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Corresponding Author	Family Name	**Thibaut**
	Particle	
	Given Name	**Aurore**
	Suffix	
	Division	Coma Science Group, GIGA Research
	Organization/University	University of Liege
	Address	Liege, Belgium
	Division	Spaulding Neuromodulation Center
	Organization/University	Harvard Medical School
	Address	Boston, MA, USA
	Email	athibaut@ulg.ac.be
Author	Family Name	**Schiff**
	Particle	
	Given Name	**Nicholas D.**
	Suffix	
	Division	Feil Family Brain and Mind Research Institute
	Organization/University	Weill Cornell Medical College
	Address	New York, NY, USA

Abstract	Neuromodulation techniques aimed at normalizing the neurophysiologic disturbance produced by brain lesions or dysfunction have been studied for years in attempts to modulate brain activity to treat several neurological diseases. The field of (non)invasive brain stimulation offers a valuable alternative to improve the recovery of severely brain-injured patients with disorders of consciousness, a population that lacks of effective treatment options, especially at the chronic stage. We here describe invasive and noninvasive brain stimulation techniques, namely, deep brain stimulation (DBS) and transcranial direct current stimulation (tDCS), as therapeutic options for patients with DOC. DBS has shown to induce extensive behavioral improvement after the implantation of an electrical stimulator in the intralaminar nuclei in case reports. However, large controlled clinical trials have to be conducted in order to confirm the clinical benefit of this treatment. Regarding tDCS, the first studies, targeting the left prefrontal cortex, have shown encouraging results, with significant behavioral improvements, in both acute and chronic patients. Besides behavioral improvements, mechanisms underlying the effects of these neuromodulation techniques need to be further investigated. The mesocircuit model, by integrating the fronto-striato-thalamic loop, provides a conceptual foundation to explain the effects of several treatments having shown some effectiveness in the recovery of patients with DOC.
Keywords (separated by " - ")	Neuromodulation - Deep brain stimulation - Transcranial direct current stimulation - Disorders of consciousness - Vegetative state/unresponsive wakefulness syndrome - Rehabilitation

AUTHOR QUERIES

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Chapter 12
New Therapeutic Options for the Treatment of Patients with Disorders of Consciousness: The Field of Neuromodulation

Aurore Thibaut and Nicholas D. Schiff

Abstract Neuromodulation techniques aimed at normalizing the neurophysiologic disturbance produced by brain lesions or dysfunction have been studied for years in attempts to modulate brain activity to treat several neurological diseases. The field of (non)invasive brain stimulation offers a valuable alternative to improve the recovery of severely brain-injured patients with disorders of consciousness, a population that lacks of effective treatment options, especially at the chronic stage. We here describe invasive and noninvasive brain stimulation techniques, namely, deep brain stimulation (DBS) and transcranial direct current stimulation (tDCS), as therapeutic options for patients with DOC. DBS has shown to induce extensive behavioral improvement after the implantation of an electrical stimulator in the intralaminar nuclei in case reports. However, large controlled clinical trials have to be conducted in order to confirm the clinical benefit of this treatment. Regarding tDCS, the first studies, targeting the left prefrontal cortex, have shown encouraging results, with significant behavioral improvements, in both acute and chronic patients. Besides behavioral improvements, mechanisms underlying the effects of these neuromodulation techniques need to be further investigated. The mesocircuit model, by integrating the fronto-striato-thalamic loop, provides a conceptual foundation to explain the effects of several treatments having shown some effectiveness in the recovery of patients with DOC.

A. Thibaut, Ph.D. (✉)
AUT Coma Science Group, GIGA Research, University of Liege, Liege, Belgium

Spaulding Neuromodulation Center, Harvard Medical School, Boston, MA, USA
e-mail: athibaut@ulg.ac.be

N.D. Schiff, M.D.
Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, New York, NY, USA

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Introduction

AU2 While significant progress has been made in understanding the neural correlates of disorders of consciousness (DOC), treatment options for patients with altered states of consciousness available today remain very limited. Moreover, when these treatments are effective, the underlying mechanisms are still almost unknown. Recent discoveries demonstrating the inherent plasticity of the brain suggest a wide range of therapeutic possibilities. Indeed, in the past 10 years, a number of studies have reported that some patients in MCS could spontaneously improve even several years after the insult [1–3]. Studies of treatments improving cognitive abilities in patients with DOC have also shown that deep brain stimulation (DBS) of the intralaminar nuclei of the thalamus [4] and some pharmacological agents such as amantadine [5, 6], apomorphine [7], intrathecal baclofen [8], and zolpidem [9, 10] can improve behavioral signs of consciousness in some patients with DOC. However, so far, only amantadine has been shown to increase signs of consciousness in a large cohort of acute and subacute patients with DOC in a placebo-controlled trial [6]. In addition, the specific mechanisms underlying the recovery of behavioral signs of consciousness observed in such patients with DOC following the administration of these drugs are still poorly understood. We hence clearly need to improve our treatment options for the small—albeit existing—minority of patients who show clinically meaningful recovery of quality of life after chronic DOC [11]. Our next challenge is to better understand the mechanisms of action of these treatments when clinical improvement of patients is observed and how to possibly improve therapeutic options.

In this chapter, we describe the use of invasive and noninvasive brain stimulation (i.e., deep brain stimulation (DBS) and transcranial direct current stimulation (tDCS)) to improve the recovery of patients with DOC, as well as the current models that could explain the underlying neurophysiological mechanisms of these two neuromodulation techniques.

What Network to Stimulate

Frontoparietal Network

Studies of regional brain metabolism have sought to identify areas specifically involved in loss of consciousness, comparing brain metabolism of patients in vegetative state/unresponsive wakefulness syndrome (VS/UWS) and in minimally conAU3 scious state (MCS) with healthy controls. The results of these studies highlight the correlation of a widespread impairment of the frontoparietal network, encompassing midline (i.e., anterior cingulate cortex (ACC)/mesiofrontal and posterior cingulate cortex (PCC)/precuneus, related to internal awareness or self-related processes) and lateral (i.e., prefrontal and posterior parietal, related to awareness of the

environment) associative cortices [12–18]. The decreased level of consciousness is correlated with the connectivity within the midline frontoparietal cortex, also called the default mode network (DMN), has been shown to reflect the level of consciousness of DOC patients [19]. Indeed, the connectivity of this network is correlated to the level of consciousness, ranging from patients in UWS/VS (low connectivity) to patients in MCS and to healthy controls (higher connectivity). In a more recent study, it has been observed that patients in UWS/VS have metabolic dysfunction in both thalami and both extrinsic/lateral and intrinsic/medial networks, also called the DMN (i.e., anterior cingulate/medial prefrontal cortex and posterior cingulate/precuneus), as compared to controls, while MCS patients showed metabolic dysfunction in both thalami but only in the intrinsic/medial network [20]. These studies point to the importance of both internal and external consciousness network in the recovery of consciousness.

