Therapeutic interventions in patients with prolonged disorders of consciousness

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The management of patients with severe brain injuries and prolonged disorders of consciousness raises important issues particularly with respect to their therapeutic options. The scarcity of treatment options is challenged by new clinical and neuroimaging data indicating that some patients with prolonged disorders of consciousness might benefit from therapeutic interventions, even years after the injury. Most studies of interventions aimed at improving patients' level of consciousness and functional recovery were behavioural and brain imaging open-label trials and case reports, but several randomised controlled trials have been done, particularly focused on the effects of drugs or use of non-invasive brain stimulation. However, only two studies on amantadine and transcranial direct current stimulation provided class II evidence. Although new therapeutic approaches seem to be valuable for patients with prolonged disorders of consciousness, optimised stimulation parameters, alternative drugs, or rehabilitation strategies still need to be tested and validated to improve rehabilitation and the quality of life of these patients.

Introduction

A lot of work has been done on the accurate diagnosis of patients with disorders of consciousness[1,2] to establish prognostic indicators[3,4] and to understand the neural correlates of consciousness.[5] This work is crucial because misdiagnosis can lead to important medical decisions, such as withdrawal of life-sustaining care.[6] Disorders of consciousness include coma (unwakefulness, reflex behaviours only), unresponsive wakefulness syndrome (previously known as vegetative state; wakefulness but reflex behaviours only), and minimally conscious state (clinical demonstration of signs of consciousness).[7,8] Once patients recover functional communication or object use, they emerge from the minimally conscious state. Additional entities have been proposed when dissociation occurs between clinical diagnosis and neuroimaging results showing atypical brain activation, including minimally conscious state* and cognitive motor dissociation (panel 1; figure 1).[14,18] Patients who have recovered from coma can remain severely disabled for several months, years, or even decades.

With regards to therapeutic options, only a few studies have investigated the treatment of patients with disorders of consciousness. Following a landmark paper on amantadine in 2012,[22] this field has evolved rapidly, with new therapeutic approaches being tested and reported, but patients' clinical management remains challenging, mostly because these patients cannot communicate and are dependent on others for care. The 2018 American practice guidelines for patients with disorders of consciousness[23] only recommend amantadine for patients with unresponsive wakefulness syndrome and minimally conscious state 4–16 weeks after a traumatic brain injury on the basis of one randomised controlled trial.[22] Given that the guidelines were developed on the basis of strict inclusion and exclusion criteria (eg, a minimum of 20 patients included, all at least 28 days after injury), many studies failed to meet their inclusion criteria and were not reported in these recommendations. In this Review, we critically evaluate the available therapeutic options for patients with prolonged disorders of consciousness (ie, more than 28 days) that have been studied in the past 6 years. We discuss pharmacological and non-pharmacological interventions with the strongest evidence and for which robust randomised controlled trials have been published. If no randomised controlled trials were available, we present open-label studies and anecdotal case reports with careful interpretation, because they might still provide insightful results to guide future research. We also report neuroimaging and neurophysiological results associated with positive treatment responses.

Pharmacological treatments

Amantadine (dopamine agonist and NMDA antagonist),[22,24–26] intrathecal baclofen (GABA agonist),[27] zolpidem (non-benzodiazepine GABA agonist),[28–32] midazolam (benzodiazepine GABA agonist),[33] and ziconotide (calcium channel blocker)[34] have been used to improve consciousness and functional recovery in patients with disorders of consciousness.

Amantadine and other neurostimulants

Only one large class II randomised controlled trial[22] on amantadine has been published. 184 patients with prolonged disorders of consciousness (28–112 days after injury) after traumatic brain injury received either amantadine (up to 200 mg twice a day) or placebo for 4 weeks and were followed for a further 2 weeks.[22] The amantadine group recovered faster than the placebo group during the course of the treatment as measured by the Disability Rating Scale.[35]

In non-traumatic brain injury, one uncontrolled case report[36] reported the positive behavioural effects of amantadine in patients in a minimally conscious state (16 months after injury). Another controlled case report[24] showed an increased metabolism in the fronto-parietal cortex during amantadine in an anoxic minimally conscious state patient (figure 2A). These two case reports should encourage the development of a randomised controlled trial that evaluates the effect of amantadine in

patients with disorders of consciousness with causes other than traumatic brain injury.

Besides amantadine, the administration of one or more neurostimulants (ie, amantadine, bromocriptine, levodopa, methylphenidate, and modafinil) has also been explored in a retrospective study in a cohort of 115 patients with disorders of consciousness (<180 days after injury).[25] The number of neurostimulants used was not associated with meaningful behavioural improvement in this study.

Zolpidem

Zolpidem is a hypnotic agent known to induce paradoxical transient effects in rare cases in patients with disorders of consciousness. A double-blind crossover randomised controlled trial[28] in 84 patients with unresponsive wakefulness syndrome or in a minimally conscious state (>4 months after injury) identified four (5%) responders following the intake of 10 mg of zolpidem. These four patients gained at least five points on the Coma Recovery Scale-Revised;[46] one patient with unresponsive wakefulness syndrome and one in minimally conscious state minus became minimally conscious state plus, and two patients emerged from their minimally conscious state for around 2 h.[28] Another randomised controlled trial[29] involving eight patients with unresponsive wakefulness syndrome (1–114 months after injury) only reported slight clinical changes, such as yawns and hiccups, combined with an EEG-recorded activity of lower amplitude after zolpidem intake. A two-phase study (ie, open-label and then a placebo-controlled trial if there was a change of Coma Recovery Scale-Revised diagnosis)[31] included 60 patients with unresponsive wakefulness syndrome or in a minimally conscious state (1 month to 24 years after injury). 12 patients (20%; 11 in a minimally conscious state and one with unresponsive wakefulness syndrome) showed behavioural improvements, such as response to command or object localisation, without a change of diagnosis. One patient in a minimally conscious state could functionally use some objects after the open trial but did not demonstrate any improvement in the placebo-controlled phase. In one case report,[30] recovery of consciousness was reported in a patient with unresponsive wakefulness syndrome (>3 years after cardiac arrest) when using a higher dose of zolpidem (30 mg instead of 10 mg). The patient showed signs of consciousness when receiving 20 mg and further improved after 30 mg of zolpidem, suggesting that higher doses might induce stronger effects.

With regard to zolpidem's brain responses, studies using EEG,[32] functional MRI,[47] and PET[37] have identified an increase in brain activity, mainly in prefrontal regions (figure 2B), which supports the mesocircuit model (figure 3). This model could explain how zolpidem can modulate thalamo-cortical connectivity through disinhibition of the thalamus by acting on the globus pallidus interna and, consequently, promote the recovery of consciousness.[50]

In summary, zolpidem shows improvement of consciousness and functional recovery (even if transient) in

Panel 1: **Clinical entities of disorders of consciousness**

Coma

Coma is the result of a severe brain injury, in which patients are unarousable (ie, eye closure even when stimulated) and unaware of themselves and their environment.[9] This state is temporary and after several days or weeks, patients might evolve to brain death (ie, irreversible coma with absence of brainstem reflexes and apnoea) or show some or full recovery.

Unresponsive wakefulness syndrome

When patients start opening their eyes but present only reflex movements, they are diagnosed with an unresponsive wakefulness syndrome (previously termed vegetative state).[10] Patients in unresponsive wakefulness syndrome exhibit no signs of awareness, but they can present a variety of reflexive movements, such as grinding teeth, yawning, or groaning.[10] This condition might be transitory, prolonged, or permanent.

