Therapeutic interventions in patients with prolonged disorders of consciousness

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Abstract

The management of patients with severe brain injuries and prolonged disorders of consciousness (DOC) raises important issues particularly with respect to their therapeutic options. The lack of treatment is challenged by new clinical and neuroimaging data indicating that some patients with prolonged DOC may benefit from therapeutic interventions, even years after the injury. The majority of the studies aiming at improving patients' level of consciousness and functional recovery includes behavioural and brain imaging open-label trials and case-reports, but several randomized clinical trials (RCT) have been conducted, especially using non-invasive brain stimulation. Only a couple of RCTs focused on the effects of drugs or sensory stimulation approaches, and only two Class II studies, on amantadine and transcranial direct current stimulation, have been published. While new therapeutic approaches seem to be valuable for patients with prolonged DOC, optimized stimulation parameters, alternative drugs or rehabilitation strategies still need to be tested and validated.

List of abbreviations:

CMD: Cognitive motor dissociation

CS: Confusional State

CRS-R: Coma recovery scale-revised

DBS: Deep brain stimulation

DLPFC: Dorsolateral prefrontal cortex

DOC: Disorders of consciousness

EEG: Electroencephalography

EMCS: Emergence from the minimally conscious state

IBP: Intrathecal baclofen pomp

LIFUP: Low intensity focused ultrasound pulse

LIS: Locked-in syndrome

MCS: Minimally conscious state

MRI: Magnetic resonance imaging

PET: Positron emission tomography

TBI: Traumatic brain injury

tDCS: Transcranial direct current stimulation

tRNS: Transcranial random noise stimulation

RCT: Randomized clinical trials

rTMS: Repetitive transcranial magnetic stimulation

VNS: Vagal nerve stimulation

UWS: Unresponsive wakefulness syndrome

Introduction

A lot of work has been accomplished to correctly diagnose patients with disorders of consciousness (DOC)[1,2] to establish prognostic indicators[3] and to understand the neural correlates of consciousness,[4] which is crucial since misdiagnosis can lead to important medical decisions such as premature withdrawal of life-sustaining care.[5,6] DOC includes the unresponsive wakefulness syndrome/vegetative state (UWS/VS; reflex behaviors only) and the minimally conscious state (MCS; clinical demonstration of signs of consciousness).[5,7] Once patients recover functional communication or object use, they emerge from the MCS (EMCS). Recently, additional entities have been proposed when there is a dissociation between clinical diagnosis and neuroimaging results showing atypical brain activation: MCS* and cognitive motor dissociation (CMD; see glossary panel).[8,9] These patients who recovered from coma can remain severely disabled for several months, years or even decades.

Regarding therapeutic options, only a limited number of studies have investigated how to treat these patients. In the past few years, the field of treatment for patients with DOC has however evolved rapidly but patients' clinical management remains challenging, mostly because these patients cannot communicate and are dependent on others for all cares. On the one hand, there is a risk of despair of the medical community that should be avoided, but on the other hand, there is also a risk of giving false hope to families that needs to be taken into account.

The American practice guidelines for DOC patients[10] published in 2018 only recommends amantadine for patients with UWS and MCS between 4 and 16 weeks after a traumatic brain injury (TBI) based on one randomized clinical trial (RCT)[11]. Given that these recommendations were developed based on explicit rules for establishing guidelines, many studies failed to meet their inclusion criteria. In this review, we provide a more extensive state of the art of available

therapeutic options for patients with prolonged DOC (i.e., more than 28 days). We discuss pharmacological and non-pharmacological interventions with the strongest evidence and for which robust RCTs have been published. If no RCTs were available, we present open-label studies and anecdotal case-reports with careful interpretation, as they may still give 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[11–14]), intrathecal baclofen (GABA agonist[15]), zolpidem (nonbenzodiazepine GABA agonist[16,17]), midazolam (benzodiazepine GABA agonist[18]) and ziconotine (calcium channel blocker[19]) have been employed to improve the level of consciousness and functional recovery in patients with DOC.

Amantadine and other neurostimulants

Only one large sample class II RCT on amantadine was conducted in 184 TBI patients with prolonged DOC (28-112 days post-injury) who received either amantadine (up to twice 200mg/day) or placebo for 4 weeks, and were followed for two extra weeks[11]. The amantadine group recovered faster than the placebo group during the course of the treatment as measured by the Disability Rating Scale.[20]

In non-TBI, one uncontrolled case-report has described the positive behavioural effects of amantadine in a MCS patient (16 months post-injury).[21] An older controlled case-report showed an increased metabolism in the fronto-parietal cortex during amantadine in an anoxic MCS

responder (figure 2A).[12] These two case-reports should encourage the development of RCT evaluating the effect of amantadine in other etiologies than TBI.

