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[Intervention Protocol]

Non-invasive brain stimulation for treatment of severe disorders of consciousness in people with acquired brain injury

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of non-invasive brain stimulation (NIBS) for the treatment of patients with severe disorders of consciousness following an acquired brain injury.

BACKGROUND

Description of the condition

Disorders of consciousness represent a challenging clinical entity, which is prone to misdiagnosis and lacks effective treatment options. This entity comprises, besides coma (that usually lasts from a few days to several weeks), two main pathologic states; the unresponsive wakefulness syndrome, also termed vegetative state (UWS/VS) (Laureys 2010), and the minimally conscious state (MCS) (Giacino 2002). Patients in the UWS/VS recover the ability to open their eyes, in contrast to patients in coma, but they do not express any signs of consciousness of themselves or of their environment. Patients in the MCS recover some small signs of consciousness (e.g. visual pursuit, following commands, localization to painful stimulus, contextualised smiles or tears). Nevertheless, by definition, they are not able to communicate, and therefore, no active rehabilitation treatment, such as conventional physical therapy or neuropsychological rehabilitation, can be used with this group of patients. When patients recover their ability to communicate functionally, either verbally or using a binary code, we say that they emerged from the MCS (Giacino 2002). The most common aetiologies are traumatic brain injury, anoxia (e.g. following a cardiac arrest) and stroke. In this review we will focus on patients in prolonged (more than 28 days) UWS/VS and MCS.

Worldwide, the prevalence of disorders of consciousness is rather low. The UWS is estimated to affect between 0.2 and 6 in 100,000 individuals, while the prevalence of the MCS has been estimated at 1.5 in 100,000 (Van Erp 2014). This low prevalence could partly explain the lack of studies looking for treatment options for this population. Regarding the evolution of patients with disorders of consciousness, few data are available. One study showed that for patients in UWS/VS as a result of traumatic brain injury, recovery of consciousness varied with time. Three months after injury, 18% of the patients had recovered consciousness (MCS); 16% had died and 61% remained in UWS/VS. Recovery of consciousness had occurred in 13% of the patients 12 months post-injury and functional recovery was reported in 20% of them. For patients in MCS at one month after a severe head injury, functional recovery was slightly better than in UWS/VS patients with 50% who recovered after six months and 53% after 12 months. At 12 months after injury, 26% had died. For anoxic aetiologies, outcome are worse for both UWS/VS and MCS patients. For UWS/VS patients at one month post-injury, recovery of consciousness and function was extremely poor: 13% after three months, 14% after six and 12 months. Mortality increased with time with 45% and 69% of patients dead at 6 and 12 months post-onset. For MCS patients, 29% recovered functions within six months; 65% died, 12% were MCS and 24% recovered functions.

Description of the intervention

Non-invasive brain stimulation (NIBS) encompasses several different techniques that aim to stimulate the brain in a non-invasive way using electrical, magnetic or thermal currents, or ultrasound.

There is evidence that NIBS may have a beneficial effect on various cognitive functions such as memory, attention or language in stroke patients and patients with Parkinson's disease or other pathologies leading to cognitive disorders (for a review, see Kubis 2016). The two most studied techniques are transcranial direct current stimulation

(tDCS) and repetitive transcranial magnetic stimulation (rTMS). These techniques aim to stimulate the patient's brain or, more specifically, to enhance the functions linked to the target area. In the case of cognitive functions, the prefrontal cortex, and more precisely the left dorsolateral prefrontal area is the preferred area to stimulate. Other brain regions have also been targeted. For example, there are promising results from stimulating Broca's area in reducing aphasic symptoms (Fridriksson 2018).

A treatment session usually lasts between 10 and 20 minutes and may be repeated over days or even weeks. The parameters of stimulation vary with the technique but mainly comprise intensity of stimulation, frequency of stimulation, wave forms, and the duration of stimulation or pulses.

After-effects also differ from one technique to another. From a general perspective, NIBS techniques are considered to be safe as they are non-invasive. Nevertheless, they can induce uncomfortable sensations such as tingling or itching. It should be noted that rTMS needs to be used with caution when applied to people with epilepsy. However, if the guidelines published by Rossi 2009 are followed, then rTMS is widely considered to be safe and the risk of seizure to be limited.

How the intervention might work

Neurophysiological effects of NIBS are complex and not yet fully understood. Below we provide a short description of the basic principles of the main four NIBS approaches.