Minimally conscious state

Once patients recover fluctuating but reproducible signs of consciousness, they enter the minimally conscious state.[11] This entity is divided into minimally conscious state minus and minimally conscious state plus on the basis of language processing.[12,13] Minimally conscious state minus describes patients showing visual pursuit and fixation, localisation to noxious stimulation, or automatic motor reactions (eg, grasping bed sheets). Patients in minimally conscious state plus follow simple commands, can make understandable verbalisations, or communicate intentionally but not functionally. Like unresponsive wakefulness syndrome, minimally conscious state can be temporary or permanent. The diagnostic label of minimally conscious state* has been suggested for unresponsive wakefulness syndrome patients who show no evidence of awareness at the bedside, while neuroimaging data show atypical brain patterns using active paradigm (eg, brain activity in motor area during a motor imagery task) or metabolic resting state (eg, preservation of the fronto-parietal network).[14-16] This entity allows a more clinically accurate diagnosis when the bedside examination shows no evidence of consciousness. The term functional locked-in syndrome (as well as covert cognition) has also been proposed to indicate a dissociation between bedside behaviour and the results of neuroimaging assessments[17] (like minimally conscious state*[14] and cognitive motor dissociation[18]).

Cognitive motor dissociation

The syndrome of cognitive motor dissociation has been proposed to specifically refer to patients in coma, unresponsive wakefulness syndrome, or minimally conscious state minus who show consistent brain activation during mental imagery tasks using functional MRI or EEG, and hence show response to command using neuroimaging technologies.[18] Cognitive motor dissociation indicates a wide range of uncertainty regarding the underlying cognitive capacity present in patients with no or little behavioural responses.

Emergence from minimally conscious state

When patients are able to functionally communicate or adequately use two different objects, they have emerged from the minimally conscious state. Most of these patients still have severe cognitive and motor impairments.[11]

Locked-in syndrome

Locked-in syndrome is defined by quadriplegia and anarthria due to a lesion in the corticospinal and corticobulbar pathways in the brainstem.[19] These patients cannot move (some recover some distal movements, termed incomplete locked-in syndrome), but their sensations remain intact and they are fully conscious. The most common way for these patients to communicate is through vertical eye movements and blinks.[20] In the case of complete locked-in syndrome, paralysis of the eyes prevents any communication and brain computer interfaces are needed.[21]

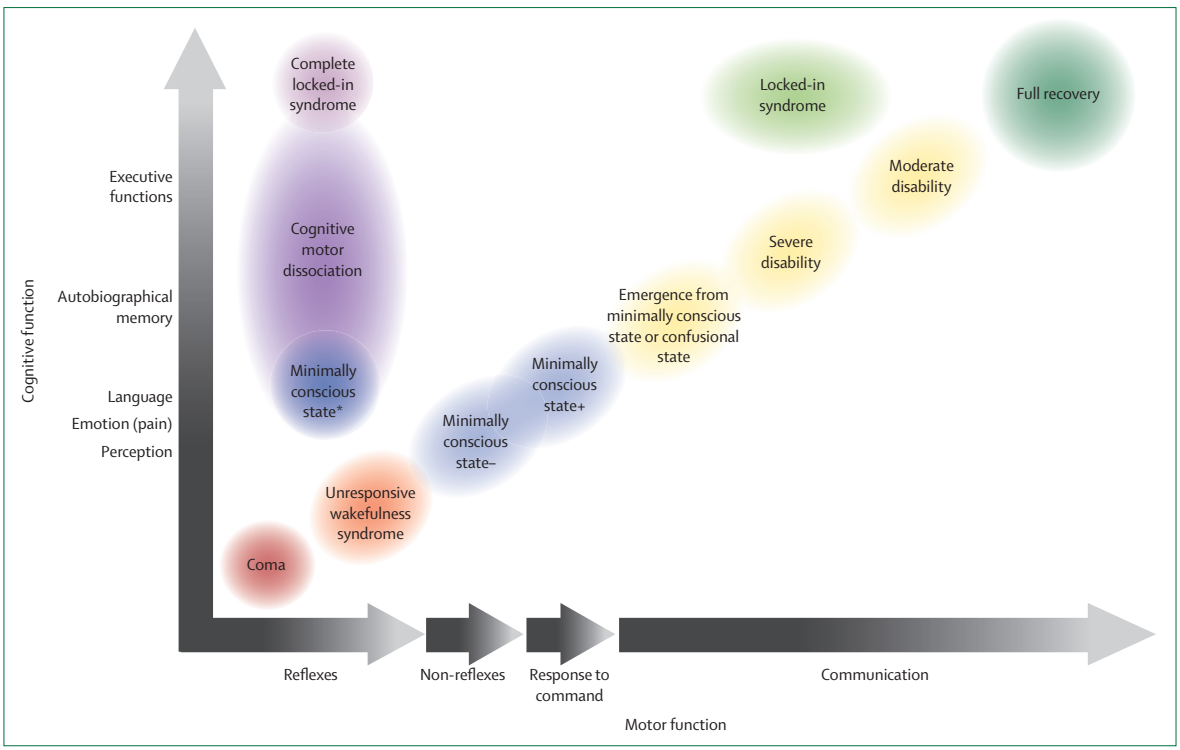

Figure 1: **Motor and cognitive evolution following a severe brain injury**
The different diagnoses after a severe brain injury can be best captured on a two-dimensional axis by comparing the degree of cognitive function against the degree of motor function. Red circles represent patients who are unconscious with only reflexive movements (coma and unresponsive wakefulness syndrome). Blue circles represent patients in a minimally conscious state (minimally conscious state plus and minimally conscious state minus depending on language preservation). When functional communication is detected (yellow circles), patients emerge from the minimally conscious state and can evolve to a confusional state or severe or moderate disability, before a full recovery (dark green circle). Dissociations between motor and cognitive functions exist in locked-in syndrome (light green circle), cognitive motor dissociation (dark purple circle), and minimally conscious state* (dark blue circle). In rare cases, the diagnosis of complete locked-in syndrome (light purple circle) can be done through neuroimaging examinations. The black-to-white gradient represents the evolution from absence (black) to the recovery of a behaviour (white; eg, from no response to command to consistent response).

around 5% of patients with disorders of consciousness. Determining the behavioural and physiological profile of zolpidem responders is crucial to better identify the patients that could benefit from this treatment.

Intrathecal baclofen and other drugs

Intrathecal baclofen is primarily used as a centrally acting treatment for spasticity but has been suggested as a potential drug to stimulate the recovery of consciousness in a few uncontrolled studies and case reports.[27,51] The effects of midazolam (benzodiazepine receptor agonist)[33] and ziconotide (atypical analgesic and selective blocker of N-type calcium channels)[34] have also been reported in two single-case studies as stimulants for the recovery of consciousness of patients with prolonged disorders of consciousness (one in a minimally conscious state and one with unresponsive wakefulness syndrome, respectively).[33,34] These anecdotal findings need to be confirmed with randomised controlled trials.

Non-pharmacological interventions

Non-pharmacological interventions have also been attempted to improve consciousness and functional recovery in patients with disorders of consciousness. These include non-invasive brain stimulations (eg, transcranial direct current stimulation, repeated transcranial magnetic stimulation, transcutaneous auricular vagal nerve stimulation, and low intensity focused ultrasound pulse), invasive brain stimulation (ie, deep brain stimulation or vagal nerve stimulation), and sensory stimulation programmes (panel 2).