Beside amantadine, the administration of one or more neurostimulants (i.e., amantadine, bromocriptine, levodopa, methylphenidate, and modafinil) has also been explored in a retrospective study in a cohort of 115 patients with DOC (< 180 days post-onset).[13] The number of neurostimulants did not induced meaningful behavioral improvement in this observational study.

Zolpidem

This hypnotic agent is known to induce paradoxical transient effects in rare cases. A double-blind crossover RCT in 84 patients in UWS and MCS (> 4 months post-injury) identified 4 responders (5%) following the intake of 10 mg of zolpidem. These 4 patients gained at least 5 points on the Coma Recovery Scale-Revised (CRS-R[1]); one UWS and one MCS- became MCS+ and two MCS+ emerged (i.e., EMCS) for around two hours.[22] Another RCT performed on 8 patients in UWS (1-114 months post-injury) only noticed slight clinical changes (i.e., yawns and hiccups – but no changes on the CRS-R) combined with an activation of electroencephalographic (EEG) activity (i.e., faster frequency and lower amplitude).[23] An additional two-phase study (i.e., open-label and then a placebo-controlled trial if there was a change of CRS-R diagnosis) included 60 patients in UWS and MCS patients (1 month to 24 years post-onset).[16] Twelve patients (20%) showed behavioral improvements (e.g., command following, object localization) without a change of diagnosis. One patient could functionally use some objects after the open trial, but did not demonstrate any improvement in the placebo-controlled phase. In a last case-report, recovery of consciousness was observed in a patient in UWS (> 3 years post-cardiac arrest) when using higher dosage of zolpidem (30 mg instead of 10 mg).[24] The patient started to

demonstrate signs of consciousness when receiving 20 mg and further improved after 30 mg of zolpidem, suggesting that higher dosage may induce stronger effects.

Regarding zolpidem's brain responses, studies using EEG[17], functional magnetic resonance imaging (fMRI)[25] and positron emission tomography (PET)[26] have identified an increase in brain activity, mainly in prefrontal regions (figure 2B), which supports the mesocircuit hypothesis (figure 3). This model explains how zolpidem can modulate the thalamo-cortical connectivity through the disinhibition of the thalamus by acting on the globus pallidus interna and, consequently, promotes the recovery of consciousness.[27]

To date, zolpidem demonstrates improvement of consciousness and functional recovery (even if transient) in around 5% of patients. It is crucial to next determine the behavioral and physiological profile of zolpidem responders to better identify which patients could benefit from this treatment.

Intrathecal baclofen and other drugs

Intrathecal baclofen is primarily used as a centrally acting treatment for spasticity but it has been suggested as a potential drug to stimulate the recovery of consciousness in a few uncontrolled studies and case-reports.[15,28] The effects of midazolam (benzodiazepine receptor agonist)[18] and ziconitide (atypical analgesic, selective blocker of N-type calcium channels)[19] have also been reported in two single-case studies as stimulant for the recovery of consciousness of patients with prolonged DOC (one MCS and one UWS, respectively).[18,19] These anecdotal findings need to be confirmed with controlled studies.

Non-pharmacological interventions

Non-pharmacological interventions have also been attempted to improve consciousness and functional recovery in patients with DOC. These include non-invasive brain stimulations (transcranial direct current stimulation – tDCS, repeated transcranial magnetic stimulation – rTMS, transcutaneous auricular vagal nerve stimulation – taVNS, low intensity focused ultrasound pulse – LIFUP), invasive brain stimulation (DBS, invasive VNS), and sensory stimulation programs.

Non-invasive brain stimulations

Transcranial direct current stimulation

A first double-blind RCT tested the effect of prefrontal tDCS (i.e., anode over the left dorsolateral prefrontal cortex – DLPFC - for 20 minutes at 2mA) on 55 patients, both in acute and prolonged DOC (1 week to 26 years post-injury).[29] At the group level, behavioral improvements (as measured by the CRS-R) were observed for MCS patients, but not for UWS patients. At the individual level, 13/30 MCS (43%) showed a tDCS-related improvement (i.e., recovery of a clinical sign of consciousness never observed before tDCS, neither during sham session). Importantly, no tDCS related side-effects were reported in any patients. In a case-report, one patient considered in UWS showed a response to command after one session of DLPFC tDCS.[30] When looking at the neuroimaging assessments, a preservation of brain activity closer to what is usually observed in MCS+ patients was identified. In another RCT, tDCS was applied once a day for 5 consecutive days in 16 patients in MCS (5 months to 30 years post-injury) and the effects were assessed daily and at one-week follow-up.[31] A clinical improvement (e.g., recovery of command following, visual pursuit, object localization or manipulation) was