Part of the external consciousness network, the dorsolateral prefrontal cortex (DLPFC) is a critical area for higher cognitive functions. This cortical region is connected to many brain areas such as the orbitofrontal cortex, the basal ganglia, the thalamus, and the associative cortical areas. It is thought to play an important integrating role in the motor and behavioral functions, as well as in the executive functions, such as planning, working memory, inhibition, and cognitive flexibility. Indeed, the DLPFC receives multisensory information from the parietal associative cortices and projects directly to subcortical monoaminergic and cholinergic neuronal populations within the brainstem [21–23]. Besides executive functions, the additional cortical and subcortical circuits with which the DLPFC is connected are more generally required for all complex mental activity. Indeed, the DLPFC is part of the functional executive control network, known to be related to external awareness [24]. Through these complex connections with cortical and subcortical brain areas, the DFPLC is a critical brain region for cognitive functions and integrations. It is part of the external consciousness network, as well as related to the recovery of consciousness [20]. Recent neuroimaging studies have shown the implication of the DFPLC in the efficacy of several treatments (e.g., zolpidem, amantadine, or noninvasive brain stimulation) aiming to improve signs of consciousness in DOC patients [5, 25, 26], further strengthening the importance of this region in recovery of consciousness (see below).

It is now widely admitted that the precuneus is another critical hub for consciousness recovery [13, 18, 27, 28]. Indeed, several studies have shown that, at rest, the precuneus is the most active area in healthy subjects, while it is the most impaired in patients in VS/UWS [29]. In addition, the recovery from VS/UWS seems to be paralleled by a recovery in brain metabolism in this region [12, 30]. Moreover, the precuneus is a critical hub of the DMN, which is also highly correlated with the level of consciousness [19, 27, 31, 32]. A recent functional magnetic resonance imaging (fMRI) study using tractography has anatomically objectified that patients with DOC demonstrate damages in fiber tracts connecting the precuneus with both cortical (i.e., temporoparietal junction and frontal medial cortex) and subcortical (i.e., thalamus and striatum) areas [33].

Mesocircuit Frontoparietal Model

In addition to the very strong evidence that activity within the frontoparietal network grades with level of recovery of consciousness, the key role of the anterior forebrain mesocircuit has been identified in recovery of consciousness after severe brain injuries [34]. These networks have critical functional and anatomical relationships that support a joint mesocircuit frontoparietal model [35] as reviewed below (Fig. 12.1).

The mesocircuit hypothesis emphasizes that the anterior forebrain is particularly vulnerable to downregulation due to widespread cerebral deafferentation that typically occurs following multifocal brain injuries [34]. The anterior forebrain mesocircuit itself prominently includes the frontal/prefrontal cortices and the striatopallidal modulatory system that regulates thalamic outflow back to the cortex and striatum. Neurons within the central thalamus have a crucial role in the mesocircuit based on their extensive anatomical connectivity with the forebrain [37], as

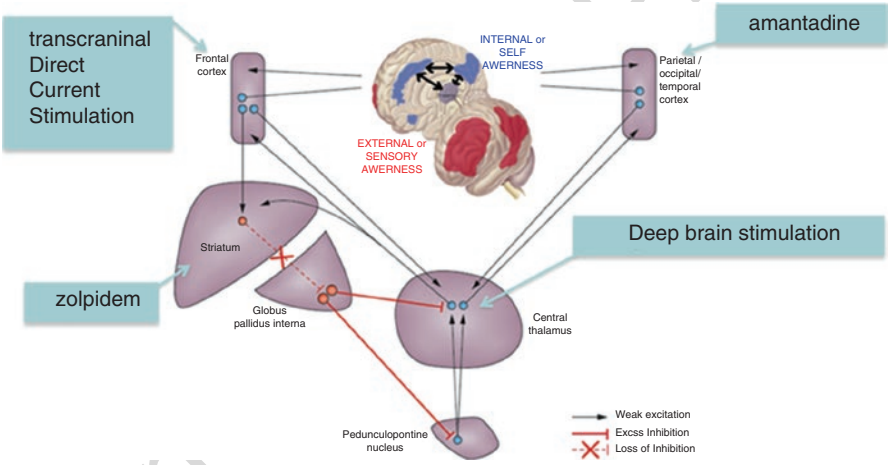

Fig. 12.1 The mesocircuit frontoparietal model. Reduction of thalamocortical and thalamostriatal outflow following deafferentation and loss of neurons from the central thalamus withdraws important afferent drive to the medium spiny neurons of the striatum, which may then fail to reach firing threshold because of their requirement for high levels of synaptic background activity. Loss of active inhibition from the striatum allows neurons of the globus pallidus interna (GPi) to tonically fire and provide active inhibition to their synaptic targets, including relay neurons of the already strongly disfacilitated central thalamus, and possibly also the projection neurons of the pedunculopontine nucleus. Several treatments that have shown promising results in the recovery of signs of consciousness in severely brain-injured patients are related to the mesocircuit model. A partial preservation of the prefrontal cortex (i.e., stimulated area) seems to be necessary to induce a clinical tDCS response [25]. The clinical improvement of a patient who responded to amantadine was correlated with an increase in brain metabolism with the frontoparietal network [5]. Zolpidem may reduce the inhibition of the thalamus by activating the striatum [34]. Finally, deep brain stimulation directly acts over the central thalamus aiming to stimulate the thalamocortical connectivity [4] (Adapted from [36])

well as their functional role in forebrain arousal regulation [38, 39]. Consistent with their unique geometry, pathological studies have shown strong correlation of the loss of these central thalamic neurons with the severity of structural brain injuries and level of functional outcomes ranging from disorders of consciousness to moderate disabilities [40]. The main hypothesis anticipates two major effects: (1) a critical decrease in central thalamic outflow secondary to disfacilitation [41] resulting from loss of corticothalamic connections and (2) direct inhibition of central thalamic neurons by disinhibited globus pallidus (GP) neurons as a result of insufficient corticostriatal and thalamostriatal input to the medium spiny neurons (MSNs) of the striatum that require high level of stimulation to reach their firing threshold [42]. Collectively, as a result, the activity across the striatum, central thalamus, and frontal/prefrontal cortices is consequently decreased.

