ideally fitted therapies. Thus, to develop patient-fitted interventions, the next necessary step is the identification of the responders' profile. For instance, depending on individual neural dysfunction, one approach might be more efficient than the other. Indeed, we may consider that since top-down approaches target the cortex, they might be a suitable therapeutic option for patients with anoxic, widespread lesions given the preexisting thalamocortical disruption (Hermann et al., 2020). Bottom-up and central approaches (e.g., tVNS), however, could be more effective for patients with other etiologies such as traumatic or hemorrhagic incidents, which tend to be more focal, since the activation cascade is thought to reach the upper brain regions traveling first by the lower and upper brainstem areas (Briand et al., 2020). Such hypotheses need to be tested in scientific studies to provide a basis for clinical interventions.

Eventually, when the sample sizes allow it, conducting subgroup analyses can provide capital information. Robust evidence from RCTs highlighted that no significant clinical improvement could be induced in UWS patients at the group level following tES interventions, suggesting that tES might only be clinically relevant for MCS patients (Zhang and Song, 2018). However, although from the same class of intervention (i.e., top-down intervention), it does not seem to be the case for rTMS, or at least with less drastic differences. Indeed, rTMS interventions have reported improvements in unresponsive patients as well as in patients in MCS. This is also true for other neurostimulation strategies but with less convincing study characteristics.

Along the same lines, the same kind of analyses should also be conducted on other factors, such as demographic variables to identify if the patient's sex or age at the time of injury could also be a predictor of response to treatment. This has already been done for some neurophysiologic data with some EEG features such as the theta band connectivity being associated with the responder status to some tES treatments (Thibaut et al., 2018). Moreover, it appears that such responders to tES, and especially tDCS interventions, demonstrate preservation of brain metabolism and gray matter integrity under the stimulated area, but also in the thalamus and the precuneus, which are highly involved in consciousness recovery (Thibaut et al., 2015b).

Although there is already existing evidence regarding certain endotype markers that may allow for response to brain stimulation treatments, the field is still at its debuts and needs massive joint efforts to provide conclusive guidelines for the clinical setting. In that matter, Whole Brain computational Models (WBMs) are a set of powerful means that enable the investigation of the dynamic interactions between neural populations from different regions of the brain (Deco et al., 2021). When applied to consciousness, WBMs have the potential to describe the neural dynamics underlying (loss of) consciousness (Cofré et al., 2020; López-González et al., 2021). Interestingly, computational neuroscience and more specifically physical models of the brain have come a long way since their origin and are gradually extending their application from theoretical physics to bedside. Over the years, WBM models have proven their worth in providing predictive insights for various neuropathologies (e.g., epilepsy, traumatic brain injury) and now possess great clinical potential to support individualized diagnosis, prognosis, and the assessment of treatment efficacy (Pathak et al., 2022), which could be applied to the DoC field (Luppi et al., 2021). Indeed, perturbations at the WBM level could reflect electrical stimulation or pharmacologic application (Perl et al., 2021). In a comparative manner, modeled perturbations could be used to assess the efficacy of different treatments in patients based on the resultant global dynamics, becoming more similar (or not) to the dynamics of healthy brains as modeled by biomarkers. Thus, the future possibilities for employing WBM are vast, one of them being related to personalized medicine. In order to advance the current state of the field, these models could be used to design and test brain stimulation treatments for individual patients. Such a goal would require the generation of models based on individual patient's data that could subsequently be tested to estimate the efficacy of different treatment options in addition to other metrics such as the likelihood of treatment success or the optimal brain regions to be stimulated. Even though such a vision is not accessible in the immediate future, it remains within the scope of plans of future modern research as it has the potential to raise the chances of successful translation to clinical settings.

CONCLUSIONS

To date, the exact mechanisms behind the emergence of human consciousness remain mostly unknown and constitute one of the greatest challenges of both fundamental and translational modern science. Revealing the way in which consciousness arises would allow clinicians and researchers to take a giant step forward in the theoretical understanding of this neurobiologic system, but also in the way to treat its main pathologic condition: DoC. Although this domain is still paved with misunderstandings and uncertainties, the field has not remained static and has been moving forward through the development of model-based non-pharmacologic therapies in an attempt to promote the recovery of postcoma patients. Through this chapter, we have identified three major lines of action in terms of therapeutic interventions, (i.e., top-down stimulations, central stimulations, bottom-up stimulation), acting upon different levels of the mesocircuit through excitatory or inhibitory effects on the stimulation site itself, but also throughout widespread distant but connected regions that are part of this network. Whether they are electrically based, magnetic-based, or ultrasound-based, there is significant evidence for the potential of brain stimulation therapies to induce neuromodulatory effects over plasticity-relevant signaling pathways involved in the mesocircuit's networks. While some of them have demonstrated low to moderate effect sizes on patients' clinical outcomes, other novel promising therapies are currently being investigated (Thibaut et al., 2019). However, in its current state, the field of brain stimulation interventions in DoC patients suffers from a number of limitations that certainly leave room for improvement (Edlow et al., 2021). In that matter, Fig. 12.3 illustrates the perspectives of evolution. First, although different studies tested various stimulation locations and parameters within various techniques, to date, the field is still missing trials directly comparing the effectiveness of multiple settings in one homogenous protocol, which would allow us to draw more robust conclusions, and thus, validate standardized protocols that could be safely employed in clinics. Second, future studies should also increasingly aim to develop biomarkers of responsiveness to treatment, which would allow us to come up with more adaptative, patient-tailored approaches in brain stimulation therapies. To achieve such a goal, large sample trials should notably focus on