observed after 5 days of tDCS and the effects remained up to a week.[31] Some patients did not respond directly after the first stimulation indicating that a single session of tDCS is insufficient to determine if a patient can benefit from the technique or not. A non-randomized controlled study evaluated the clinical effects of sham then active tDCS applied either over the DLPFC or the primary sensorimotor cortex for 5 days in UWS or MCS (6 months to 10 years post-injury).[32] The 3 MCS improved regardless of the site of stimulation (1 MCS received prefrontal tDCS and 2 sensorimotor tDCS), while none of the 7 patients in UWS responded. Another double-blind RCT showed that the observed behavioral improvement (CRS-R total score) in 5/13 patients following 5 sessions of tDCS were paralleled with EEG changes (enhancement of EEG background).[33] One more double-blind RCT included 26 patients with DOC (1-17 months post-onset) who received 20 sessions of active or sham prefrontal tDCS over 10 days.[34] Clinical improvement was observed in the MCS group but not in the UWS group, combined with an increase in P300 amplitude for the responders. Finally, another RCT in 27 patients in MCS (10 months to 33 years post-injury) evaluated the effects of 20 sessions within 4 weeks of DLPFC tDCS applied by the patients' relatives or caregivers at home or in nursing homes.[35] While the overall compliance was good (i.e., 96% of sessions completed), the behavioral effect was not significant. However, when excluding the 5 patients who did not receive at least 80% of the tDCS sessions, a significant treatment effect was observed for the remaining 22 patients. Patients can thus demonstrate tDCS clinical improvements, such as the recovery of objects manipulation or functional communication, even years after the brain injury, but a chronic application of the proposed tDCS treatment is required. Beside, tDCS, 101-640Hz transcranial random noise stimulation was applied over the prefrontal cortex for 5 daily sessions of 20 minutes in a pilot

RCT on 9 patients in UWS (30 days to 4 months post-injury) which showed no clinical improvement.[36]

Regarding neuroimaging data of tDCS responders, a common pattern of metabolic and grey matter preservations has been observed in 8 responders compared to 13 non-responders patients in MCS.[37] Clinical improvement following tDCS seems to require a partial functional and structural preservation of the stimulated area (DLPFC) and other critical brain regions involved in consciousness recovery such as the precuneus and the thalamus (figure 2C). A higher cortical connectivity within the theta band was also observed in responders as compared to non-responders.[38] Additionally, recent EEG studies identified an increase in fronto-parietal coherence in the theta band after active DFPLC tDCS in MCS patients and an increased in global cortical excitability as measured with TMS-EEG.[39,40]

Compared to DLPFC stimulation, tDCS on the precuneus or the orbitofrontal cortex has shown less promising results.[41,42] In a double-blind RCT, tDCS was applied over the precuneus once a day for 20 minutes during 5 days in 33 patients in MCS (1-26 months post-injury).[41] An improvement at the group level was observed after the tDCS sessions but the effect did not last when reassessed 5 days later. At the single subject level, 6/33 patients were identified as responders (18%) with the recovery of visual pursuit, command following, automatic motor reaction or objects manipulation or localization. In one prospective open-label study, no behavioral changes were observed after tDCS applied over the orbitofrontal cortex in 22 patients with prolonged DOC (4-33 months post-onset).[42] Note that cortical connectivity and excitability were increased after tDCS in all MCS and in some UWS patients.

The prefrontal cortex seems therefore to be a better target for stimulation. DLPFC stimulation may induce a stronger connectivity between the prefrontal cortex and the thalamus since the

prefrontal cortex has many connections with the striatum. By stimulating the striatum, a disinhibition of the thalamus may occur, and this may reinforce thalamo-cortical connectivity (figure 3).[43,44]