Several studies have found evidence in support of the mesocircuit hypothesis. A recent study compared the metabolic profiles of severely brain-injured patients with DOC, with healthy controls, and identified that metabolism within ventral and association striatum (excluding the sensorimotor portion), as well as in the central thalamus, was reduced in patients, while an increase was observed in the GPi (Fridman et al. [43]—see Fig. 12.2). These reversal profiles in patients as compared to controls in the GPi and the central thalamus give another strong support to the mesocircuit model.

This mesocircuit model provides an economical explanation of the vulnerability of the anterior forebrain in patients with DOC who suffer from widespread

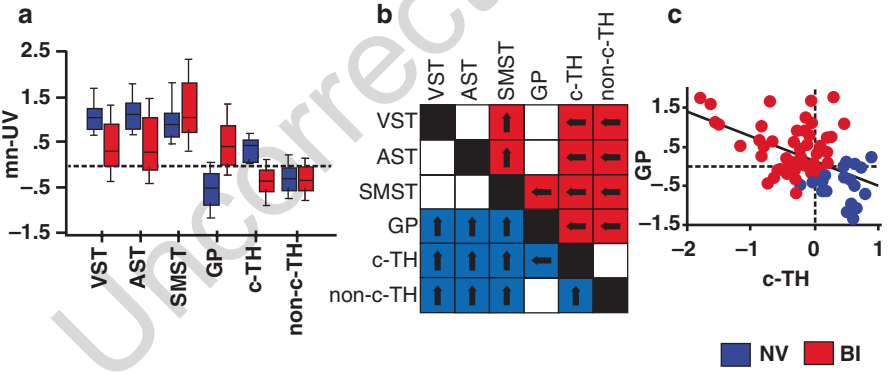

Fig. 12.2 Group data displaying glucose uptake values in deep brain structures measured in healthy controls (in *blue*) and brain-injured subjects (in *red*). (**a**) *Box plot*. A significant reduction in relative glucose metabolism of the ventral striatum (VST), associative striatum (AST), and central thalamus (c-TH) in brain-injured subjects is seen compared with healthy controls. No difference in sensorimotor striatum (SMST) mn-UV is present between healthy controls and brain-injured subjects. A significant increase in GP metabolism is present in the group of BI subjects. (**b**) Significant results are shown in *blue* for healthy controls and *red* for brain-injured patients, whereas *white boxes* denote no significant differences; *arrows* indicate the direction of the significance (i.e., pointing toward the higher mn-UV values). (**c**) Bivariate scattergram demonstrates an inverse linear correlation between glucose metabolic rate of the c-TH (*x*-axis) and the GP (*y*-axis) (From [43])

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deafferentation and neuronal cell loss. Interestingly, bulk activation of the anterior forebrain based on the mesocircuit model can explain the effect of several pharmacological interventions, as well as thalamic DBS [34]. An interesting example is zolpidem, a short-acting non-benzodiazepine GABA agonist hypnotic drug that has shown to induce paradoxical responses in some patients with DOC. In a recent study, Chatelle et al. [26] have shown that the recovery of consciousness of three zolpidem responders (i.e., patients who transiently recovered a functional communication under zolpidem) was correlated with an increase in brain metabolism within the dorsolateral prefrontal and mesiofrontal cortices (see Fig. 12.3). Zolpidem could inhibit the GPi by inhibiting the GABAAa-1 subunit, expressed in large quantities in the GPi. This would substitute for the normal inhibition of the GPi from the striatum, hence increasing the thalamic excitatory influence on prefrontal cortices. Additionally, direct excitatory effects at the level of the cortex and striatum likely play a key role in the response [44]. Activation of frontal EEG in zolpidem responders is further consistent with the model and the findings of Chatelle et al. [26]. Interestingly, in all neuroimaging studies investigating the cerebral patterns of zolpidem responders [26, 45, 46], the brain areas showing increased metabolism after zolpidem did not show significant structural lesions, a finding consistent either with the proposal that zolpidem responders have consciousness impairments mainly due to inhibitory functional effects rather than by structural damage [47] or that reduced firing rates produced by disfacilitation are present and that a widening of the dynamic range of these neuronal populations is achieved by release of a circuit-level blockage [44].

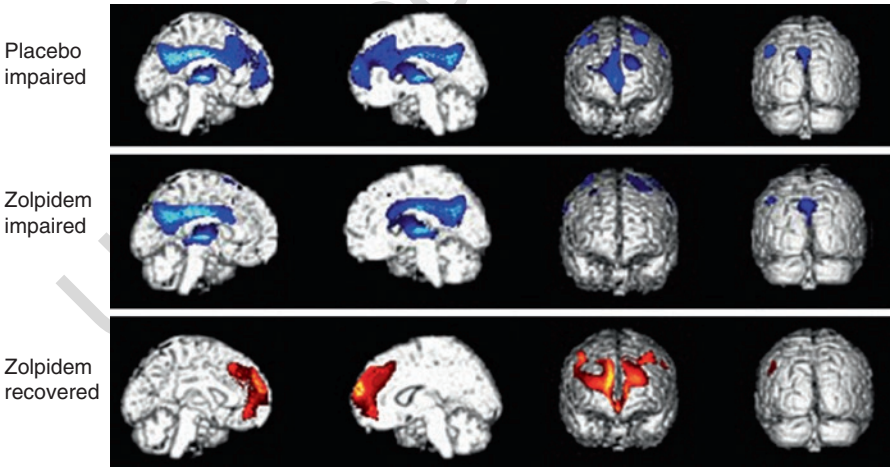

Fig. 12.3 Impaired brain metabolism after placebo and zolpidem intake and areas showing relative recovery after zolpidem. Brain areas showing impaired metabolism (in *blue*) following placebo and zolpidem administration and regions which were impaired following placebo but showed relative recovery of activity after zolpidem intake (in *red*). From left to right, medial right and left view and frontal and posterior view (From [26])

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The linkage of the mesocircuit and the frontoparietal model has been specifically supported by both anatomical and functional studies. Loss of structural connections between the thalamus and the posterior medial complex (including posterior cingulate cortex and precuneus, see below) has been statistically correlated with behavioral outcomes after severe brain injuries [48]. Anatomical projections from the central thalamus to the posterior medial cortical regions are strong [49], and a compelling functional correlation has been demonstrated in experimental studies of anesthetized healthy volunteers. Once in a stable plane of anesthesia, pharmacologically induced emergence from deep sedation using physostigmine produced a recovery of consciousness reflected in the ability to engage in command following in some subjects, recovery of command following correlated with co-activation of both the central thalamus and PMC [50]. Collectively, these studies show evidence of an interdependence of the functional integrity of the central thalamus and posterior medial complex and level of consciousness.