Non-invasive brain stimulation

Transcranial direct current stimulation

A double-blind randomised controlled trial[59] tested the effect of prefrontal transcranial direct current stimulation (ie, anode over the left dorsolateral prefrontal cortex for 20 min at 2 mA) on 55 patients, both in acute and prolonged disorders of consciousness (1 week to 26 years after injury). At the group level, behavioural improvements, as measured by the Coma Recovery Scale-Revised,[46] were reported for patients in a minimally conscious state, but not for those with unresponsive wakefulness syndrome. At the individual level, 13 (43%) of 30 patients in a minimally conscious state showed an improvement (ie, recovery of a clinical sign of consciousness never

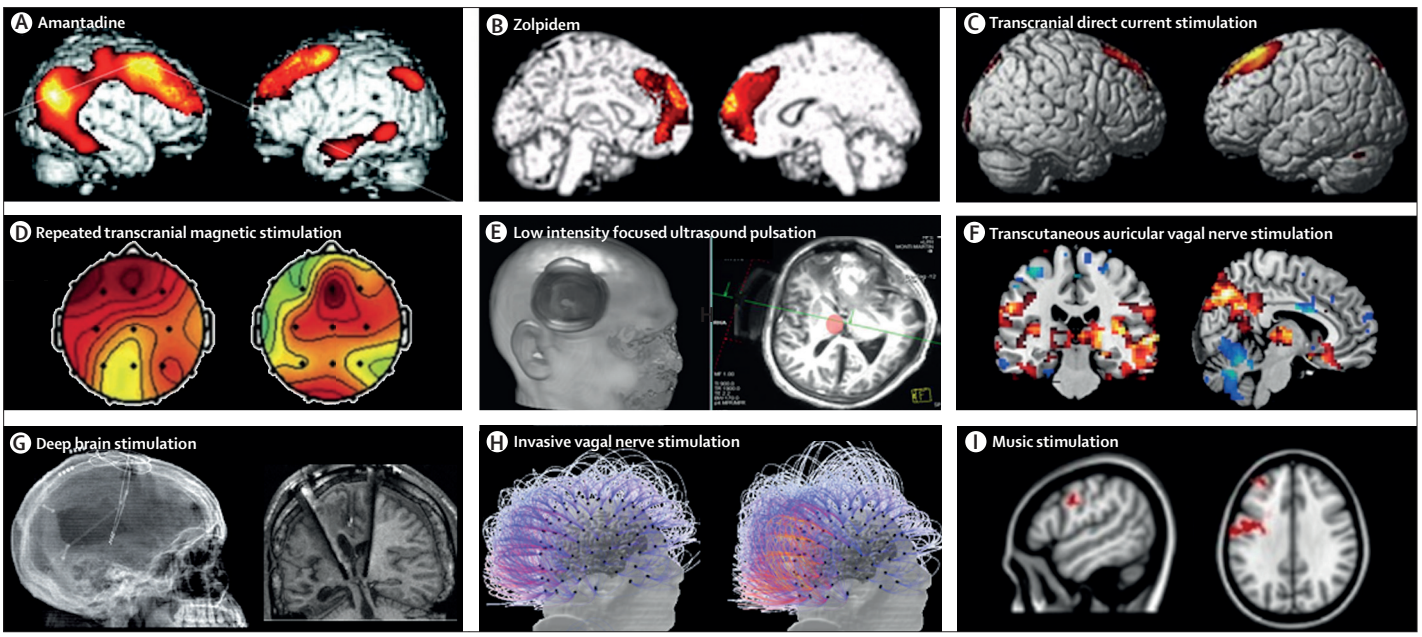

Figure 2: **Pharmacological and non-pharmacological interventions to improve consciousness in patients with disorders of consciousness**
(A) Amantadine has been shown to increase brain metabolism in the fronto-parietal network in one patient in a minimally conscious state. Reproduced from Schnakers and colleagues.[24] (B) Zolpidem induced an increase in brain metabolism in the prefrontal and mesiofrontal cortex in three minimally conscious state responders. Reproduced from Chatelle and colleagues.[37] (C) Patients responding to transcranial direct current stimulation (n=8) had more preservation of brain metabolism in the prefrontal cortex (stimulated area) compared with non-responders (n=13). Reproduced from Thibaut and colleagues.[38] (D) Repeated transcranial magnetic stimulation of 20 Hz on the primary motor cortex induced EEG increases in beta (shown), alpha, and delta band power in one minimally conscious state responder. Reproduced from Piccione and colleagues,[39] by permission of SAGE Publishing. (E) Low intensity focused ultrasound pulsation is shown in a patient with unresponsive wakefulness syndrome who became minimally conscious after stimulating the thalamic target (red circle). Reproduced from Monti and colleagues,[40] by permission of Elsevier. (F) Transcutaneous auricular vagal nerve stimulation induced increases in functional connectivity between posterior cingulate, precuneus, hypothalamus, thalamus, and prefrontal and temporal cortex (red), and decreases between the posterior cingulate, precuneus, and cerebellum gyrus (blue) in one patient with unresponsive wakefulness syndrome who transitioned to a minimally conscious state after stimulation. Reproduced from Yu and colleagues,[41] by permission of Elsevier. (G) Deep brain stimulation electrode placement, as seen with MRI, in one patient in a minimally conscious state who subsequently recovered.[42,43] Reproduced from Schiff and colleagues.[42] (H) Brain connectivity patterns before (left) and after (right) invasive vagal nerve stimulation as measured with high-density EEG in one unresponsive wakefulness syndrome patient who improved to a minimally conscious state after stimulation. Reproduced from Corazzol and colleagues,[44] by permission of Elsevier. (I) Music stimulation induced an increase in functional connectivity in the auditory network (and in the default mode network; not shown) in five patients with disorders of consciousness. Reproduced from Heine and colleagues.[45]

observed before transcranial direct current stimulation, nor during sham session). No transcranial direct current stimulation related side-effects were reported in any patients. In a case report,[60] one patient considered to have unresponsive wakefulness syndrome showed a response to command after one session of transcranial direct current stimulation over the dorsolateral prefrontal cortex. When looking at the neuroimaging assessments, a preservation of brain activity closer to what is usually observed in conscious individuals was identified, suggesting that the patient was in minimally conscious state*. In another randomised controlled trial,[61] transcranial direct current stimulation was applied once a day for 5 consecutive days in 16 patients in a minimally conscious state (5 months to 30 years after injury) and the effects were assessed daily and at 1-week follow-up. A clinical improvement (eg, recovery of response to command, visual pursuit, or object localisation or manipulation) was observed after 5 days of transcranial direct current stimulation and the effects remained up to a week in some patients, with a signficant treatment effect observed at the group level after 1-week follow-up.[61] However, only four patients responded directly after the first stimulation, indicating that a single session is insufficient to determine if a patient can benefit from the technique or not. A non-randomised controlled study[62] evaluated the clinical effects of 5 days of sham then 5 days of active transcranial direct current stimulation applied either over the dorsolateral prefrontal cortex or the primary sensorimotor cortex in ten patients with unresponsive wakefulness syndrome or minimally conscious state (6 months to 10 years after injury). The three patients in a minimally conscious state improved regardless of the site of stimulation (one patient in a minimally conscious state received prefrontal stimulation and two received sensorimotor stimulation), whereas none of the seven patients in unresponsive wakefulness syndrome responded. Another double-blind randomised controlled trial[63] showed that the observed behavioural improvement (Coma Recovery Scale-Revised total score) in five (38%) of 13 patients following five sessions of transcranial direct current stimulation were paralleled with EEG changes (enhancement of EEG background). Another double-blind randomised controlled trial[64] included 26 patients with disorders of consciousness (1–17 months after injury) who received 20 sessions of