Repeated transcranial magnetic stimulation

In a first double-blind RCT on 11 patients with UWS (9-85 months post-injury), no behavioral improvements were identified following rTMS sessions at 20Hz applied over M1 for 10 minutes.[45] The second RCT trial reported no behavioral improvement after one session of M1 20Hz rTMS for ~10 minutes in 10 patients with DOC (1-26 months post-onset) but improved hemodynamic functions (i.e., cerebral blood flow velocity) in the MCS as compared to the UWS group.[46] 5-Hz rTMS was applied on M1 for ~7 minutes in a third RCT in 5 UWS and 5 MCS patients (5-23 months post-injury) evaluating its effects on sleep-wake cycles.[47] Even if there was no behavioral effect reported, significant rTMS after-effects regarding the slow wave activity power were detected in the MCS but not in the UWS group. The last small sample crossover RCT evaluated the effects of 5 sessions of M1 20 Hz rTMS, lasting ~10 minutes, in 3 UWS, 2 MCS and 1 EMCS patients (1-28 months post-injury).[48] At the group level, no treatment effect was found, but at the single subject level, one UWS patient recovered localization to painful stimulation and maintained this behavior at 1-week follow-up. This clinical improvement was paralleled with an increase in alpha and beta power. Additionally, in a case-report, an increased absolute and relative power in delta, alpha and beta frequency bands was found with improved signs of consciousness in 1 patient in MCS after M1 rTMS[49] (figure 2D).

Besides M1, the DLPFC has also been targeted in a few uncontrolled studies. The effect of 20 sessions of 10Hz DLPFC rTMS (each session lasting 11 minutes) was evaluated in 16 patients with DOC (3-35 months post-injury) in a single-blind uncontrolled study.[50] CRS-R total score

increased in all 5 patients in MCS and in 4/11 patients with UWS, and the improvements were more important in MCS patients. In a small sample open-label study, 10 post-anoxic patients with UWS (4-15 months post-onset) received a single session of DLPFC 10-Hz rTMS for 60 minutes.[51] While no clinical effects were observed at the group level, 3 patients demonstrated behavioral improvements (i.e., recovery of pain localization for all 3 patients) associated with an increase in brain connectivity (as measured with dual-coil TMS). Finally, the safety of repeated DLPFC rTMS was reported in two patients with DOC, months and 9 years post-onset, who received 30 sessions of rTMS and who showed no serious adverse-event related to rTMS.[52] The absence of severe adverse-events linked to prolonged use of rTMS is encouraging, but no conclusion can be drawn based on these two case-reports only.

As for tDCS, it may be possible that prefrontal area could be a better target, rather than the motor cortex, as all M1 rTMS studies have failed to demonstrate clinical improvements. Preliminary results of uncontrolled studies should encourage the design of rTMS RCTs targeting the prefrontal region.

Other novel approaches

Novel non-invasive brain stimulation techniques, including LIFUP, taVNS and spinal cord stimulation, have been tested in a few case-reports.[53–55] The only published report of a patient in MCS (19 days post-TBI) who received one session of LIFUP targeting the central thalamus (figure 2E) showed a recovery of language comprehension and spatio-temporal orientation a few days later.[56] The effects of taVNS were presented in another case-report of UWS patient (50 days post-anoxia) (figure 2F[53]). After 4 weeks of treatment (two daily stimulation sessions for 30 minutes each, with an intensity of 4-6 mA, at a frequency of 20 Hz), the patient regained some signs of consciousness. The caloric vestibular stimulation is another technique that has been

tested in two patients in MCS (1 hemorrhagic stroke and 1 anoxia, about 6 months post-onset).[54] The protocol included two active and two sham daily sessions during 4 or 5 days per week. Both patients demonstrated clinical improvement with the CRS-R (i.e., arousal and auditory scales) and the Wessex Head Injury Matrix (i.e., gesture making and selective responses to relatives). Spinal cord stimulation has also been explored in some case-reports or uncontrolled studies.[55,57] However, no RCT evaluating their effects have been performed so far, and the majority of the available studies did not use standardized scales or well-defined outcomes to assess the effects of these interventions. As for all uncontrolled trials, the results of these case-reports could be linked to spontaneous recovery; however, these articles can be seen as feasibility studies.

In sum, regarding the growing field of non-invasive brain stimulation techniques (10 out of the 14 RCTs reviewed from these last 5 years investigated the effect of non-invasive brain stimulation – see table 1), tDCS is the only intervention that has shown a clinical effect in multiple RCTs, more specifically in patients in MCS. However, not all patients respond, its effects are limited to the recovery of a few signs of consciousness (e.g., recovery of visual pursuit, command following, object localization or manipulation) and change of diagnosis are transient and only observed in rare cases. It thus needs to be optimized to induce long-lasting clinically relevant improvements such as recovery of communication. In addition, others brain areas could be stimulated according to patients' remaining brain structures and function as it has been shown that patients' clinical responsiveness is associated to the relative preservation of grey matter, brain metabolism, and cortical connectivity.[37,38] The emerging field of current modelling could also help the development of patients' tailored stimulation montages based on individual structural brain changes.[58] To this aim, neuroimaging should be performed before brain stimulation (i.e., tDCS and rTMS) to document the exact area to be stimulated and to tailor

patients' stimulation based on their brain lesions. One important note is the absence of side-effects observed in all tDCS or rTMS studies assessing side-effects (3 studies did not mention if they collected possible adverse-events).