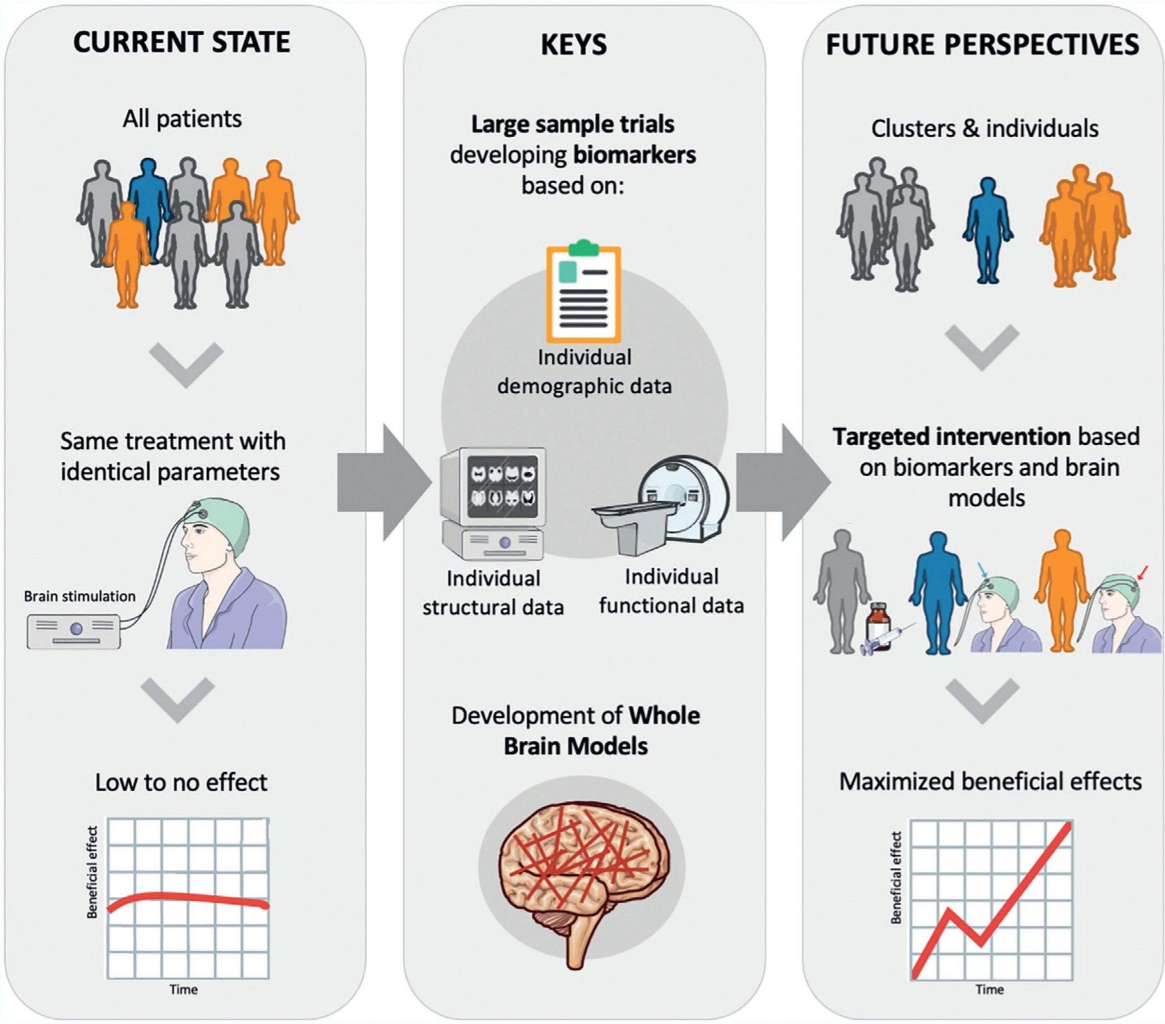

Fig. 12.3. Future perspectives for brain stimulation therapies in disorders of consciousness. The current state of the therapeutic field in disorders of consciousness implies trying homogenous brain stimulation protocols on DoC patients in order to restore consciousness following severe brain injuries. This can lead to unsatisfying effects due to the large variety of patients' profile for a small adaptation of protocols. Key levers to move the field forward include performing large sample randomized controlled trials testing different parameters and aiming at developing biomarkers of responsiveness based on individual demographic and structural data (e.g., age, sex, time since injury, etiology, preexisting structural distorted anatomy) as well as functional data from neuroimaging and neurophysiology (e.g., functional network connectivity, regional glucose metabolism). Together with the development of whole brain models, this will allow to identify the optimal techniques and stimulation parameters for a given patient's phenotype (e.g., based on their phenotype, the gray patient should benefit more from pharmacologic intervention, the blue patient from frontal brain stimulation and the orange patient from parietal brain stimulation) and thus pave the way to targeted patient-fitted therapy, which should maximize interventions' benefits.

gathering demographic data and including alternative measures from neuroimaging and neurophysiologic technologies, as well as serum markers (Mattsson et al., 2017). Finally, in that context, computational modeling will provide insights into how different stimulation parameters applied on different patients functionally and physiologically affect the underlying neural network and will therefore be useful for the design of future treatment protocols with a higher chance of success at the individual level.