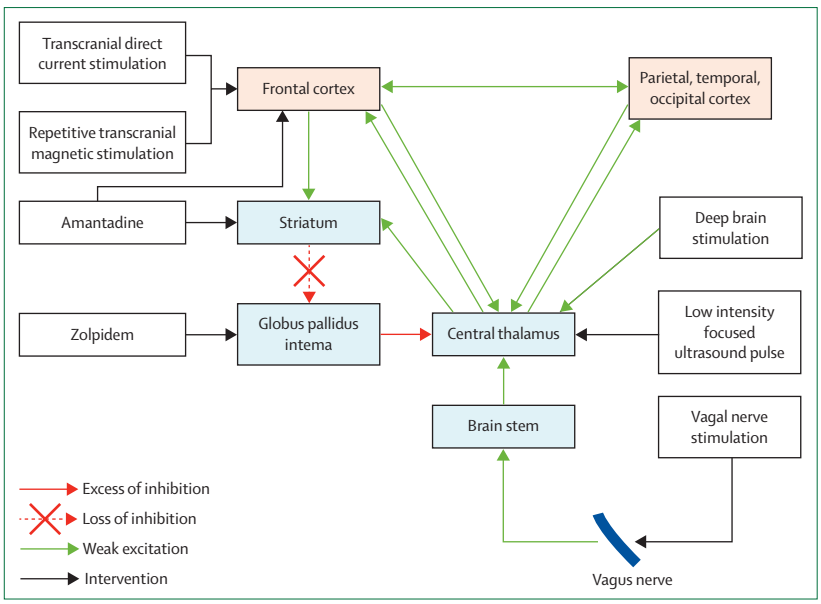

Figure 3: **The mesocircuit fronto-parietal model for mechanisms underlying the effects of interventions in severe brain injuries**

This model provides a framework that explains the potential mechanisms of action of various therapeutic interventions and the neural mechanisms of impaired consciousness. This model supports the idea that, in normal cognitive processing, the central thalamus is regulated by both the dominant corticothalamic feedback provided by (pre)frontal regions (bidirectional green arrow) and through an inhibitory modulation by the internal globus pallidus, which itself is regulated by cortico-striatal and thalamo-striatal inputs. Activation of the central thalamus broadly drives activity of associative fronto-parietal cortical areas.[48] However, in case of brain injury, a reduction of corticothalamic and thalamo-striatal 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 globus pallidus interna to tonically fire and provide active inhibition (red line) to their synaptic targets, including relay neurons of the already strongly disfacilitated central thalamus. This mesocircuit model might explain the potential mechanisms of several treatments that have shown promising results in the recovery of consciousness in patients with severe brain injuries. Partial preservation of the stimulated prefrontal cortex seems to be necessary to induce a clinical response to transcranial direct current stimulation,[38] whereas repeated transcranial magnetic stimulation seems to induce a global increase in cortical oscillations when applied over the primary motor cortex.[39] The clinical improvement of a patient who responded to amantadine correlated with increased fronto-parietal brain metabolism.[24] Zolpidem might produce broad excitation across the frontal cortices and striatum through direct excitation and through inhibition of the globus pallidus.[32,49] Deep brain stimulation directly acts over the central thalamus, aiming to stimulate the thalamo-cortical connectivity,[42] whereas low intensity focused ultrasound pulse stimulates the thalamus in a non-invasive way.[40] Invasive and non-invasive vagal nerve stimulation directly stimulate the vagal nerve.[43,44] Blue rectangles represent subcortical regions, and pink rectangles represent cortical areas. Adapted from Giacino and colleagues.[7]

active or sham prefrontal stimulation over 10 days. Clinical improvement was observed in the minimally conscious state group but not in the unresponsive wakefulness syndrome group, combined with an increase in P300 amplitude for the responders. A randomised controlled trial[65] in 27 patients in a minimally conscious state (10 months to 33 years after injury) evaluated the effects of 20 sessions within 4 weeks of transcranial direct current stimulation over the dorsolateral prefrontal cortex applied by the patients' relatives or caregivers at home or in nursing homes. Although the overall compliance was good (ie, 96% of sessions completed), the behavioural effect was not significant. However, when the five patients who did not receive at least 80% of the stimulation sessions were excluded, a significant treatment effect was observed for the remaining 22 patients. Therefore, patients with prolonged disorders of consciousness can show clinical improvements after transcranial direct current stimulation, such as the recovery of object manipulation or functional communication, even years after the brain injury, but a continuous application of transcranial direct current stimulation seems to be required. Beside transcranial direct current stimulation, 101–640 Hz transcranial random noise stimulation was applied over the prefrontal cortex for 5 daily sessions of 20 min in a pilot randomised controlled trial[66] on nine patients with unresponsive wakefulness syndrome (30 days to 4 months after injury) which showed no clinical improvement. However, the small sample size prevents us from drawing any generalisable conclusions.

With regard to neuroimaging data of responders, a common pattern of metabolic and grey matter preservations has been reported in eight responders compared with 13 non-responder patients in a minimally conscious state.[38] Clinical improvement following transcranial direct current stimulation seems to require partial functional and structural preservation of the stimulated area (dorsolateral prefrontal cortex) and other brain regions crucial in consciousness recovery, such as the precuneus and the thalamus (figure 2C). A higher cortical connectivity within the theta band, known to be important for consciousness processes,[67] was also reported in responders compared with non-responders in a minimally conscious state.[68] Additionally, EEG studies[69,70] identified an increase in fronto-parietal coherence in the theta band after active transcranial direct current stimulation of the dorsolateral prefrontal cortex in patients in a minimally conscious state and an increase in global cortical excitability as measured with transcranial magnetic stimulation coupled with EEG, highlighting the possible neural effects of prefrontal transcranial direct current stimulation in patients with disorders of consciousness.

Compared with dorsolateral prefrontal cortex stimulation, transcranial direct current stimulation of the precuneus or the orbitofrontal cortex has shown less promising results.[71,72] In a double-blind randomised controlled trial,[71] stimulation was applied over the precuneus once a day for 20 min for 5 days in 33 patients in a minimally conscious state (1–26 months after injury). A behavioural improvement at the group level was reported after the transcranial direct current stimulation sessions, but the effect did not last when reassessed 5 days later. At the individual level, six (18%) of 33 patients were identified as responders with the recovery of visual pursuit, response to command, automatic motor reaction or objects manipulation, or localisation. In one prospective open-label study,[72] no behavioural changes were observed after transcranial direct current stimulation applied over the orbitofrontal cortex in 22 patients with prolonged disorders of consciousness (4–33 months after injury). Cortical connectivity and excitability were increased after transcranial direct current stimulation in all patients in a minimally conscious

state and in some patients with unresponsive wakefulness syndrome, showing the possible neuroplasticity effects of transcranial direct current stimulation in patients with disorders of consciousness.

The prefrontal cortex seems to be a better target for stimulation compared with the precuneus and the motor cortex. Dorsolateral prefrontal cortex stimulation might induce a stronger connectivity between the prefrontal cortex and the thalamus because the prefrontal cortex has many connections with the striatum. By stimulating the striatum, a disinhibition of the thalamus might occur, reinforcing thalamo-cortical connectivity (figure 3),[49,73] and facilitating recovery from consciousness.