Regarding the other non-invasive interventions, rTMS did not show significant effect at the group level in any RCTs (all class III). Nonetheless, many parameters (e.g., type, frequency or duration of stimulation) could be optimized to enhance its efficacy.

Invasive brain stimulation

A 7-year well-designed prospective open-label study on the effects of DBS in patients with DOC (>6 months post-injury) report that only a very limited number of patients met the inclusion criteria (5/40) (e.g., EEG desynchronized activity <5% of the recorded time, somatosensory and auditory evoked potentials evoked on at least one side).[59] Out of the 5 eligible patients, two did not receive surgery due to issue with the legal representative. The 3 patients who could undergo the procedure showed limited behavioral improvements (CRS-R total scores improved from 1 to 3 points) or even worsened behaviorally (decrease in CRS-R compared to baseline). In addition, the electrodes had to be removed for 1 patient due to a scalp infection. Given these results, the use of DBS to improve patients' recovery seems limited. In another prospective open-label study including 14 patients in UWS and MCS (2 months to 11.5 years post-injury), the positive effects of DBS of the thalamic reticular nuclei on clinical recovery were observed in 4 patients (29%).[60] Three patients in MCS emerged and 1 patient with UWS regained response to command. It is however tricky to disentangle DBS effects from spontaneous recovery since these patients were enrolled between 2 and 11 months post-injury. Beside these two open-label studies, the only other study to employ a standardized and validated outcome measure (i.e., the CRS-R) to evaluate the efficacy of DBS in DOC is the seminal paper published in 2007,[61] in which a TBI

patient in MCS for 6 years was treated with DBS of thalamic intralaminar nuclei in a double-blind alternating crossover study (figure 2G).[61] Clinically, after a few months of treatment, the patient recovered consistent command followings, oral feeding, and functional communication during the 'on' periods. When DBS 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 DBS in DOC. A treatment protocol still needs to be established along testing the generalizable effects of DBS against a common set of criteria. In addition, many clinical and ethical issues should still be addressed, as previously reported.[62]

Finally, invasive VNS has been employed in one uncontrolled case-study of a patient who was in UWS for 15 years.[63] The patient improved from UWS to MCS, and presented enhanced brain connectivity patterns (i.e., activity increase in occipito-parieto-frontal and basal ganglia regions; figure 2H). This case report needs to be taken cautiously as for all previous uncontrolled studies, but it illustrates the possibility of using this approach in patients with DOC.

Sensory stimulation programs

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

In a single-blind RCT, the effects of conventional tilt table and its combination with a stepping device were assessed in 50 DOC patients (1-6 months post-injury).[64] Behavioral improvements were noticed in both groups at the end of the 3-week intervention period, as well as at 3-week follow-up. No information was however provided regarding the type of behavioral recovery, and

since the study did not include a group with no therapy, the improvement could also be related to spontaneous recovery.

The familiar auditory stimulation training (FAST[65]) was used in a double-blind RCT in 15 patients with prolonged DOC (average of 70 days post-onset) after TBI.[66] The FAST is composed of 5-min stories told by the patient's relatives that involve autobiographical events, while the placebo protocol was "silence". Both behavioral (using the Coma/Near Coma Scale – CNC[20]) and neuroimaging data showed better results for the FAST group than for the control group (i.e., more CNC gains and higher MRI activation in language regions and whole brain). Clinical improvements were however comprised within the boundaries of the CRS-R and the CNC scale, without changes of diagnosis and the reported baseline difference between groups may also be a bias in this study, as well as the small sample size.[66]

The effects of music therapy were evaluated in a controlled case-series (two cycles of 15 sessions of, separated by two weeks) in 10 patients with prolonged DOC (time range not specified) showing a slight behavioral enhancement (e.g., more eye contacts and smiles with less suffering expressions) and an improvement of hemodynamic parameters (i.e., systolic and diastolic pressure) in patients in MCS.[67] Even if, to date, no double-blind RCT has been conducted to evaluate the clinical effects of music in patients with DOC, neuroimaging has shown higher activation of the auditory network and stronger neurophysiological responses (i.e., increase in P300 response) following music compared to other random sounds (figure 2I).[68–71]

A recent uncontrolled ABAB protocol tested the effects of a multi-sensory stimulation program including auditory, visual, tactile, olfactory, and gustatory stimuli (20 minutes per session applied 3 days per week for 4 weeks).[72] Higher CRS-R total scores were observed during the treatments periods (B) compared to baselines (A) in MCS but not in UWS patients groups.