In summary, it seems that two important circuit mechanisms are combined in impaired consciousness following a severe brain injury and recovery [35]: (1) a strong link between the level of consciousness (from coma to emergence from MCS) and the preservation of resting metabolism in medial parietal cortex/posterior medial complex (i.e., precuneus, retrosplenial, posterior cortex) and (2) a key role for the central thalamus in regulating the anterior forebrain activation.

Deep Brain Stimulation (DBS)

DBS is widely used to treat several neurological and psychiatric disorders such as motor disorders (e.g., essential tremor, dystonia, Parkinson's disease), chronic pain, or obsessive-compulsive disorders and is FDA approved [51]. Basically, DBS encompasses a pulse generator that sends current to a brain electrode that delivers electrical and magnetic impulses to a targeted brain region. For some diseases, like Parkinson's and dystonia, DBS conceptually "inhibits" the targeted regions, while for other diseases, it has been employed to "excite" brain regions. The detailed underlying mechanisms of DBS are not yet fully understood and mainly depend on the targeted pathological process. At the basic level of initial effect on the brain, however, a primary effect of excitation of axonal action potentials is generally agreed upon outside of very high frequency or amplitude stimulation regimes which may induce conduction blockade [52, 53]. In the context of disorders of consciousness and central thalamic stimulation, direct excitation of projecting thalamocortical afferents is identified as the basic effect through a wide range of basic and clinical neuroscience studies (reviewed in [54]).

DBS in DOC patients aims at stimulating thalamocortical loops across frontostriatal regions responsible for cognitive functions such as attention, memory, language, or executive functions. The intralaminar nuclei were chosen because the central thalamus is suggested to be altered in regard to the pathophysiological mechanisms linked to the brain injury and cellular loss in central thalamus seems to

be particularly associated with DOC patients' level of recovery [40, 55]. Therefore, DBS could facilitate the induction and support the activity in a large network of neurons through the entire brain and thus lead to the recovery of cognitive functions underlined by these networks. In addition, the central thalamus plays a key role in arousal regulation. Indeed, neurons in the intralaminar nuclei of the thalamus are linked and located between the forebrain (involved in premotor shifts of attention and adjustments of vigilance level) and the arousal system in the brainstem [37].

The first DBS studies in DOC, performed between the 1960s and 1990s, failed to demonstrate any clinical improvements related to DBS. More recently, the effects of DBS of the midbrain reticular formation and the median-parafascicular complex were investigated in DOC patients [56]. Eight patients in VS/UWS recovered a response to commands (i.e., MCS+), and four patients in MCS recovered a functional communication (i.e., emerged from MCS). Unfortunately, the protocol did not encompass a controlled arm, and therefore, the exclusive relationship between clinical improvement and DBS cannot be stated.

In 2007, Schiff and collaborators have reported the case of a chronic posttraumatic patient in MCS treated with DBS of thalamic intralaminar nuclei in a double-blind design with recording of several baselines [4]. This was the first study that employed standardized reliable and validated outcome measures (such as the Coma Recovery Scale-Revised—CRS-R [57]) to investigate the efficacy of DBS. Clinically, the patient was in a minimally conscious state for 6 years at a considerably higher level of baseline behavior (CRS-R 19 at initiation of trial) than prior studies (CRS-R estimated ~7–9) and did not show any improvement despite rehabilitation program. DBS was applied bilaterally to the central thalamus and alternated on and off phases in 30-day intervals over 6 months. Intelligible verbalizations and functional object use were directly observed as soon as the stimulator was turned on during the titration period (following continuous stimulation for 18 h) but not within the initial 3-day testing with lower currents and limited times of exposure to stimulation. After a few months of stimulations, responses to command, spontaneous limb movements, oral feeding, and functional communication were objectified during DBS *on* periods. When DBS was turned *off*, behavioral performance decreased significantly but remained above baseline level, suggesting some remnant effects. These functional gains were maintained across the 24-month follow-up phase and for 6 years until the patient's death. Even if more clinical trials are required to confirm these effects in a large population of patients and to better understand the mechanisms of DBS in DOC, these findings are very encouraging for the potential to develop a therapy and the further recovery of some chronic patients with DOC.

Transcranial Direct Current Stimulation (tDCS)

In the past 15 years, many studies have shown that tDCS can modify neuronal excitability and induce behavioral changes in both healthy controls and patients with motor or cognitive dysfunctions [58–61]. Currently, a lot of clinical trials have been

conducted to study the effect of tDCS on poststroke motor and language deficits, in psychiatric disorders, chronic pain, memory impairment, and tinnitus in order to decrease symptoms [62–66]. tDCS represents a safe, cheap, and easy-to-use technique that could be easily integrated in rehabilitation programs. However, its therapeutic effect remains to be more extensively explored [67, 68]. Physiologically, tDCS involves passing a weak (usually ≤2 mA) direct current through the brain between two electrodes, the anode (i.e., excitatory) and the cathode (i.e., inhibitory). By decreasing or increasing the action potential threshold, anodal tDCS enhances excitability, whereas cathodal tDCS reduces it [69]. The formation of the long-lasting aftereffects is not entirely understood but seems to depend on membrane potential changes, modulations of NMDA receptor efficacy, as well as modification of ion channels (e.g., calcium, Liebetanz et al. [70]). In other words, tDCS does not induce the firing of otherwise resting neurons, such as TMS, but rather modulates the spontaneous firing rate of neurons by acting on the membrane potential.

In a first sham-controlled double-blind randomized crossover study, the effect of a single prefrontal tDCS was evaluated in a heterogeneous population of patients with DOC, VS/UWS and MCS, and acute-subacute (<3 months) and chronic, with traumatic or non-traumatic etiologies [71]. At the individual level, tDCS responders were defined as patients who presented a new sign of consciousness (e.g., command following; visual pursuit; recognition, manipulation, or localization of objects; Giacino et al. [72]), after the real tDCS session, that was not present before nor during the sham tDCS session. 13/30 patients in MCS showed a tDCS-related improvement. Two acute (<3 months) patients in VS/UWS out of 25 showed a tDCS response (i.e., showed command following and visual pursuit present after the anodal stimulation not present at baseline or pre- or post-sham tDCS). At group level, a treatment effect, as measured by the CRS-R, was observed in the MCS but not in the VS/UWS patients' group. In addition, no tDCS-related side effects were observed.