Repeated transcranial magnetic stimulation

In one double-blind randomised controlled trial[74] of 11 patients with unresponsive wakefulness syndrome (9–85 months after injury), no behavioural improvements were reported following five repeated sessions at 20 Hz applied over the primary motor cortex (M1) for 10 min. Another randomised controlled trial[75] also reported no behavioural improvement after one session of M1 20 Hz repeated transcranial magnetic stimulation for about 10 min in ten patients with disorders of consciousness (1–26 months after injury), but haemodynamic functions (ie, cerebral blood flow velocity) were improved in the minimally conscious state group but not in the unresponsive wakefulness syndrome group. 5 Hz stimulation was applied on M1 for about 7 min in a third randomised controlled trial[76] in five patients with unresponsive wakefulness syndrome and five patients in a minimally conscious state (5–23 months after injury) evaluating its effects on sleep–wake cycles. Although no behavioural effect was reported, significant after-effects on slow wave activity power were reported in the minimally conscious state group but not in the unresponsive wakefulness syndrome group. A small sample crossover randomised controlled trial[77] evaluated the effects of five sessions of M1 20 Hz repeated transcranial magnetic stimulation, lasting about 10 min, in three patients with unresponsive wakefulness syndrome, two in a minimally conscious state, and one emerging from a minimally conscious state (1–28 months after injury). At the group level, no treatment effect was found, but at the individual level, one patient with unresponsive wakefulness syndrome recovered localisation to painful stimulation and maintained this behaviour at 1-week follow-up. This clinical improvement was paralleled with an increase in alpha and beta power, showing higher brain activity and supporting the recovery of a sign of consciousness. Additionally, in a case report,[39] an increased absolute and relative power in delta, alpha, and beta frequency bands was found with improved signs of consciousness in one patient in a minimally conscious state after stimulation over M1 (figure 2D).

The dorsolateral prefrontal cortex has also been targeted in a few uncontrolled studies. The effect of 20 sessions of 10 Hz dorsolateral prefrontal cortex repeated transcranial magnetic stimulation (each session lasting 11 min) was evaluated in 16 patients with disorders of consciousness (3–35 months after injury) in a single-blind uncontrolled study.[78] Coma Recovery Scale-Revised[46] total score increased in all five patients in a minimally conscious state and in four (36%) of 11 patients with unresponsive wakefulness syndrome, and the improvements scored higher on the Coma Recovery Scale-Revised in patients in a minimally conscious state. In a small open-label study,[79] ten anoxic patients with unresponsive wakefulness

Panel 2: Neuromodulation techniques

Transcranial direct current stimulation

This neuromodulation technique modulates cortical excitability through the application of a weak (usually ≤2 mA) direct current through the brain between two electrodes. Physiologically, the establishment of the long-lasting after-effects depends on membrane potential changes as well as modulations of NMDA receptor efficacy, which can induce long-term potentiation and long-term depression-like effects.[52–54] However, more mechanistic and in-vivo studies need to be done to better understand how transcranial direct current stimulation can influence cortical activity and act on neuroplasticity.

Transcranial magnetic stimulation

Transcranial magnetic stimulation uses an electromagnetic pulse to induce focalised neural depolarisation and firing. Repeated transcranial magnetic stimulation, compared with single pulse transcranial magnetic stimulation, can influence brain plasticity and cortical organisation through alterations of neuronal excitability. Repeated transcranial magnetic stimulation has been used to induce a sustained inhibition (about 1 Hz frequency) or activation (5–20 Hz frequency) of the neuronal population.

Low intensity focused ultrasound pulse

This technique uses low-energy sound waves to excite or inhibit brain activity. Compared with transcranial direct current stimulation and repeated transcranial magnetic stimulation, it is theoretically capable of directly targeting and stimulating subcortical and deep brain structures, such as the thalamus.

Vagal nerve stimulation

Vagal nerve stimulation can be invasive and surgically placed or non-invasive through transcutaneous auricular stimulation. Transcutaneous auricular vagal nerve stimulation consists of the injection of a thermal current to the external ear canal, which modifies the density of the endolymph in the internal ear and, consequently, alters the firing rate of the vestibular nerve. This technique is thought to induce compensatory responses, through basal forebrain or brainstem projections through the central thalamus and hypothalamus, in distal fronto-parietal and striatal networks.[55] Invasive vagal nerve stimulation involves the surgical implantation of a vagus nerve stimulator, using a current of 1–2 mA. Mechanisms of stimulation are similar to transcutaneous auricular vagal nerve stimulation.

Deep brain stimulation

This neurosurgical procedure involves the implantation of a brain electrode that delivers a current to a targeted brain area. The underlying mechanisms of deep brain stimulation are not yet fully understood.[56] In patients with severe brain injuries, the main target is the central thalamus to induce excitation of the projecting thalamo-cortical afference. The electrodes are usually implanted in the intralaminar nuclei, because this region seems to be particularly associated with recovery in patients with disorders of consciousness,[57] and because of the pathophysiological mechanisms linked to the brain injury and cellular loss in the central thalamus.[58]

syndrome (4–15 months after injury) received a single session at 10 Hz for 60 min. Although no clinical effects were observed at the group level, three (30%) patients showed behavioural improvements (ie, recovery of pain localisation) associated with an increase in brain connectivity (as measured with dual-coil transcranial magnetic stimulation). The long-term safety of repeated transcranial magnetic stimulation over the dorsolateral prefrontal cortex was reported in two patients with disorders of consciousness, 6 months and 9 years after injury, who received 30 sessions of stimulation (300 trains of paired stimuli; 100-ms interpulse interval, 5-s intertrain interval) over 6 weeks and who showed no serious adverse event related to repeated transcranial magnetic stimulation.[80] The absence of severe adverse events linked to prolonged use of repeated stimulation is encouraging, but no conclusion can be drawn on the basis of these two case reports alone.

As for transcranial direct current stimulation, the prefrontal cortex could be a better target than the primary motor cortex, because all studies of repeated transcranial magnetic stimulation over M1 have not shown clinical improvements. Preliminary results of uncontrolled studies should encourage the design of repeated transcranial magnetic stimulation randomised controlled trials targeting the prefrontal region.

Other novel non-invasive brain stimulation approaches

Novel non-invasive brain stimulation techniques, including low intensity focused ultrasound pulse, transcutaneous auricular vagal nerve stimulation, and spinal cord stimulation, have been tested in a few case reports.[40,41,81] The only published report[40] of a patient in a minimally conscious state (19 days after traumatic brain injury) who received one session of low intensity focused ultrasound pulse targeting the central thalamus (figure 2E) showed a recovery of language comprehension and spatio-temporal orientation a few days later. The effects of transcutaneous auricular vagal nerve stimulation were presented in another case report of a patient with unresponsive wakefulness syndrome (50 days after anoxia; figure 2F).[41] After 4 weeks of treatment (two daily stimulation sessions for 30 min each, with an intensity of 4–6 mA, at a frequency of 20 Hz), the patient regained some signs of consciousness. Caloric vestibular stimulation is another technique that has been tested in two patients in a minimally conscious state (one caused by haemorrhagic stroke and one due to anoxia, about 6 months after injury).[82] The protocol included two active or two sham daily sessions 4 or 5 days per week for 2 weeks. Both patients showed clinical improvement with the Coma Recovery Scale-Revised[46] (ie, arousal and auditory scales) and the Wessex Head Injury Matrix[83,84] (ie, gesture making and selective responses to relatives). Spinal cord stimulation has also been explored in some case reports or uncontrolled studies with mixed results.[81,85] However, no randomised controlled trial evaluating the effects of spinal cord stimulation has been done, and studies did not use standardised scales or well-defined outcomes to assess the effects of the intervention. As for all uncontrolled trials, the results of these case reports on novel non-invasive brain stimulation techniques could be linked to spontaneous recovery; however, these studies can be considered as feasibility studies.