Double-blind RCTs need to further evaluate the possible superiority of a multi-sensory approach as compared to only one type of stimulation.

Hyperbaric oxygen therapy[73] and acupuncture[74] have also been tested in uncontrolled studies. However, most studies were not available in English and did not use validated scales.

Until now, only one double-blind RCT has been conducted on sensory stimulations, showing that auditory stimulations (i.e., FAST protocol) could speed up recovery in patients with prolonged DOC as shown in a small sample double-blind class III RCT.

Conclusion and future directions

Management of patients with DOC is challenging because of the absence of communication, the scarcity of interaction with their environment and their severe motor disability. Therefore, adapted therapeutic approaches that do not require patients' active participation need to be developed. Present findings suggest that some patients may benefit from rehabilitative interventions,[32,64,66] even years after the brain injury,[29,33,35] which highlights the importance of management of patients with prolonged DOC. To date, as highlighted in the American practice guidelines for DOC patients,[10] most studies are open-label studies and case-reports, in which results need to be taken with caution, and cannot yet be translated into clinical practice. However, several RCTs are being published in the last 5 years (table 1) but more robust designs and larger samples are still needed.

Regarding pharmacological treatment, only a few RCTs have been conducted, among them, amantadine[11] is the only drug tested showing class II evidence for patients with TBI during rehabilitation and the only intervention recommended by the American practice guidelines for DOC.[10] For neuromodulation, on the other hand, many studies and RCTs have been conducted in

this patient cohort, showing the growing interest in this field, that may be partially explained by the low cost and absence of severe side-effects reported. TDCS applied over DLPFC has been shown to induce some clinical improvement in 5 RCTs, 4 class III[31,33–35] and 1 class II,[29] in patients in MCS from TBI and non-TBI etiologies. Even if the sample sizes were relatively small (13 to 55 patients enrolled per study) and the field of non-invasive brain stimulation for patients with DOC is still at its infancy, tDCS seems a promising treatment approach for patients in MCS. For patients in UWS, no treatment effects were found at the group level using this intervention.[29,32,33] rTMS has also been investigated in RCT in patients with DOC. However, at the group level, no behavioral enhancements were noticed in any of the RCTs when applied over M1.[45,46,48] Future RCTs should target the DLPFC, similarly to tDCS, as two uncontrolled observational rTMS studies show some positive effects.[50,51] Demographic and clinical characteristics of responders should also be investigated in larger RCTs or meta-analyses. Others brain areas could also be targeted according to patients' brain lesions and neural residual function since patients' clinical responsiveness seems to depend on this.[37]

To move forward the field of therapeutic options for patients with DOC, large sample multi-center RCT, stratified for the level of consciousness, etiology and duration of the disease, should be performed to confirm and validate the efficacy of a therapeutic intervention and to better target the clinical profile of patients who could benefit from this intervention. All future RCT also need to report how many patients were screened, enrolled or were lost at follow-up, especially when the sample size is small, which was not systematically done in the reported RCTs (table 1). Side-effects should also always be collected and reported.

To advance the treatment of patients with prolonged DOC, 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. In addition, there is a crucial need to develop biomarkers of responsiveness to provide a personalized intervention based on the patients' clinical characteristics and their brain lesions.

In conclusion, several RCTs have been conducted but only two show class II evidence (on amantadine and tDCS) and large double-blind RCTs are still needed. Given the numerous challenges that represent this population (e.g., high rate of drop-out due to medical complications, ethical issues) such RCTs are nonetheless difficult to conduct. Based on the promising effects of some treatments in patients with prolonged DOC, especially in TBI (for amantadine[11]) and in MCS (for tDCS[29]), and given that some patients may still improve even years after the brain injury, we are convinced that the field of therapeutic interventions will make important scientific progress in the next years.

Search strategy and selection criteria

We searched on PubMed for articles published in English between January 1st 2013 and October 31st 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. Out of 558 papers, 45 matched our inclusion criteria: clinical trial, open label study, observational study, and case report using validated behavioral tools on therapeutic intervention for patients with prolonged (> 28 days post-injury) disorders of consciousness aiming at improving consciousness and functional recovery. Sixteen of them were randomized controlled clinical trials. We did not include articles on rehabilitation methods not aiming at improving consciousness (e.g., speech therapy, spasticity management). We also excluded papers that did not use a validated scale. Additional references were collected and

reviewed from the included articles' bibliography. Out of the 45 articles that matched our inclusion criteria, articles were selected based on their originality and relevance to this topic. Note that if no RCT were found for a therapeutic option but open-label studies or case-reports were available, we included them in the present review.