These findings appear of critical importance especially if we consider that there are only limited evidence-based pharmacological or non-pharmacological treatment options for severely brain-damaged patients with DOC and particularly in the chronic setting. Indeed, in the aforementioned study, out of the 13 patients in MCS who showed a tDCS response, 5 were included more than 12 months after the acute insult. This suggests that chronic MCS patients, even years after the brain injury, have still the ability to improve and recover some new signs of consciousness. On the other hand, no improvements were observed in patients in VS/UWS, in line with previous studies showing capacity for neural plasticity in patients in MCS rather than VS/UWS [73].

The main limit of this study was the short-term clinical effects of tDCS. Indeed, behavioral improvements were observed for not longer than 2 h from the stimulation. The literature of tDCS seems to convey that the number of sessions is a critical parameter to induce larger effects [74, 75]. As in daily clinical practice longer effects are required, studies using repeated tDCS sessions are warranted to elucidate whether this technique might be a feasible treatment for patients with DOC. To answer that question, another study aiming to evaluate the long-term effect of tDCS

was performed in chronic MCS patients. All participants received sham tDCS, 5 days/week, for 1 week, and anodal tDCS 5 days/week, for 1 week, separated by 1-week period of washout. The level of consciousness (i.e., CRS-R total score) improved after 5 days of tDCS in 56% of the patients included in that study, and the effects lasted 1 week after the end of the stimulations. In addition, a longitudinal increase of the CRS-R total scores was identified for the real session but not for the sham one. Those results suggest that repeated (5 days) anodal left prefrontal tDCS can improve the recovery of consciousness in chronic MCS patients up to 1 week after the last stimulation [76].

In another study, five repeated tDCS sessions (one daily) were performed on ten chronic (>6 months) patients with DOC. The left primary sensorimotor cortex (2 MCS – 3 VS/UWS) or the left DLPF cortex (1 MCS – 4 VS/UWS) was stimulated [77]. All patients in MCS showed clinical improvement immediately after tDCS session, while no effects were observed in patients in VS/UWS, in accordance with the previous tDCS study [71].

Using multimodal neuroimaging analyses, the previously described subgroup of tDCS responders (Thibaut et al. [71]) has been characterized. A common pattern of metabolic gray matter preservation was observed in tDCS responders as compared to nonresponders. This study showed that the transient improvement of signs of consciousness following tDCS seems to require gray matter integrity and/or residual metabolic activity in three brain regions: (1) the medial prefrontal cortex (encompassing the DLPFC, stimulated area), (2) the precuneus, and (3) the thalamus (see Fig. 12.4).

The residual brain metabolism and preserved gray matter in tDCS responders in the medial prefrontal cortex, posterior cingulate/precuneus, and thalamus highlight the role played by these structures in the recovery of consciousness. As previously mentioned, PET studies on VS/UWS patients identified metabolic impairment in the DMN (i.e., medial prefrontal cortex and the posterior cingulate/precuneus), as well as in the lateral frontoparietal regions including the DLPFC, emphasizing their critical role in consciousness recovery processes [19, 20].

The remaining metabolic and structural integrity of the medial prefrontal cortex and the thalamus observed in tDCS responders also supports the key role of these structures in the disturbances of consciousness and corroborates with previous studies showing that the corticothalamic loop has a critical role in consciousness recovery [78], as well as with the mesocircuit model [34, 43].

Which Technique to Choose?

As regard to the published tDCS studies on DOC patients, it is worth to stress that tDCS seems to be a safe device. Indeed, so far, no severe side effects were observed, even considering that many of these patients had severe brain injuries with widespread lesion possibly involving the stimulated areas. Moreover, although it is well known that brain-injured patients are more vulnerable to epileptic seizure, and some

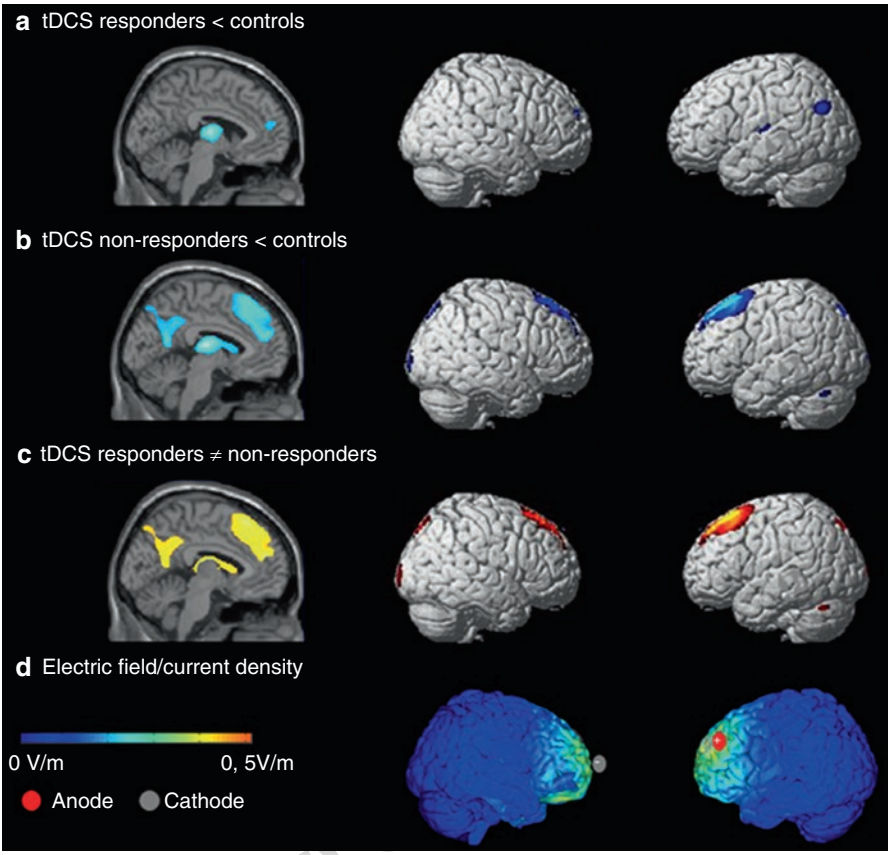

Fig. 12.4 Positron emission tomography (PET). Brain areas showing hypometabolism (in *blue*), as compared to controls, in patients in a minimally conscious state (FEW corrected): (**a**) 8 tDCS responders and (**b**) 13 nonresponders. (**c**) Regions with less hypometabolism in responders as compared to nonresponders (in *red*). (**d**) Theoretical tDCS-induced electric fields. Note that behavioral responsiveness to short duration left dorsolateral prefrontal cortex (DLPFC) tDCS correlates with less impaired metabolism in the areas presumed to be stimulated by tDCS (left DLPFC and mesiofrontal cortices) but also of distant cortical (precuneus) and subcortical (thalamus) regions (From [25])

of them were even under an epileptic treatment due to previous seizures, no seizures as side effects were observed.