Optimisation of non-invasive brain stimulation

Within the growing field of non-invasive brain stimulation techniques (ten out of the 14 randomised controlled trials reviewed investigated the effect of non-invasive brain stimulation; table), transcranial direct current stimulation is the only intervention that has shown a clinical effect in multiple randomised controlled trials, more specifically in patients in a minimally conscious state.[59,63,64] However, not all patients respond, its effects are limited to the recovery of a few signs of consciousness (eg, recovery of visual pursuit, response to command, or object localisation or manipulation), and changes of diagnosis are transient and only observed in some cases. Therefore, the technique needs to be optimised to induce long-lasting clinically meaningful improvements, such as recovery of communication. Additionally, other brain areas could be stimulated according to patients' remaining brain structures and function because patients' clinical responsiveness is associated with the relative preservation of grey matter, brain metabolism, and cortical connectivity.[38,68] The emerging field of current modelling could also help the development of tailored stimulation montages based on individual structural brain changes.[88] To this aim, neuroimaging should be done before brain stimulation to document the exact area to be stimulated and to tailor patients' stimulation based on their brain lesions. Of note, no side-effects have been reported in all transcranial direct current stimulation or repeated transcranial magnetic stimulation studies (three studies[63,64,77] did not mention if they collected possible adverse events).

With regard to the other non-invasive interventions, repeated transcranial magnetic stimulation did not have a significant effect at the group level in any randomised controlled trials (all class III). Nonetheless, many parameters (eg, target area, frequency, or duration of stimulation) could be optimised to enhance its efficacy.

Invasive brain stimulation

A 7-year well-designed prospective open-label study[89] on the effects of deep brain stimulation of the thalamic reticular nuclei in patients with disorders of consciousness (>6 months after injury) reported that only five (13%) of 40 patients met the inclusion criteria (eg, EEG desynchronised activity <5% of the recorded time, somatosensory and auditory evoked potentials evoked on at least one side). Of the five eligible patients, two did not receive surgery owing to issues with the legal representative. The three patients who underwent the procedure showed small

	Study design	Class of evidence	N	Diagnosis	Time since injury	Procedure	Results	Effect sizes	Study caveats
Pharmacological interventions									
Zolpidem[28]	Double-blind, crossover	III	84 TBI and non-TBI patients (no details on numbers of each); 253 screened; 104 eligible	66 MCS, 18 UWS	>4 months	Single dose of 10 mg zolpidem, and if improvement placebo-controlled phase; evaluations at baseline and 1, 2, and 3 h after zolpidem or placebo intake	4 responders identified (ie, >5 points increase on the CRS-R in the placebo controlled double-blind phase); 2 patients in MCS emerged, 1 patient with UWS, and 1 patient in MCS– regained response to command (ie, MCS+); side-effects: 1 severe with zolpidem, 24 mild (20 [83%] of 24 with zolpidem)	Responders 1 h after zolpidem intake: d=2·09; 2 h later: 1·78*	Very low ratio of responders; heterogeneous population
Zolpidem[29]	Double-blind, crossover	III	8 (1 TBI, 7 non-TBI); no information on patients screened or eligible	8 UWS	>1 month	Single dose of 10 mg of zolpidem or placebo in two sessions, separated by 10–14 days; evaluations at baseline and 90 min after zolpidem or placebo intake	Signs of arousal after zolpidem intake (yawns and hiccups), activation of EEG, and a vagolytic chronotropic effect in all patients; no information on side-effects	No behavioural data available to calculate the effect size	Small sample; heterogeneous population
Non-pharmacological interventions									
Transcranial direct current stimulation[59]	Double-blind, crossover	II	55 (25 TBI, 30 non-TBI); 62 eligible	30 MCS, 25 UWS	1 week to 19 years	Comparison of a single session (20 min) of active and sham stimulation over the left DLPFC with CRS-R before and after stimulation	13 (43%) patients in MCS and 2 (1%) patients with UWS clinically improved (recovery of visual pursuit or response to command); at the group level, clinical improvement (2 points on the CRS-R) for patients in MCS; no side-effects observed	For patients in MCS: d=0·38*	One session of stimulation; no follow-up; heterogeneous population
Transcranial direct current stimulation[61]	Double-blind, crossover	III	16 (11 TBI, 5 non-TBI); 21 eligible	16 MCS	>3 months	Comparison of 5 sessions of active and sham transcranial direct current stimulation (20 minutes a day) over the DLPFC, separated by a week of washout; CRS-R performed before and after 5 days of stimulation, and at 1-week follow-up	9 (56%) responders; clinical improvement (2 points on the CRS-R) maintained up to 1 week after the end of the stimulation; no side-effects observed	After stimulation (before washout): d=0·43; at 1-week follow-up: d=0·57	Short washout period; no long-term follow-up; heterogeneous population
Transcranial direct current stimulation[63]	Double-blind, crossover	III	13 (1 TBI, 12 non-TBI); 15 eligible	7 UWS, 6 MCS	>3 months	Comparison of 5 days of active and sham stimulation over the DLPFC for 20 min a day; EEG and CRS-R done at baseline, after 5 days of stimulation, and up to 3-month follow-up	At the group level, no statistical difference between the two groups; at individual level, behavioural (CRS-R total score) and EEG changes in 5 (38%) patients (3 [50%] patients in MCS and 2 [29%] with UWS); no information on side-effects	No difference between groups	Small sample; unequal group split (4 in one and 7 in the other); parallel not crossover design; heterogeneous population
Transcranial direct current stimulation[64]	Double-blind, parallel	III	26 (12 TBI, 14 non-TBI); no information on patients screened or eligible	11 UWS, 15 MCS	1–18 months	Comparison of 20 sessions of active or sham transcranial direct current stimulation over DLPFC for 20 min twice a day for 10 days	CRS-R improvement in patients in MCS at the group level in the active group, coupled with increase in P300 amplitude; no information on side-effects	For patients in MCS: d=2·22*	Heterogeneous population; no follow-up
Transcranial direct current stimulation[65]	Double-blind, crossover	III	27 (12 TBI, 15 non-TBI); 86 screened	27 MCS	10 months to 14 years	Comparison of 20 sessions of active and sham transcranial direct current stimulation (20 min per day) over DLPFC, separated by 8 weeks; CRS-R before and after 4 weeks of stimulation (20 sessions), and at 8-week follow-up	No improvement at the group level; for patient group who received at least 80% of the stimulation sessions, increase in CRS-R total scores; no difference between active and sham stimulation at 8-week follow-up; no stimulation-related side-effects observed	Group level: d=0·47; subgroup of patients who received >80% of stimulation sessions: d=0·53	Heterogeneous population; high rate of drop-out; few assessments done

(Table continues on next page)