ACKNOWLEDGMENTS

We would like to express our gratitude to the University and University Hospital of Liège, the Belgian National Funds for Scientific Research (FRS-FNRS) in the framework of the research projects No PDR/BEJ T.0134.21 and MIS F.4521.23, the ERA-Net FLAG-ERA JTC2021 project ModelDXConsciousness (Human Brain Project Partnering Project), the Horizon 2020 MSCA—Research and Innovation Staff exchange (101131344—DOCBOX), the European Space Agency (ESA) and the Belgian Federal Science Policy Office (BELSPO) in the framework of the PRODEX Programme, the BIAL Foundation, the Mind Science Foundation, the fund Generet of the King Baudouin Foundation, the Mind-Care foundation and AstraZeneca Foundation.

S.L. is a research director, A.T. and O.G. are research associates, and M.M.V. is research fellow at FRS-FNRS.

CONFLICT OF INTEREST STATEMENT

Authors have no conflict of interest to declare.

ABBREVIATIONS

CRS-R, Coma Recovery Scale-Revised; DBS, deep brain stimulation; DoC, disorders of consciousness; EEG, electroencephalography; eMCS, emergence from the minimally conscious state; LIFU, low-intensity focused ultrasound; MCS, minimally conscious state; MNS, median nerve stimulation; RCT, randomized controlled trial; rTMS, repeated transcranial magnetic stimulation; SCS, spinal cord stimulation; tDCS, transcranial direct current stimulation; tES, transcranial electrical stimulation; TMS, transcranial magnetic stimulation; tVNS, transcutaneous vagus nerve stimulation; VNS, vagus nerve stimulation; WBM, whole brain models.

References

Adams JH, Graham DI, Jennett B (2000). The neuropathology of the vegetative state after an acute brain insult. Brain 123: 1327–1338. https://doi.org/10.1093/BRAIN/123.7.1327.

Amassian VE, Cracco RQ, Maccabee PJ et al. (1989). Suppression of visual perception by magnetic coil stimulation of human occipital cortex. Electroencephalogr Clin Neurophysiol 74: 458–462. https://doi.org/10.1016/0168-5597(89)90036-1.

Annen J, Filippini MM, Bonin E et al. (2019). Diagnostic accuracy of the CRS-R index in patients with disorders of consciousness. Brain Inj 33: 1409–1412. https://doi.org/10.1080/02699052.2019.1644376.

Aru J, Bachmann T, Singer W et al. (2012). Distilling the neural correlates of consciousness. Neurosci Biobehav Rev 36: 737–746. https://doi.org/10.1016/J.NEUBIOREV.2011.12.003.

Aubinet C, Cassol H, Bodart O et al. (2021). Simplified evaluation of CONsciousness disorders (SECONDs) in individuals with severe brain injury: a validation study. Ann Phys Rehabil Med 64: 432. https://doi.org/10.1016/J.REHAB.2020.09.001.

Bagnato S, Boccagni C, Prestandrea C et al. (2017). Changes in standard electroencephalograms parallel consciousness improvements in patients with unresponsive wakefulness syndrome. Arch Phys Med Rehabil 98: 665–672. https://doi.org/10.1016/J.APMR.2016.09.132.

Bai Y, Xia X, Kang J et al. (2017a). TDCS modulates cortical excitability in patients with disorders of consciousness. Neuroimage Clin 15: 702–709. https://doi.org/10.1016/J.NICL.2017.01.025.

Bai Y, Xia X, Li X et al. (2017b). Spinal cord stimulation modulates frontal delta and gamma in patients of minimally consciousness state. Neuroscience 346: 247–254. https://doi.org/10.1016/J.NEUROSCIENCE.2017.01.036.

Bai Y, Xia X, Wang Y et al. (2018). Fronto-parietal coherence response to tDCS modulation in patients with disorders of consciousness. Int J Neurosci 128: 587–594. https://doi.org/10.1080/00207454.2017.1403440.

Barra A, Rosenfelder M, Mortaheb S et al. (2022). Transcranial pulsed-current stimulation versus transcranial direct current stimulation in patients with disorders of consciousness: a Pilot, Sham-Controlled Cross-Over Double-Blind Study. Brain Sci 12: https://doi.org/10.3390/BRAINSCI12040429.

Boly M, Massimini M, Tsuchiya N et al. (2017). Are the neural correlates of consciousness in the front or in the back of the cerebral cortex? Clinical and neuroimaging evidence. J Neurosci 37: 9603–9613. https://doi.org/10.1523/JNEUROSCI.3218-16.2017.

Briand MM, Gosseries O, Staumont B et al. (2020). Transcutaneous auricular vagal nerve stimulation and disorders of consciousness: a hypothesis for mechanisms of action. Front Neurol 11. https://doi.org/10.3389/FNEUR.2020.00933.

Bruno MA, Vanhaudenhuyse A, Thibaut A et al. (2011). From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J Neurol 258: 1373–1384. https://doi.org/10.1007/S00415-011-6114-X.

Cain JA, Spivak NM, Coetzee JP et al. (2021). Ultrasonic thalamic stimulation in chronic disorders of consciousness. Brain Stimul 14: 301–303. https://doi.org/10.1016/J.BRS.2021.01.008.