Authors' contributions

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

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Conflict of interest

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Glossary panel I – clinical entities (see figure 1)

Coma

Coma is the result of a severe brain injury, in which patients are unarousable (i.e., eyes closure even when stimulated) and unaware of themselves and their environment.[75] This state is temporary and after several days or weeks, patients may either evolve to brain death (i.e., irreversible coma with absence of brainstem reflexes and apnea) 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 (UWS) (previously termed 'vegetative state').[76] Patients in UWS exhibit no signs of awareness, but they can present a variety of reflexive movements, such as grinding teeth, yawning, or groaning.[76] This condition may be transitory, prolonged or permanent.

Minimally conscious state

Once patients recover fluctuating but reproducible signs of consciousness, they enter into the minimally conscious state (MCS). This entity is divided into MCS- and MCS+ based on language processing.[77,78] MCS- describes patients showing visual pursuit and fixation,

localization to noxious stimulation and/or automatic motor reactions (e.g., grasping bed sheets). Patients in MCS+ follow simple commands, can make understandable verbalizations or communicate intentionally but not functionally. As in UWS, MCS can be temporary or permanent.

The diagnostic label of MCS* has been suggested for UWS patients who show no evidence of awareness at the bedside while neuroimaging data show atypical brain patterns using active paradigm (e.g., brain activity in motor area during a motor imagery task) and/or metabolic resting state (e.g., preservation of the fronto-parietal network).[8,79,80] This entity allows a more clinically accurate diagnosis when the bedside examination shows no evidence of consciousness.

Emergence from MCS

When patients are able to functionally communicate and/or use adequately 2 different objects, they have emerged from the MCS. Most of these patients have still severe cognitive and motor impairements.[77,78] Patients who are disoriented remain in a confusional state.

Locked-in syndrome

The locked-in syndrome (LIS) is defined by quadriplegia and anarthria due to a lesion in the corticospinal and corticobulbar pathways in the brainstem.[81] These patients cannot move (some recover some distal movements – incomplete LIS) but their sensations remain intact and they are fully conscious. The most common way for these patients to communicate is via vertical eye movements and blinks.[82] In the case of complete LIS (cLIS), a paralysis of the eyes prevent any communication and brain computer interfaces are needed.[83] Finally, the term “functional LIS” (as well as “covert cognition”) has been proposed to indicate a dissociation between bedside

behaviour and the results of neuroimaging assessments[84] (like MCS*[8] and cognitive motor dissociation - CMD[9])

Cognitive motor dissociation

The syndrome of cognitive motor dissociation (CMD) has been proposed to specifically refer to patients in coma, UWS or MCS- who show consistent brain activation during mental imagery tasks using functional magnetic resonance imaging (fMRI) or electroencephalography (EEG), and hence show command following using neuroimaging technologies.[9] CMD indicates a wide range of uncertainty regarding the underlying cognitive capacity present in patients with no or little behavioural responses.

Glossary panel II – neuromodulation techniques

Transcranial Direct Current Stimulation (tDCS)

This neuromodulation technique modulates cortical excitability through the application of a weak (usually ≤ 2mA) direct current through the brain between 2 electrodes, from the anode to the cathode. Physiologically, the establishment of the long-lasting after-effects depends on membrane potential changes as well as modulations of N-methyl-D-aspartate (NMDA) receptor efficacy, which can induce long-term potentiation and long-term depression like effects.[85–87] However, more mechanistic and in vivo studies need to be performed to better understand how tDCS can influence cortical activity and act on neuroplasticity.

Transcranial Magnetic Stimulation (TMS)

TMS uses an electromagnetic pulse to induce focalized neural depolarization and firing. Repeated TMS (rTMS), as compared to single pulses TMS, can influence brain plasticity and cortical organization via alterations of neuronal excitability. It has been used to induce a

sustained inhibition (~1Hz frequency) or activation (5-20 Hz frequency) of the neuronal population.

Low intensity focused ultrasound pulse (LIFUP)

This technique employs low-energy sound waves to excite or inhibit brain activity. Compared to tDCS and rTMS, it is, theoretically, capable of directly targeting and stimulating subcortical and deep brain structure such as the thalamus.

Vagal nerve stimulation (VNS)

VNS can be invasive and surgically placed or non-invasive via a transcutanous auricular stimulation (taVNS). taVNS 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, as a consequence, alter the firing rate of the vestibular nerve. This technique is thought to induce compensatory responses, via basal forebrain/brainstem projections through central thalamus and hypothalamus, in distal fronto-parietal and striatal networks.[88] Invasive VNS involves the surgical implantation of a vagus nerve stimulator, using a current of 1-2 mA. Mechanisms of stimulation are similar to taVNS.