	Study design	Class of evidence	N	Diagnosis	Time since injury	Procedure	Results	Effect sizes	Study caveats
(Continued from previous page)									
Transcranial direct current stimulation[71]	Double-blind, crossover	III	33 (20 TBI, 13 non-TBI); 37 eligible	33 MCS	>3 months	Comparison of active or sham transcranial direct current stimulation applied for 5 days over the posterior parietal cortex (20 min a day), separated by a week of washout; CRS-R performed before and after 5 days of stimulation, and at 5 days follow-up	9 responders; clinical improvement immediately after the 5 days of active stimulation (increase by 1 point on the CRS-R); no effects at 1-week follow-up; no side-effects observed.	After stimulation: d=0·31	Short washout period; heterogeneous population; no long-term follow-up (1 week only)
Transcranial random noise stimulation[66]	Double-blind, parallel	III	9 (1 TBI, 8 non-TBI); no information on patients screened or eligible	9 UWS	30 days to 4 months	Comparison of 5 sessions of transcranial random noise stimulation (101–640 Hz) over DLPFC for 20 min; CRS-R performed at baseline, after each session, and at 3-day follow-up; EEG at baseline, the end of the 5 days protocol, and 3-day follow-up	No behavioural or neurophysiological improvement at the group level; no side-effects observed.	No difference between groups	Small sample; unequal group split (4 in one and 5 in the other); parallel not crossover design; heterogeneous population (only 1 TBI)
Repetitive transcranial magnetic stimulation[74]	Double-blind, crossover	III	11 (2 TBI, 9 non-TBI); no information on patients screened or eligible	11 UWS	9–85 months	Five sessions of active or sham 20 Hz repetitive transcranial magnetic stimulation for 10 min, for a total of 1000 pulses delivered in 5 trains, over left primary motor cortex for 5 consecutive days; EEG and CRS-R performed before and after stimulation	No behavioural or EEG improvements; no side-effects observed	No difference between groups	Small sample; heterogeneous population
Repetitive transcranial magnetic stimulation[75]	Double-blind, crossover	III	10 (4 TBI, 6 non-TBI); no information on patients screened or eligible	5 MCS, 5 UWS	1–28 months	One session of active or sham 20 Hz repetitive transcranial magnetic stimulation over M1 for 10 min, for a total of 1000 pulses delivered in 20 trains, CRS-R scores and cerebral blood flow velocity of the middle cerebral artery before and after stimulation	No behavioural (CRS-R) changes; temporary increase in peak systolic velocity and mean flow velocity of the left middle cerebral artery for patients in MCS; no effects in patients with UWS or in sham group; no side-effects observed	No difference between groups	One session of stimulation; small sample; heterogeneous population
Repetitive transcranial magnetic stimulation[77]	Double-blind, crossover	III	6 (4 TBI, 2 non-TBI); no information on patients screened or eligible	3 UWS, 2 MCS, 1 EMCS	1–28 months	Five sessions of active or sham 20 Hz repetitive transcranial magnetic stimulation over primary motor cortex for a total of 1000 pulses delivered in 20 trains; CRS-R scores and EEG reactivity collected before, after stimulation, and 1-week follow-up	No treatment effect on the CRS-R or on the EEG metrics; clinical improvement in 1 patient maintained at 1-week follow-up (a patient with UWS improved to MCS–), which was paralleled by EEG power spectra improvement; no information on side-effects	No difference between groups	Crossover study in acute patients but data analysesd as parallel owing to carryover effects; small sample; heterogeneous population

(Table continues on next page)

behavioural improvements (Coma Recovery Scale-Revised total scores improved 1–3 points compared with baseline). Additionally, the electrodes had to be removed for one patient due to a scalp infection. Given these results, the use of deep brain stimulation to improve patients' recovery seems limited to a small proportion of patients with prolonged disorders of consciousness and does not induce drastic clinical improvements. In another prospective open-label study[90] including 14 patients in unresponsive wakefulness syndrome or minimally conscious state (2 months to 11·5 years after injury), positive effects of deep brain stimulation of the thalamic reticular nuclei on clinical recovery were reported in four patients (29%). Three of four patients in a minimally conscious state emerged and one of ten patients with unresponsive wakefulness syndrome regained response to command. However, disentangling the effects of deep brain stimulation from spontaneous recovery is difficult, because these patients were enrolled 2–11 months after injury. Beside these two open-label studies, the only other study to employ a standardised and validated outcome measure (ie, the Coma Recovery Scale-Revised[46]) to evaluate the efficacy of deep brain stimulation in disorders of consciousness is the seminal paper published in 2007,[42] in which a traumatic brain injured patient in minimally conscious state for 6 years was treated with deep brain stimulation of thalamic intralaminar nuclei in a double-blind alternating crossover study (figure 2G). Clinically, the patient recovered consistent responses to commands, oral feeding, and functional communication. Improvements were seen immediately and over the course of 6 months. When deep brain stimulation was turned off, even if the clinical state of the patient decreased, it remained above baseline level suggesting some carryover effects.

To date, no sham-controlled trial has been published on deep brain stimulation in patients with disorders of consciousness. A treatment protocol still needs to be established that tests the generalisable effects of deep brain stimulation against a common set of criteria. Additionally, many clinical and ethical issues (eg, risk of infection and, consequently, clinical deterioration) should still be addressed.[91]

Invasive vagal nerve stimulation has been used in one uncontrolled case study[44] of a patient with unresponsive wakefulness syndrome for 15 years. The patient improved to a minimally conscious state and presented enhanced brain connectivity patterns (ie, activity increase in occipito-parieto-frontal and basal ganglia regions; figure 2H). This case report needs to be interpreted cautiously, but it illustrates the feasibility of using this approach in patients with disorders of consciousness.

Sensory stimulation programmes

Stimulation programmes include, among others, motor-based therapy, auditory-based training, music therapy, and multi-sensory training programmes.

	Study design	Class of evidence	N	Diagnosis	Time since injury	Procedure	Results	Effect sizes	Study caveats
(Continued from previous page)									
Tilt table and integrated stepping device[86]	Single-blind, parallel	III	50 (16 TBI, 34 non-TBI); 422 screened	UWS, MCS (no details on patient number)	4 weeks to 6 months	Comparison of regular tilt table therapy with or without integrated stepping device on level of consciousness; patients received the intervention 10 times for 60 min over a 3-week period	Both groups presented improvements (5 points on the CRS-R); no information on side-effects	At 3-week follow-up: d=0·34; at 6-week follow-up: d=0·42	Single blind; no non-intervention group because all had tilt table therapy; heterogeneous population
Sensory stimulation[87]	Double-blind, parallel	III	15 TBI; 55 screened	5 UWS, 10 MCS	1–6 months	Comparison of FAST and placebo (silence) applied 10 min 4 times per day for 6 weeks	Behavioural improvements in both groups; more improvement in the FAST group using Coma/Near Coma Scale; FAST patients had more functional MRI activation in language regions and whole brain in response to vocal stimuli; no information on side-effects	d=1·88	Small sample; placebo condition was silence; unclear double-blind procedure; heterogeneous population

Only randomised controlled trials published since 2013 that aimed to improve patients' awareness and used validated scale are listed. TBI=traumatic brain injury. UWS=unresponsive wakefulness syndrome. MCS=minimally conscious state. DLPFC=dorsolateral prefrontal cortex. CRS-R=Coma Recovery Scale-Revised. CBF=cerebral blood flow. EMCS=Emergence from MCS. FAST=familiar auditory sensory training. *Effect sizes were taken from the articles when available or calculated (Cohen's effect size small: d=0·2; medium: d=0·5; large: d=0·8) on the basis of data provided between active and controlled condition when a statistical difference was found.

Table: **Randomised controlled trials assessing pharmacological and non-pharmacological interventions in patients with disorders of consciousness**

In a single-blind randomised controlled trial,[86] the effects of conventional tilt table and its combination with a stepping device were assessed in 50 patients with disorders of consciousness (1–6 months after injury). Behavioural improvements were reported in both groups at the end of the 3-week intervention period and at the 3-week follow-up. No information was however provided regarding the type of behavioural recovery, and since the study did not include a group with no therapy, the improvement could also be related to spontaneous recovery.