Carboncini MC, Piarulli A, Virgillito A et al. (2014). A case of post-traumatic minimally conscious state reversed by midazolam: clinical aspects and neurophysiological correlates. Restor Neurol Neurosci 32: 767–787. https://doi.org/10.3233/RNN-140426.

Carrière M, Mortaheb S, Raimondo F et al. (2020). Neurophysiological correlates of a single session of prefrontal tDCS in patients with prolonged disorders of consciousness: a pilot double-blind randomized controlled study. Brain Sci 10: 469. https://doi.org/10.3390/BRAINSCI10070469.

Cavinato M, Genna C, Formaggio E et al. (2019). Behavioural and electrophysiological effects of tDCS to prefrontal cortex in patients with disorders of consciousness. Clin Neurophysiol 130: 231–238. https://doi.org/10.1016/J.CLINPH.2018.10.018.

Chatelle C, Majerus S, Whyte J et al. (2012). A sensitive scale to assess nociceptive pain in patients with disorders of consciousness. J Neurol Neurosurg Psychiatry 83: 1233–1237. https://doi.org/10.1136/JNNP-2012-302,987.

Chennu S, Annen J, Wannez S et al. (2017). Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness. Brain 140: 2120–2132. https://doi.org/10.1093/BRAIN/AWX163.

Chudy D, Deletis V, Almahariq F et al. (2018). Deep brain stimulation for the early treatment of the minimally conscious state and vegetative state: experience in 14 patients. J Neurosurg 128: 1189–1198. https://doi.org/10.3171/2016.10.JNS161071.

Cincotta M, Giovannelli F, Chiaramonti R et al. (2015). No effects of 20 Hz-rTMS of the primary motor cortex in vegetative state: a randomised, sham-controlled study. Cortex 71: 368–376. https://doi.org/10.1016/J.CORTEX.2015.07.027.

Cirillo G, di Pino G, Capone F et al. (2017). Neurobiological after-effects of non-invasive brain stimulation. Brain Stimul 10: 1–18. https://doi.org/10.1016/J.BRS.2016.11.009.

Cofré R, Herzog R, Mediano PAM et al. (2020). Whole-brain models to explore altered states of consciousness from the bottom up. Brain Sci 10: 626. https://doi.org/10.3390/BRAINSCI10090626.

Cooper EB, Cooper JB (2003). Electrical treatment of coma via the median nerve. Acta Neurochir Suppl (Wien) 7–10. https://doi.org/10.1007/978-3-7091-6081-7_2/COVER/.

Corazzol M, Lio G, Lefevre A et al. (2017). Restoring consciousness with vagus nerve stimulation. Curr Biol 27: R994–R996. https://doi.org/10.1016/J.CUB.2017.07.060.

Davey NJ, Romaiguère P, Maskill DW et al. (1994). Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. J Physiol 477: 223–235. https://doi.org/10.1113/JPHYSIOL.1994.SP020186.

Deco G, Vidaurre D, Kringelbach ML (2021). Revisiting the global workspace orchestrating the hierarchical organization of the human brain. Nat Hum Behav 5: 497–511. https://doi.org/10.1038/s41562-020-01003-6.

Dehaene S, Naccache L (2001). Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. Cognition 79: 1–37. https://doi.org/10.1016/S0010-0277(00)00123-2.

Edlow BL, Claassen J, Schiff ND et al. (2020). Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. Nat Rev Neurol 17: 135–156. https://doi.org/10.1038/s41582-020-00428-x.

Edlow BL, Sanz LRD, Polizzotto L et al. (2021). Therapies to restore consciousness in patients with severe brain injuries: a gap analysis and future directions. Neurocrit Care 35: 68–85. https://doi.org/10.1007/S12028-021-01227-Y.

Fan J, Zhong Y, Wang H et al. (2022). Repetitive transcranial magnetic stimulation improves consciousness in some patients with disorders of consciousness. Clin Rehabil 36: 916–925. https://doi.org/10.1177/02692155221089455.

Feller D, Vinante C, Trentin F et al. (2021). The effectiveness of median nerve electrical stimulation in patients with disorders of consciousness: a systematic review. Brain Inj 35: 385–394. https://doi.org/10.1080/02699052.2021.1887522.

Fins JJ, Bernat JL (2018). Ethical, palliative, and policy considerations in disorders of consciousness. Neurology 91: 471–475. https://doi.org/10.1212/WNL.0000000000005927.

Fomenko A, Neudorfer C, Dallapiazza RF et al. (2018). Low-intensity ultrasound neuromodulation: an overview of mechanisms and emerging human applications. Brain Stimul 11: 1209–1217. https://doi.org/10.1016/J.BRS.2018.08.013.

Forgacs PB, Conte MM, Fridman EA et al. (2014). Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. Ann Neurol 76: 869–879. https://doi.org/10.1002/ANA.24283.

Fridman EA, Beattie BJ, Broft A et al. (2014). Role of anterior forebrain mesocircuit dysfunction in the severely injured brain. Proc Natl Acad Sci USA 111: 6473–6478. https://www.pnas.org/doi/full/10.1073/pnas.1320969111.

Ge X, Zhang Y, Xin T et al. (2021). Effects of 10 Hz repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in the vegetative state. Exp Ther Med 21: 206. https://doi.org/10.3892/ETM.2021.9626.