On the other hand, DBS exposes the patient to several more risks due to the brain surgery than tDCS but can stimulate the brain centrally in systems evolved to have far-reaching and powerful modulatory effects. In most cases, the postoperative side effects of DBS are limited. It should also be noted that the use of DBS is only investigational and even the study inclusion criteria to receive this stimulation were very strict such that the number of patients likely to be eligible for this approach will be limited.

DBS as compared to tDCS, by stimulating the thalamus, can directly activate the thalamocortical connectivity, which has a critical role for consciousness recovery [35, 78], while tDCS can only directly stimulate cortico-cortical and corticothalamic connectivity. Though activation of the entire network is expected for both techniques to varying degrees, neurons in the central thalamus are specialized for broad activation across the entire frontostriatal system as recently demonstrated using fiberoptic optogenetic activation techniques coupled to functional magnetic resonance imaging (Liu et al. [ ]). Therefore, DBS might induce more significant clinical improvements than tDCS. Other advantages of DBS are the continuous effect and the permanent stimulation of patients' brain. Indeed, since the stimulator is placed and stays implanted for several years, it does not need to be repeatedly applied in order to induce long-term clinical effects, while for tDCS, repeating the stimulation daily seems to be necessary to induce prolonged behavioral improvements. In addition, since tDCS needs to be repeatedly performed, it requires more human resources, which might be an issue; even tDCS stays a relatively inexpensive and easy-to-use technique.

Consistency with the Mesocircuit Model

Interestingly, tDCS and DBS protocols that have been shown to induce promising results on consciousness recovery in DOC patients were focusing on brain areas which are part of the mesocircuit frontoparietal model. Indeed, DLPFC tDCS increases neuronal excitability of the prefrontal cortex, while DBS directly stimulates the central thalamus. These observations are in line with the study of Laureys et al. where a recovery of the connectivity between the thalamus and the frontal area was detected in patients who spontaneously regain consciousness from a vegetative state [78]. Furthermore, it is well known that prefrontal areas are critical in cognitive processes [79], and, more recently, it has been shown that stimulating this regions, even in an noninvasive way, seems to improve signs of consciousness of acute and chronic patients with DOC, though at a lower level as compared to central thalamus DBS. As schematized in Fig. 12.1, this mesocircuit model, by integrating this fronto-striato-thalamic loop, efficiently predicts both the impact of central thalamic DBS and prefrontal tDCS and the effects of a variety of specific pharmacological interventions known to be, in some cases, effective in improving behavioral responsiveness in severely brain-injured patients. In addition, it highlights once more the critical role of the thalamus and its connectivity with the frontal areas for consciousness recovery.

Conclusion

The aforementioned neuromodulation techniques, namely, DBS and tDCS, are thought to excite mainly forebrain regions and restore the connectivity between the thalamus and prefrontal cortex. Depending on patients specificities (e.g., damaged

brain areas), one of these techniques could be tested to improve patients' signs of consciousness and recovery. It would also be interesting to investigate if tDCS responsiveness could be a predictor of DBS efficacy, since both neuromodulation techniques are involved in the fronto-striato-thalamic loop, while tDCS is clearly less invasive than DBS.

Understanding the neural mechanisms of consciousness recovery will help neuroscientists and clinicians to develop new therapeutic options to stimulate the recovery of higher levels of functioning. On the other hand, deepening our knowledge on the mechanisms of how neuromodulation therapies work might help to understand the phenomena occurring in the process of consciousness recovery.

In the years to follow, more work has to be done to strengthen our understanding of the mechanisms of and potential treatments to promote the recovery of consciousness in patients with DOC. This will help improve daily care, comfort, and rehabilitation in this population in acute as well as in chronic stages.

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References

1. Voss HU, Uluc AM, Dyke JP, et al. Possible axonal regrowth in late recovery from the minimally conscious state. J Clin Invest. 2006;116:2005–11. doi:10.1172/JCI27021.
2. Estraneo A, Moretta P, Loreto V, et al. Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. Neurology. 2010;75:239–45. doi:10.1212/WNL.0b013e3181e8e8cc.
3. Bruno M-A, Ledoux D, Vanhaudenhuyse A, et al. Prognosis of patients with altered state of consciousness. Coma Disord Conscious. 2012; doi:10.1007/978-1-4471-2440-5_2.
4. Schiff ND, Giacino JT, Kalmar K, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature. 2007;448:600–3. doi:10.1038/nature06041.
5. Schnakers C, Hustinx R, Vandewalle G, et al. Measuring the effect of amantadine in chronic anoxic minimally conscious state. J Neurol Neurosurg Psychiatry. 2008;79:225–7. doi:10.1136/jnnp.2007.124099.
6. Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med. 2012;366:819–26. doi:10.1056/NEJMoa1102609.
7. Fridman EA, Calvar J, Bonetto M, et al. Fast awakening from minimally conscious state with apomorphine. Brain Inj. 2009;23:172–7. doi:10.1080/02699050802649662.
8. Sara M, Sacco S, Cipolla F, et al. An unexpected recovery from permanent vegetative state. Brain Inj. 2007;21:101–3. doi:10.1080/02699050601151761.
9. Whyte J, Rajan R, Rosenbaum A, et al. Zolpidem and restoration of consciousness. Am J Phys Med Rehabil. 2014;93:101–13. doi:10.1097/PHM.0000000000000069.
10. Thonnard M, Gosseries O, Demertzi A, et al. Effect of zolpidem in chronic disorders of consciousness: a prospective open-label study. Funct Neurol. 2014;28:259–64.
11. Jox RJ, Bernat JL, Laureys S, Racine E. Disorders of consciousness: responding to requests for novel diagnostic and therapeutic interventions. Lancet Neurol. 2012;11:732–8. doi:10.1016/S1474-4422(12)70154-0.
12. Laureys S, Lemaire C, Maquet P, et al. Cerebral metabolism during vegetative state and after recovery to consciousness. J Neurol Neurosurg Psychiatry. 1999;67:121.
13. Laureys S, Goldman S, Phillips C, et al. Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. Neuroimage. 1999;9:377–82. doi:10.1006/nimg.1998.0414.