Familiar auditory stimulation training (FAST)[92] was used in a double-blind randomised controlled trial in 15 patients with prolonged disorders of consciousness (mean of 70 days after injury) after traumatic brain injury.[87] FAST is composed of 5-min stories told by the patient's relatives that involve autobiographical events (10 min, 4 times a day, with at least 2 h between, for 6 weeks), and the placebo protocol was silence. Both behavioural (using the Coma/Near Coma Scale[35] and Coma Recovery Scale-Revised[46]) and neuroimaging data showed better results for the FAST group than for the control group (ie, more Coma/Near Coma Scale gains and higher MRI activation in language regions and whole brain). However, clinical improvements were within the boundaries of the Coma Recovery Scale-Revised and the Coma/Near Coma Scale without changes of diagnosis. Additionally, baseline difference between groups and the small sample size might also be a source of bias in this study, reducing its interpretability.[87]

The effects of music therapy were evaluated in a controlled case series[93] (two cycles of 15 sessions separated by 2 weeks) in ten patients with prolonged disorders of consciousness (time range not specified) showing some behavioural improvement (eg, more eye contact and smiles with fewer suffering expressions) and an improvement of haemodynamic parameters (ie, systolic and diastolic pressure) in patients in a minimally conscious state. Although no double-blind randomised controlled trial has been done to evaluate the clinical effects of music in patients with disorders of consciousness, neuroimaging has shown greater activation of the auditory network (figure 2I) and stronger neurophysiological responses (ie, increase in P300 response), showing a possible enhancement of attentional processes following music compared with other random sounds.[45,94–96]

An uncontrolled A-B-A-B design study[97] including eight patients with unresponsive wakefulness syndrome and 18 in a minimally conscious state tested the effects of a multisensory stimulation programme including auditory, visual, tactile, olfactory, and gustatory stimuli (20 min per session applied 3 days per week for 4 weeks). Higher Coma Recovery Scale-Revised total scores were reported during the treatments periods (B) compared with baseline and treatment withdrawal periods (A) in the minimally conscious state group but not in unresponsive wakefulness syndrome group. Double-blind randomised controlled trials need to evaluate the possible superiority of a multi-sensory approach compared with just one type of sensory stimulation.

Hyperbaric oxygen therapy[98] and acupuncture[99] have also been tested in uncontrolled studies. Some studies reported clinical improvements following hyperbaric oxygen therapy, but the articles were either not available in English or they did not use validated scales to objectify the clinical improvements. Therefore, these articles do not meet our inclusion criteria.

Taken together, only one double-blind randomised controlled trial[92] has been done on sensory stimulations, showing that auditory stimulations (ie, FAST protocol) could speed up recovery in patients with prolonged disorders of consciousness.

Conclusions and future directions

Management of patients with disorders of consciousness is challenging because of the absence of communication, the scarcity of interaction with their environment, and their severe motor disability. Adapted therapeutic approaches that do not require patients' active participation need to be developed rapidly. Present findings suggest that some patients might benefit from rehabilitative interventions,[62,86,87] even years after the brain injury.[59,63,65] As highlighted in the American practice guidelines for patients with disorders of consciousness,[23] most studies are open-label studies and case reports, so results need to be interpreted with caution and cannot be translated directly into clinical practice. However, several randomised controlled trials have been published since 2013, even if not included in the guidelines (table), but more robust designs and larger samples are still needed.

Only a few randomised controlled trials on pharmacological interventions have been done, and amantadine[22] is the only drug tested that shows class II evidence for patients with traumatic brain injury during rehabilitation and is the only intervention recommended by the American practice guidelines for patients with disorders of consciousness.[23] By contrast, many studies and randomised controlled trials have used neuromodulation techniques in this patient cohort, showing the growing interest in this field, which might be partly explained by the low cost and absence of severe side-effects. Transcranial direct current stimulation applied over the dorsolateral prefrontal cortex induced some clinical improvement in five randomised controlled trials (four class III[61,63–65] and one class II[59]) in patients in minimally conscious states from traumatic brain injury and non-traumatic brain injury aetiologies. Although the sample sizes were relatively small (13–55 patients enrolled per study) and the field of non-invasive brain stimulation for patients with disorders of consciousness is still in its infancy, transcranial direct current stimulation seems a promising treatment approach for patients in a minimally conscious state. For patients in unresponsive wakefulness

Search strategy and selection criteria

We searched PubMed for articles published in English between Jan 1, 2013, and Oct 31, 2018, using the following search terms: "disorders of consciousness", "vegetative state", "unresponsive wakefulness syndrome" or "minimally conscious state", and "therapy", "treatment", "therapeutics", "revalidation", or "drugs". Of 558 papers, 45 matched our inclusion criteria: clinical trial, open label study, observational study, and case report using validated behavioural tools to evaluate therapeutic interventions aiming at improving consciousness and functional recovery for patients with prolonged (>28 days after injury) disorders of consciousness. 16 of them were randomised controlled clinical trials. We did not include articles on rehabilitation methods not aimed at improving consciousness (eg, speech therapy or spasticity management). Additional references were collected and reviewed from the included articles' bibliographies. From the 45 articles that matched our inclusion criteria, articles were selected on the basis of their originality and relevance to the topic. If no randomised controlled trial was found for a therapeutic option but open-label studies or case reports were available, we included them in this Review.

syndrome, no treatment effects were found at the group level using this intervention.[59,62,63] Repeated transcranial magnetic stimulation has also been investigated in three randomised controlled trials in patients with disorders of consciousness. However, at the group level, no behavioural enhancements were noticed in any of the randomised controlled trials when applied over M1.[74,75,77] Future randomised controlled trials should target the dorsolateral prefrontal cortex, similar to transcranial direct current stimulation, because two uncontrolled observational studies using repeated transcranial magnetic stimulation have shown some positive effects.[78,79] Demographic and clinical characteristics of responders should also be investigated in larger randomised controlled trials or meta-analyses. Other brain areas could also be targeted according to patients' brain lesions and neural residual function, because patients' clinical responsiveness seems to depend on each patient's brain damage or lesion.[38]

To advance the field of therapeutic options for patients with disorders of consciousness, large sample multicentre randomised controlled trials, stratified for the level of consciousness, cause, and duration of the disease, should be done to confirm and validate the efficacy of a therapeutic intervention and to better target the clinical profile of patients who could benefit from specific interventions. All future randomised controlled trials also need to report how many patients were screened, enrolled, and lost to follow-up, especially when the sample size is small, because systematic reporting was not done in the randomised controlled trials described (table). Side-effects should also always be collected and reported.

Combining therapeutic interventions with neuroimaging or neurophysiological assessments would also help to improve our understanding of the neural correlates of a clinical response and, therefore, of the possible neuroplastic mechanisms after an acquired brain injury. Additionally, biomarkers of responsiveness are needed to provide a personalised intervention based on the patients' clinical characteristics and their brain lesions.

In conclusion, several randomised controlled trials have been done, but only two show class II evidence (for amantadine[22] and transcranial direct current stimulation[59]), and large double-blind randomised controlled trials are still needed to confirm possible therapeutic effects of other interventions. Because of the numerous challenges presented by this population (eg, high rate of drop-out due to medical complications and ethical issues), such randomised controlled trials are difficult to do. Given the promising effects of some treatments in patients with prolonged disorders of consciousness, we are convinced that the field of therapeutic interventions will make important progress in the years to come.

Contributors

AT reviewed the literature. AT and OG drafted the article. NS, JG, and SL revised it critically for important intellectual content. All authors gave final approval of the revised manuscript.

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