Giacino JT, Ashwal S, Childs N et al. (2002). The minimally conscious state: definition and diagnostic criteria. Neurology 58: 349–353. https://doi.org/10.1212/WNL.58.3.349.

Giacino JT, Kalmar K, Whyte J (2004). The JFK coma recovery scale-revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 85: 2020–2029. https://doi.org/10.1016/J.APMR.2004.02.033.

Giacino JT, Whyte J, Bagiella E et al. (2012). Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med 366: 819–826. https://doi.org/10.1056/NEJMOA1102609.

Giacino JT, Fins JJ, Laureys S et al. (2014). Disorders of consciousness after acquired brain injury: the state of the science. Nat Rev Neurol 10: 99–114. https://doi.org/10.1038/NRNEUROL.2013.279.

Giacino J, Katz D, Schiff N et al. (2018a). Comprehensive systematic review update summary: disorders of consciousness: report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. Neurology 91: 461–470.

Giacino JT, Katz DI, Schiff ND et al. (2018b). Practice guideline update recommendations summary: disorders of consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. Arch Phys Med Rehabil 99: 1699–1709. https://doi.org/10.1016/j.apmr.2018.07.001.

Golestanirad L, Rouhani H, Elahi B et al. (2012). Combined use of transcranial magnetic stimulation and metal electrode implants: a theoretical assessment of safety considerations. Phys Med Biol 57: 7813. https://doi.org/10.1088/0031-9155/57/23/7813.

Graham DI, Adams JH, Murray LS et al. (2005). Neuropathology of the vegetative state after head injury. Neuropsychol Rehabil 15: 198–213. https://doi.org/10.1080/09602010443000452.

Grillner S, Hellgren J, Ménard A et al. (2005). Mechanisms for selection of basic motor programs—roles for the striatum and pallidum. Trends Neurosci 28: 364–370. https://doi.org/10.1016/J.TINS.2005.05.004.

Guleyupoglu B, Schestatsky P, Edwards D et al. (2013). Classification of methods in transcranial Electrical Stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. J Neurosci Methods 219: 297–311. https://doi.org/10.1016/J.JNEUMETH.2013.07.016.

Hakon J, Moghiseh M, Poulsen I et al. (2020). Transcutaneous vagus nerve stimulation in patients with severe traumatic brain injury: a feasibility trial. Neuromodulation 23: 859–864. https://doi.org/10.1111/NER.13148.

\He F, Wu M, Meng F et al. (2018). Effects of 20 Hz repetitive transcranial magnetic stimulation on disorders of consciousness: a resting-state electroencephalography study. Neural Plast 2018: https://doi.org/10.1155/2018/5036184.

He RH, Wang HJ, Zhou Z et al. (2021). The influence of high-frequency repetitive transcranial magnetic stimulation on endogenous estrogen in patients with disorders of consciousness. Brain Stimul 14: 461–466. https://doi.org/10.1016/J.BRS.2021.02.014.

Hein E, Nowak M, Kiess O et al. (2013). Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study. J Neural Transm (Vienna) 120: 821–827. https://doi.org/10.1007/S00702-012-0908-6.

Heine L, Castro M, Martial C et al. (2015). Exploration of functional connectivity during preferred music stimulation in patients with disorders of consciousness. Front Psychol 6: https://doi.org/10.3389/FPSYG.2015.01704.

Hermann B, Raimondo F, Hirsch L et al. (2020). Combined behavioral and electrophysiological evidence for a direct cortical effect of prefrontal tDCS on disorders of consciousness. Sci Rep 10: 1–16. https://doi.org/10.1038/s41598-020-61,180-2.

Herrold AA, Pape TLB, Guernon A et al. (2014). Prescribing multiple neurostimulants during rehabilitation for severe brain injury. ScientificWorldJournal 2014: https://doi.org/10.1155/2014/964578.

Hoshide R, Jandial R (2018). Regaining consciousness: the effect of vagal nerve stimulation on a patient in a permanent vegetative state. Clin Neurosurg 82: N29–N30. https://doi.org/10.1093/NEUROS/NYX597.

Huang W, Wannez S, Fregni F et al. (2017). Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: a sham-controlled randomized clinical trial. Brain Stimul 10: 718–720. https://doi.org/10.1016/J.BRS.2017.02.001.

James W (1890). The principles of psychology. In: The principles of psychology, Henry Holt and Co, https://doi.org/10.1037/10538-000.

James W (1894). The physical bases of emotion. Psychol Rev. https://doi.org/10.1037/0033-295X.101.2.205.

Johnson RL, Wilson CG (2018). A review of vagus nerve stimulation as a therapeutic intervention. J Inflamm Res 11: 203–213. https://doi.org/10.2147/JIR.S163248.

Kobayashi M, Pascual-Leone A (2003). Transcranial magnetic stimulation in neurology. Lancet Neurol 2: 145–156. https://doi.org/10.1016/S1474-4422(03)00321-1.

Kondziella D, Bender A, Diserens K et al. (2020). European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. Eur J Neurol 27: 741–756. https://doi.org/10.1111/ENE.14151.

Kraus T, Hösl K, Kiess O et al. (2007). BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. J Neural Transm (Vienna) 114: 1485–1493. https://doi.org/10.1007/S00702-007-0755-Z.