14. Beuthien-Baumann B, Handrick W, Schmidt T, et al. Persistent vegetative state: evaluation of brain metabolism and brain perfusion with PET and SPECT. Nucl Med Commun. 2003;24:643–9. doi:10.1097/01.mnm.0000075192.18521.9d.
15. Juengling FD, Kassubek J, Huppertz HJ, et al. Separating functional and structural damage in persistent vegetative state using combined voxel-based analysis of 3-D MRI and FDG-PET. J Neurol Sci. 2005;228:179–84. doi:10.1016/j.jns.2004.11.052.
16. Nakao S, Takata S, Uemura H, et al. Relationship between Barthel Index scores during the acute phase of rehabilitation and subsequent ADL in stroke patients. J Med Investig. 2010;57:81–8.
17. Lull N, Noe E, Lull JJ, et al. Voxel-based statistical analysis of thalamic glucose metabolism in traumatic brain injury: relationship with consciousness and cognition. Brain Inj. 2010;24:1098–107. doi:10.3109/02699052.2010.494592.
18. Silva S, Alacoque X, Fourcade O, et al. Wakefulness and loss of awareness: brain and brain-stem interaction in the vegetative state. Neurology. 2010;74:313–20. doi:10.1212/WNL.0b013e3181cbcd96.
19. Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJ, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain. 2010;133:161–71. doi:10.1093/brain/awp313.
20. Thibaut A, Bruno MA, Chatelle C, et al. Metabolic activity in external and internal awareness networks in severely brain-damaged patients. J Rehabil Med. 2012;44:487–94.
21. D'Esposito M, Aguirre GK, Zarahn E, et al. Functional MRI studies of spatial and nonspatial working memory. Brain Res Cogn Brain Res. 1998;7:1–13.
22. D'Esposito M, Detre JA, Alsop DC, et al. The neural basis of the central executive system of working memory. Nature. 1995;378:279–81. doi:10.1038/378279a0.
23. Devinsky O, D'Esposito M. Neurology of cognitive and behavioural disorders. Oxford: Oxford University; 2004.
24. Lieberman MD. Social cognitive neuroscience: a review of core processes. Annu Rev Psychol. 2007;58:259–89. doi:10.1146/annurev.psych.58.110405.085654.
25. Thibaut A, Di Perri C, Chatelle C, et al. Clinical response to tDCS depends on residual brain metabolism and grey matter integrity in patients with minimally conscious state. Brain Stimul. 2015;8:1116–23. doi:10.1016/j.brs.2015.07.024.
26. Chatelle C, Thibaut A, Gosseries O, et al. Changes in cerebral metabolism in patients with a minimally conscious state responding to zolpidem. Front Hum Neurosci. 2014;8:917. doi:10.3389/fnhum.2014.00917.
27. Boly M, Tshibanda L, Vanhaudenhuyse A, et al. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. Hum Brain Mapp. 2009;30:2393–400. doi:10.1002/hbm.20672.
28. Silva S, de Pasquale F, Vuillaume C, et al. Disruption of posteromedial large-scale neural communication predicts recovery from coma. Neurology. 2015;85:2036–44. doi:10.1212/WNL.0000000000002196.
29. Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. Neuroimage. 2007;37:1083–9. doi:10.1016/j.neuroimage.2007.02.041.
30. Laureys S, Boly M, Maquet P. Tracking the recovery of consciousness from coma. J Clin Invest. 2006;116:1823–5. doi:10.1172/JCI29172.
31. Crone C, Nielsen J, Petersen N, et al. Disynaptic reciprocal inhibition of ankle extensors in spastic patients. Brain. 1994;117(Pt 5):1161–8.
32. Crone JS, Schurz M, Höller Y, et al. Impaired consciousness is linked to changes in effective connectivity of the posterior cingulate cortex within the default mode network. Neuroimage. 2015;110:101–9. doi:10.1016/j.neuroimage.2015.01.037.
33. Lant ND, Gonzalez-Lara LE, Owen AM, Fernández-Espejo D. Relationship between the anterior forebrain mesocircuit and the default mode network in the structural bases of disorders of consciousness. Neuroimage Clin. 2016;10:27–35. doi:10.1016/j.nicl.2015.11.004.

34. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci. 2010;33:1–9. doi:10.1016/j.tins.2009.11.002.
35. Laureys S, Schiff ND. Coma and consciousness: paradigms (re)framed by neuroimaging. Neuroimage. 2012;61:478–91. doi:10.1016/j.neuroimage.2011.12.041.
36. Giacino JT, Fins JJ, Laureys S, Schiff ND. Disorders of consciousness after acquired brain injury: the state of the science. Nat Rev Neurol. 2014;10:99–114. doi:10.1038/nrneurol.2013.279.
37. van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. Brain Res Rev. 2002;39:107–40. doi:10.1016/S0165-0173(02)00181-9.
38. Schiff ND. Central thalamic contributions to arousal regulation and neurological disorders of consciousness. Ann N Y Acad Sci. 2008;1129:105–18. doi:10.1196/annals.1417.029.
39. Mair RG, Onos KD, Hembrook JR. Cognitive activation by central thalamic stimulation: the Yerkes–Dodson law revisited. Dose Response. 2011;9:313–31. doi:10.2203/dose-response.10-017.Mair.
40. Maxwell WL, MacKinnon MA, Smith DH, et al. Thalamic nuclei after human blunt head injury. J Neuropathol Exp Neurol. 2006;65:478–88. doi:10.1097/01.jnen.0000229241.28619.75.
41. Gold L, Lauritzen M. Neuronal deactivation explains decreased cerebellar blood flow in response to focal cerebral ischemia or suppressed neocortical function. Proc Natl Acad Sci U S A. 2002;99:7699–704. doi:10.1073/pnas.112012499.
42. Grillner S, Hellgren J, Menard A, et al. Mechanisms for selection of basic motor programs—roles for the striatum and pallidum. Trends Neurosci. 2005;28:364–70. doi:10.1016/j.tins.2005.05.004.
43. Fridman EA, Beattie BJ, Broft A, et al. Regional cerebral metabolic patterns demonstrate the role of anterior forebrain mesocircuit dysfunction in the severely injured brain. Proc Natl Acad Sci U S A. 2014;111:6473–8. doi:10.1073/pnas.1320969111.
44. Williams ST, Conte MM, Goldfine AM, et al. Common resting brain dynamics indicate a possible mechanism underlying zolpidem response in severe brain injury. Elife. 2013;2:e01157. doi:10.7554/eLife.01157.
45. Brefel-Courbon C, Payoux P, Ory F, et al. Clinical and imaging evidence of zolpidem effect in hypoxic encephalopathy. Ann Neurol. 2007;62:102–5. doi:10.1002/ana.21110.
46. Clauss RP, Güldenpfennig WM, Nel HW, et al. Extraordinary arousal from semi-comatose state on zolpidem. A case report. S Afr Med J. 2000;90:68–72.
47. Shames JL, Ring H. Transient reversal of anoxic brain injury-related minimally conscious state after zolpidem administration: a case report. Arch Phys Med Rehabil. 2008;89:386–8. doi:10.1016/j.apmr.2007.08.137.
48. Fernandez-Espejo D, Soddu A, Cruse D, et al. A role for the default mode network in the bases of disorders of consciousness. Ann Neurol. 2012;72:335–43. doi:10.1002/ana.23635.
49. Buckwalter JA, Parvizi J, Morecraft RJ, Van Hoesen GW. Thalamic projections to the posteromedial cortex in the macaque. J Comp Neurol. 2008;507:1709–33. doi:10.1002/cne.21647.
50. Xie G, Deschamps A, Backman SB, et al. Critical involvement of the thalamus and precuneus during restoration of consciousness with physostigmine in humans during propofol anaesthesia: a positron emission tomography study. Br J Anaesth. 2011;106:548–57. doi:10.1093/bja/aeq415.
51. Olanow CW, Brin MF, Obeso JA. The role of deep brain stimulation as a surgical treatment for Parkinson's disease. Neurology. 2000;55:S60–6.
52. McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol. 2004;115:1239–48. doi:10.1016/j.clinph.2003.12.024.
53. Agnesi F, Johnson MD, Vitek JL. Deep brain stimulation. How does it work? Handb Clin Neurol. 2013;116:39–54. doi:10.1016/B978-0-444-53497-2.00004-8.
54. Shah SA, Schiff ND. Central thalamic deep brain stimulation for cognitive neuromodulation—a review of proposed mechanisms and investigational studies. Eur J Neurosci. 2010;32:1135–44. doi:10.1111/j.1460-9568.2010.07420.x.

55. Adams JH, Graham DI, Jennett B. The neuropathology of the vegetative state after an acute brain insult. Brain. 2000;123(Pt 7):1327–38.
56. Yamamoto T, Kobayashi K, Kasai M, et al. DBS therapy for the vegetative state and minimally conscious state. Acta Neurochir Suppl. 2005;93:101–4.
57. Giacino JT, Kalmar K, Whyte J. The JFK coma recovery scale-revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85:2020–9.
58. Boggio PS, Ferrucci R, Rigonatti SP, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci. 2006;249:31–8. doi:10.1016/j.jns.2006.05.062.
59. Ferrucci R, Mameli F, Guidi I, et al. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. Neurology. 2008;71:493–8. doi:10.1212/01.wnl.0000317060.43722.a3.
60. Kang EK, Kim DY, Paik NJ. Transcranial direct current stimulation of the left prefrontal cortex improves attention in patients with traumatic brain injury: a pilot study. J Rehabil Med. 2012;44:346–50. doi:10.2340/16501977-0947.
61. Nelson JT, McKinley RA, Golob EJ, et al. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). Neuroimage. 2012; doi:10.1016/j.neuroimage.2012.11.061.
62. Antal A, Terney D, Kuhnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manag. 2010;39:890–903. doi:10.1016/j.jpainsymman.2009.09.023.
63. Baker JM, Rorden C, Fridriksson J. Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke. 2010;41:1229–36. doi:10.1161/STROKEAHA.109.576785.
64. Frank E, Schecklmann M, Landgrebe M, et al. Treatment of chronic tinnitus with repeated sessions of prefrontal transcranial direct current stimulation: outcomes from an open-label pilot study. J Neurol. 2012;259:327–33. doi:10.1007/s00415-011-6189-4.
65. Loo CK, Alonzo A, Martin D, et al. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry. 2012;200:52–9. doi:10.1192/bjp.bp.111.097634.
66. Zaehle T, Sandmann P, Thorne JD, et al. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci. 2011;12:2. doi:10.1186/1471-2202-12-2.
67. George MS, Padberg F, Schlaepfer TE, et al. Controversy: repetitive transcranial magnetic stimulation or transcranial direct current stimulation shows efficacy in treating psychiatric diseases (depression, mania, schizophrenia, obsessive-compulsive disorder, panic, posttraumatic stress disorder). Brain Stimul. 2009;2:14–21. doi:10.1016/j.brs.2008.06.001.
68. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 2008;1:206–23. doi:10.1016/j.brs.2008.06.004.
69. Nitsche MA, Seeber A, Frommann K, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol. 2005;568:291–303. doi:10.1113/jphysiol.2005.092429.
70. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125:2238–47.
71. Thibaut A, Bruno MA, Ledoux D, et al. tDCS in patients with disorders of consciousness: sham-controlled randomised double blind study. Neurology. 2014;82:1112–8.
72. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58:349–53.
73. Monti MM. Cognition in the vegetative state. Annu Rev Clin Psychol. 2012;8:431–54. doi:10.1146/annurev-clinpsy-032511-143050.
74. Castillo-Saavedra L, Gebodh N, Bikson M, et al. Clinically effective treatment of fibromyalgia pain with high-definition transcranial direct current stimulation: phase II open-label dose optimization. J Pain. 2016;17:14–26. doi:10.1016/j.jpain.2015.09.009.

75. Brunoni AR, Valiengo L, Baccaro A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70:383–91. doi:10.1001/2013.jamapsychiatry.32.
76. Thibaut A, Bruno MA, Wannez S, et al. Long term effect of repeated tDCS in minimally conscious patients. Submitted.
77. Angelakis E, Liouta E, Andreadis N, et al. Transcranial direct current stimulation effects in disorders of consciousness. Arch Phys Med Rehabil. 2014;95:283–9. doi:10.1016/j.apmr.2013.09.002.
78. Laureys S, Faymonville ME, Luxen A, et al. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. Lancet. 2000;355:1790–1.
79. Dehaene S, Sergent C, Changeux JP. A neuronal network model linking subjective reports and objective physiological data during conscious perception. Proc Natl Acad Sci U S A. 2003;100:8520–5. doi:10.1073/pnas.1332574100.

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