Deep brain stimulation

This neurosurgical procedure involves the implantation of brain electrode that delivers a current to a targeted brain area. The underlying mechanisms of DBS are not yet fully understood.[89] 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 DOC patients'

level of recovery,[90] and because of the pathophysiological mechanisms linked to the brain injury and cellular loss in the central thalamus.[91]

Figures legends

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 2-dimensional axis by comparing the degree of impaired cognitive function against the degree of motor function. Red circles represent patients who are unconscious with limited reflexive movements (coma and unresponsive wakefulness syndrome – UWS). Blue circles represent patients in minimally conscious state (MCS+ and MCS- depending on language preservation). When functional communication is detected (yellow circles) patients emerge from MCS (EMCS) and can evolve to a confusional state (CS), severe or moderated disability, before a full recovery (green circle). Dissociations between motor and cognitive functions exist in the locked-in syndrome (LIS, green circle), in the cognitive motor dissociation (CMD), and in the MCS* (purple circles). In rare cases, the diagnosis of complete LIS (cLIS) can be done through neuroimaging exams. See glossary panel for more information. Black-white gradient represents the evolution from absence (black) to the recovery of a behavior (white) (e.g., no command following to consistent command following).

Figure 2: **Neuroimaging results and neurophysiology associated with potential pharmacological and non-pharmacological interventions to improve consciousness in patients with disorders of consciousness (DOC).** (A) Amantadine has been shown to increase brain metabolism in the fronto-parietal network in one patient in minimally conscious state (MCS)[12] while (B) zolpidem induced an increase in brain metabolism in the prefrontal and mesiofrontal cortex in 3 MCS responders.[26] (C) Transcranial direct current stimulation (tDCS)

responders (n=8) presented more preservation of brain metabolism in the prefrontal cortex (stimulated area) as compared to non-responders (n=13);[37] (D) repetitive transcranial magnetic stimulation (rTMS) of 20 Hz on the primary motor cortex induced EEG increases in beta (shown), alpha, and delta, bands power in one MCS responder;[49] (E) Low intensity focused ultrasound pulsation (LIFUP[56]) is shown in a patient with unresponsive wakefulness syndrome (UWS) who became MCS after LIFUP with the transducer with the thalamic target (red circle); (F) Transcutaneous auricular vagal nerve stimulation (taVNS) induced increases in functional connectivity between posterior cingulate/precuneus and hypothalamus, thalamus, prefrontal cortex, temporal gyrus (red) and decrease between the posterior cingulate/precuneus and cerebellum (blue) in one UWS patient who became MCS after taVNS.[53] (G) Deep brain stimulation (DBS) electrode placement, as seen with MRI, in one MCS patient who recovered subsequently;[61,92] (H) Brain connectivity patterns after invasive vagal nerve stimulation (VNS) as measured with high-density electroencephalography (EEG) in one UWS patient who became MCS.[63] (I) Music stimulation induced an increase in functional connectivity in the auditory network (and in the default mode network – not shown) in 5 DOC patients.[68]

Figure 3: The mesocircuit fronto-parietal model. This model provides a framework that explains the potential mechanisms of action of various therapeutic interventions and sheds light on 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 and via an inhibitory modulation by the internal globus pallidus which itself is regulated by cortico-striatal and thalamostriatal inputs. Activation of the central thalamus broadly drives activity of associative fronto-parietal cortical areas.[93] On the other hand, in case of brain injury, a reduction of thalamocortical and

thalamostriatal outflow following deafferentation and loss of neurons from the central thalamus withdraws important afferent drive to the medium spiny neurons of the striatum (green lines). This 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 (dashed red line) allows neurons of the globus pallidus interna (GPI) 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 may explain the potential mechanisms of several treatments that have shown promising results in the recovery of consciousness in severely brain-injured patients. A partial preservation of the stimulated prefrontal cortex seems to be necessary to induce a clinical tDCS response,[37] while rTMS seems to induce a global increase in cortical oscillations when applied over the primary motor cortex.[49] The clinical improvement of a patient who responded to amantadine correlated with an increased fronto-parietal brain metabolism.[12] Zolpidem may reduce the inhibition of the thalamus by activating the striatum.[27] DBS directly acts over the central thalamus aiming to stimulate the thalamo-cortical connectivity,[61] while LIFUP stimulates the thalamus in a non-invasive way.[56] Finally, invasive and non-invasive VNS directly stimulate the vagal nerve.[53,63] Blue circles represent subcortical regions; while purple rectangles represent cortical areas. Green lines stand for weak excitation, red lines for excess of inhibition and crossed-dashed lines for loss of inhibition between 2 regions. Adapted from[5].

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