Lefaucheur JP, Aleman A, Baeken C et al. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clin Neurophysiol 131: 474–528. https://doi.org/10.1016/J.CLINPH.2019.11.002.

Lei J, Wang L, Gao G et al. (2015). Right median nerve electrical stimulation for acute traumatic coma patients. J Neurotrauma 32: 1584–1589. https://doi.org/10.1089/NEU.2014.3768.

Lemaire JJ, Sontheimer A, Pereira B et al. (2018). Deep brain stimulation in five patients with severe disorders of consciousness. Ann Clin Transl Neurol 5: 1372. https://doi.org/10.1002/ACN3.648.

Liu X, Meng F, Gao J et al. (2018). Behavioral and resting state functional connectivity effects of high frequency rTMS on disorders of consciousness: a sham-controlled study. Front Neurol 9. https://doi.org/10.3389/FNEUR.2018.00982.

Lopez L, Chan CY, Okada YC et al. (1991). Multimodal characterization of population responses evoked by applied electric field in vitro: extracellular potential, magnetic evoked field, transmembrane potential, and current-source density analysis. J Neurosci 11: 1998–2010. https://doi.org/10.1523/JNEUROSCI.11-07-01998.1991.

López-González A, Panda R, Ponce-Alvarez A et al. (2021). Loss of consciousness reduces the stability of brain hubs and the heterogeneity of brain dynamics. Commun Biol 4: 1–15. https://doi.org/10.1038/s42003-021-02537-9.

Luppi AI, Cain J, Spindler LRB et al. (2021). Mechanisms underlying disorders of consciousness: bridging gaps to move toward an integrated translational science. Neurocrit Care 35: 37–54. https://doi.org/10.1007/S12028-021-01281-6/TABLES/3.

Machado C, Estévez M, Rodriguez-Rojas R (2018). Zolpidem efficacy and safety in disorders of consciousness. Brain Inj 32: 530–531. https://doi.org/10.1080/02699052.2018.1429664.

Magrassi L, Maggioni G, Pistarini C et al. (2016). Results of a prospective study (CATS) on the effects of thalamic stimulation in minimally conscious and vegetative state patients. J Neurosurg 125: 972–981. https://doi.org/10.3171/2015.7.JNS15700.

Majerus S, Bruno MA, Schnakers C et al. (2009). The problem of aphasia in the assessment of consciousness in brain-damaged patients. Prog Brain Res 177: 49–61. https://doi.org/10.1016/S0079-6123(09)17705-1.

Martens G, Fregni F, Carrière M et al. (2019). Single tDCS session of motor cortex in patients with disorders of consciousness: a pilot study. Brain Inj. https://doi.org/10.1080/02699052.2019.1667537.

Martens G, Kroupi E, Bodien Y et al. (2020). Behavioral and electrophysiological effects of network-based frontoparietal tDCS in patients with severe brain injury: a randomized controlled trial. Neuroimage Clin 28: 426. https://doi.org/10.1016/J.NICL.2020.102426.

Martens G, Ibáñez-Soria D, Barra A et al. (2021). A novel closed-loop EEG-tDCS approach to promote responsiveness of patients in minimally conscious state: a study protocol. Behav Brain Res 409. https://doi.org/10.1016/J.BBR.2021.113311.

Mattsson N, Zetterberg H, Nielsen N et al. (2017). Serum tau and neurological outcome in cardiac arrest. Ann Neurol 82: 665–675. https://doi.org/10.1002/ANA.25067.

Mélotte E, Belorgeot M, Herr R et al. (2021). The development and validation of the SWADOC: a study protocol for a multicenter prospective cohort study. Front Neurol 12. https://doi.org/10.3389/FNEUR.2021.662634.

Mensen A, Bodart O, Thibaut A et al. (2020). Decreased evoked slow-activity after tDCS in disorders of consciousness. Front Syst Neurosci 14. https://doi.org/10.3389/FNSYS.2020.00062.

Merton PA, Morton HB (1980). Stimulation of the cerebral cortex in the intact human subject. Nature 285: 227. https://doi.org/10.1038/285227A0.

Mishra A, Maiti R, Mishra BR et al. (2019). Effect of repetitive transcranial magnetic stimulation on seizure frequency and epileptiform discharges in drug-resistant epilepsy: a meta-analysis. J Clin Neurol 16: 9–18. https://doi.org/10.3988/JCN.2020.16.1.9.

Monti MM, Schnakers C, Korb AS et al. (2016). Non-invasive ultrasonic thalamic stimulation in disorders of consciousness after severe brain injury: a first-in-man report. Brain Stimul 9: 940–941. https://doi.org/10.1016/J.BRS.2016.07.008.

Naro A, Russo M, Leo A et al. (2015). A single session of repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex in patients with unresponsive wakefulness syndrome: preliminary results. Neurorehabil Neural Repair 29: 603–613. https://doi.org/10.1177/1545968314562114.

Naro A, Russo M, Leo A et al. (2016). Cortical connectivity modulation induced by cerebellar oscillatory transcranial direct current stimulation in patients with chronic disorders of consciousness: a marker of covert cognition? Clin Neurophysiol 127: 1845–1854. https://doi.org/10.1016/J.CLINPH.2015.12.010.

Noé E, Ferri J, Colomer C et al. (2020). Feasibility, safety and efficacy of transauricular vagus nerve stimulation in a cohort of patients with disorders of consciousness. Brain Stimul 13: 427–429. https://doi.org/10.1016/J.BRS.2019.12.005.

O'Kelly J, James L, Palaniappan R et al. (2013). Neurophysiological and behavioral responses to music therapy in vegetative and minimally conscious states. Front Hum Neurosci 7. https://doi.org/10.3389/FNHUM.2013.00884.

O'Neal CM, Schroeder LN, Wells AA et al. (2021). Patient outcomes in disorders of consciousness following transcranial magnetic stimulation: a systematic review and meta-analysis of individual patient data. Front Neurol 12. https://doi.org/10.3389/FNEUR.2021.694970.

Odegaard B, Knight RT, Lau H (2017). Should a few null findings falsify prefrontal theories of conscious perception? J Neurosci 37: 9593–9602. https://doi.org/10.1523/JNEUROSCI.3217-16.2017.

Osińska A, Rynkiewicz A, Binder M et al. (2022). Non-invasive vagus nerve stimulation in treatment of disorders of consciousness—longitudinal case study. Front Neurosci 16. https://doi.org/10.3389/FNINS.2022.834507.

Pape TLB, Rosenow JM, Harton B et al. (2012). Preliminary framework for Familiar Auditory Sensory Training (FAST) provided during coma recovery. J Rehabil Res Dev 49: 1137–1152. https://doi.org/10.1682/JRRD.2011.08.0154.

Pascual-Leone A, Tarazona F, Keenan J et al. (1998). Transcranial magnetic stimulation and neuroplasticity. Neuropsychologia 37: 207–217. https://doi.org/10.1016/S0028-3932(98)00095-5.

Pathak A, Roy D, Banerjee A (2022). Whole-brain network models: from physics to bedside. Front Comput Neurosci 57. https://doi.org/10.3389/FNCOM.2022.866517.

Perl YS, Pallavicini C, Ipiña IP et al. (2021). Perturbations in dynamical models of whole-brain activity dissociate between the level and stability of consciousness. PLoS Comput Biol 17. https://doi.org/10.1371/JOURNAL.PCBI.1009139.

Perlmutter JS, Mink JW (2006). Deep brain stimulation. Annu Rev Neurosci 29: 229. https://doi.org/10.1146/ANNUREV.NEURO.29.051605.112824.

Peuker ET, Filler TJ (2002). The nerve supply of the human auricle. Clin Anat 15: 35–37. https://doi.org/10.1002/CA.1089.

Piarulli A, Bergamasco M, Thibaut A et al. (2016). EEG ultradian rhythmicity differences in disorders of consciousness during wakefulness. J Neurol 263: 1746–1760. https://doi.org/10.1007/S00415-016-8196-Y.

Plum F, Posner JB (1972). The diagnosis of stupor and coma. Contemp Neurol Ser 10: 1–286. https://doi.org/10.1001/jama.1981.03310320080042.

Radman T, Ramos RL, Brumberg JC et al. (2009). Role of cortical cell type and morphology in sub- and suprathreshold uniform electric field stimulation. Brain Stimul 2: 215. https://doi.org/10.1016/J.BRS.2009.03.007.

Ray PG, Meador KJ, Epstein CM et al. (1998). Magnetic stimulation of visual cortex: factors influencing the perception of phosphenes. J Clin Neurophysiol 15: 351–357. https://doi.org/10.1097/00004691-199,807,000-00007.

Reed T, Cohen Kadosh R (2018). Transcranial electrical stimulation (tES) mechanisms and its effects on cortical excitability and connectivity. J Inherit Metab Dis 41: 1123. https://doi.org/10.1007/S10545-018-0181-4.

Rohan JG, Carhuatanta KA, McInturf SM et al. (2015). Modulating hippocampal plasticity with in vivo brain stimulation. J Neurosci 35: 12824–12832. https://doi.org/10.1523/JNEUROSCI.2376-15.2015.

Samaha J, Gosseries O, Postle BR (2017). Distinct oscillatory frequencies underlie excitability of human occipital and parietal cortex. J Neurosci 37: 2824–2833. https://doi.org/10.1523/JNEUROSCI.3413-16.2017.

Sanz LRD, Aubinet C, Cassol H et al. (2021). SECONDs Administration Guidelines: a fast tool to assess consciousness in brain-injured patients. J Vis Exp 2021: e61968. https://doi.org/10.3791/61968.

Schiff ND (2008). Central thalamic contributions to arousal regulation and neurological disorders of consciousness. Ann N Y Acad Sci 1129: 105–118. https://doi.org/10.1196/ANNALS.1417.029.

Schiff ND (2010). Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci 33: 1–9. https://doi.org/10.1016/J.TINS.2009.11.002.

Schiff ND (2016). Central thalamic deep brain stimulation to support anterior forebrain mesocircuit function in the severely injured brain. J Neural Transm (Vienna) 123: 797–806. https://doi.org/10.1007/S00702-016-1547-0.

Stefan H, Kreiselmeyer G, Kerling F et al. (2012). Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. Epilepsia 53. https://doi.org/10.1111/J.1528-1167.2012.03492.X.

Terranova C, Rizzo V, Cacciola A et al. (2019). Is there a future for non-invasive brain stimulation as a therapeutic tool? Front Neurol 10: 1146. https://doi.org/10.3389/FNEUR.2018.01146/BIBTEX.

Thibaut A, Chatelle C, Wannez S et al. (2015a). Spasticity in disorders of consciousness: a behavioral study. Eur J Phys Rehabil Med 51: 389–397.

Thibaut A, di Perri C, Chatelle C et al. (2015b). Clinical response to tDCS depends on residual brain metabolism and grey matter integrity in patients with minimally conscious state. Brain Stimul 8: 1116–1123. https://doi.org/10.1016/J.BRS.2015.07.024.

Thibaut A, Wannez S, Donneau AF et al. (2017). Controlled clinical trial of repeated prefrontal tDCS in patients with chronic minimally conscious state. Brain Inj 31: 466–474. https://doi.org/10.1080/02699052.2016.1274776.

Thibaut A, Chennu S, Chatelle C et al. (2018). Theta network centrality correlates with tDCS response in disorders of consciousness. Brain Stimul 11: 1407–1409. https://doi.org/10.1016/J.BRS.2018.09.002.

Thibaut A, Schiff N, Giacino J et al. (2019). Therapeutic interventions in patients with prolonged disorders of consciousness. Lancet Neurol 18: 600–614. https://doi.org/10.1016/S1474-4422(19)30031-6.

Thonnard M, Gosseries O, Demertzi A et al. (2013). Effect of zolpidem in chronic disorders of consciousness: a prospective open-label study. Funct Neurol 28: 259–264. https://doi.org/10.11138/FNEUR/2013.28.4.259.

Tononi G (2012). Integrated information theory of consciousness: an updated account. Arch Ital Biol 150: 293–329. https://doi.org/10.4449/aib.v149i5.1388.

Tononi G, Edelman GM (1998). Consciousness and complexity. Science 282: 1846–1851. https://doi.org/10.1126/SCIENCE.282.5395.1846.

Vanzan S, Wilkinson D, Ferguson H et al. (2017). Behavioural improvement in a minimally conscious state after caloric vestibular stimulation: evidence from two single case studies. Clin Rehabil 31: 500–507. https://doi.org/10.1177/0269215516646167.

Vogel D, Shah A, Coste J et al. (2020). Anatomical brain structures normalization for deep brain stimulation in movement disorders. Neuroimage Clin 27: 271. https://doi.org/10.1016/J.NICL.2020.102271.

Vöröslakos M, Takeuchi Y, Brinyiczki K et al. (2018). Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun 9. https://doi.org/10.1038/S41467-018-02928-3.

Wang Y, Bai Y, Xia X et al. (2020). Spinal cord stimulation modulates complexity of neural activities in patients with disorders of consciousness. Int J Neurosci 130: 662–670. https://doi.org/10.1080/00207454.2019.1702543.

Wannez S, Heine L, Thonnard M et al. (2017). The repetition of behavioral assessments in diagnosis of disorders of consciousness. Ann Neurol 81: 883–889. https://doi.org/10.1002/ANA.24962.

Whyte J, Rajan R, Rosenbaum A et al. (2014). Zolpidem and restoration of consciousness. Am J Phys Med Rehabil 93: 101–113. https://doi.org/10.1097/PHM.0000000000000069.

Xia X, Bai Y, Zhou Y et al. (2017a). Effects of 10 Hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in disorders of consciousness. Front Neurol 8: 182. https://doi.org/10.3389/FNEUR.2017.00182/BIBTEX.

Xia X, Liu Y, Bai Y et al. (2017b). Long-lasting repetitive transcranial magnetic stimulation modulates electroencephalography oscillation in patients with disorders of consciousness. Neuroreport 28: 1022–1029. https://doi.org/10.1097/WNR.0000000000000886.

Yamamoto T, Watanabe M, Obuchi T et al. (2017). Spinal cord stimulation for vegetative state and minimally conscious state: changes in consciousness level and motor function. Acta Neurochir Suppl (Wien) 124: 37–42. https://doi.org/10.1007/978-3-319-39,546-3_6/FIGURES/2.

Yang Y, He Q, Xia X et al. (2022). Long-term functional prognosis and related factors of spinal cord stimulation in patients with disorders of consciousness. CNS Neurosci Ther 28: 1249. https://doi.org/10.1111/CNS.13870.

Yifei W, Yi Y, Yu W et al. (2022). Transcutaneous auricular vague nerve stimulation improved brain connection activity on patients of disorders of consciousness: a pilot study. J Tradit Chin Med 42: 463–471. https://doi.org/10.19852/J.CNKI.JTCM.2022.03.012.

Yu YT, Yang Y, Wang L-B et al. (2017). Transcutaneous auricular vagus nerve stimulation in disorders of consciousness monitored by fMRI: The first case report. Brain Stimul 10: 328–330. https://doi.org/10.1016/J.BRS.2016.12.004.

Zhang Y, Song W (2018). Transcranial direct current stimulation in disorders of consciousness: a review. Int J Neurosci 128: 255–261. https://doi.org/10.1080/00207454.2017.1381094.

Ziemann U, Siebner HR (2015). Inter-subject and inter-session variability of plasticity induction by non-invasive brain stimulation: boon or bane? Brain Stimul 8: 662–663. https://doi.org/10.1016/J.BRS.2015.01.409.

Ziemann U, Paulus W, Nitsche MA et al. (2008). Consensus: motor cortex plasticity protocols. Brain Stimul 1: 164–182. https://doi.org/10.1016/J.BRS.2008.06.006.