1. Transcranial direct current stimulation (tDCS): this neuromodulation technique modulates cortical excitability through the application of a weak (usually ≤ 2 mA) direct current through the brain between two electrodes, mainly one anode to one cathode, although new devices offer multichannel montages with multiple anodes and multiple cathodes. Physiologically, the establishment of long-lasting effects depends on membrane potential changes as well as modulations of N-methyl-D-aspartate receptor efficacy, which can induce long-term potentiation and long-term depression-like effects (Stagg 2011).
2. Transcranial magnetic stimulation (TMS): uses an electromagnetic pulse to induce focalised neural depolarization and firing. Repetitive TMS (rTMS), as compared to single-pulse TMS, can influence brain plasticity and cortical organization via alterations of neuronal excitability, as for tDCS. It has been used to induce a sustained inhibition (~ 1 Hz frequency) or facilitation (5 to 20 Hz frequency) of the excitability of neuronal populations (Klomeij 2015).
3. Vagal nerve stimulation (VNS): can be invasive, delivered via a surgically placed electrode, or non-invasive, via transcutaneous 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, alters the firing rate of the vestibular nerve. This technique is thought to stimulate basal forebrain/brainstem projections through central thalamus and hypothalamus, in distal fronto-parietal and striatal networks (Rutecki 1990).
4. Low-intensity focused ultrasound pulse (LIFUP): this technique employs low-energy sound waves to excite or inhibit brain activity. Compared to tDCS and rTMS, which can only modulate the activity of the neurons in the cortex and not in deeper brain

regions. it is, theoretically, capable of directly targeting and stimulating subcortical and deep brain structures such as the thalamus in a non-invasive way, as opposed to thalamic deep brain stimulation, an invasive technique (Monti 2016).

Why it is important to do this review

Until recently, the medical community has viewed patients in the UWS/VS and MCS with great pessimism regarding both prognosis and effective treatments. Unfortunately, this pessimism results in the neglect of patients in terms of healthcare as no improvement is expected. Nevertheless, in the past 10 years a number of studies have reported that some patients in MCS could improve even years after the insult, and several treatments (e.g. amantadine, zolpidem, or deep brain stimulation) can enhance signs of consciousness in some patients with disorders of consciousness (Giacino 2018a). At present, only amantadine has been proposed by the American Academy of Neurology guidelines published in 2018 (Giacino 2018b). However, recent randomised clinical studies using NIBS have demonstrated promising results to enhance patients' responsiveness (Thibaut 2019).

Some Cochrane Reviews on NIBS have been published in the last eight years (e.g. Elsner 2016; Elsner 2019; Hao 2013; O'Connell 2018; Zhang 2018), however no recent Cochrane Reviews on disorders of consciousness are available; the only Cochrane Review on disorders of consciousness was published more than 15 years ago and only focused on sensory stimulations (Lombardi 2002).

OBJECTIVES

To assess the efficacy and safety of non-invasive brain stimulation (NIBS) for the treatment of patients with severe disorders of consciousness following an acquired brain injury.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with parallel-group or cross-over design.

Types of participants

We will include studies of children and adults with severe disorders of consciousness caused by traumatic or non-traumatic injury of any aetiology. Severe disorders of consciousness may be categorized into different severity levels, that is, unresponsive wakefulness syndrome (UWS), minimally conscious state (MCS)-minus, and minimally conscious state (MCS)-plus. MCS-minus describes patients with non-reflexive behaviours such as visual pursuit or fixation, oriented movements and localization to pain but no language-related behaviours (Bruno 2011). MCS-plus characterizes patients who recover command-following, intelligible verbalization, and/or intentional communication. We will include all categories in this review. Although we are aware of the potential for misdiagnosis in this patient group, we will not exclude any studies on the basis of the diagnostic criteria. Rather, we will describe the diagnostic procedure in detail and discuss the tools used in light of known diagnostic accuracy and psychometric properties.

Types of interventions

We will include studies that compared any type of NIBS method for the treatment of severe disorders of consciousness to a control intervention.

NIBS may be, for example, tDCS, rTMS, or similar methods applied by means of any type of non-invasive stimulators to modulate brain activity. We will include studies where the NIBS was applied as the exclusive treatment as well as NIBS applied as part of a combined treatment. The control interventions may be a placebo or sham stimulation, no treatment, or any active control intervention.

Interventions may be applied during rehabilitation treatment in any setting (e.g. home care, nursing home, etc.). When NIBS are applied during rehabilitation treatment, that is, in combination with other forms of treatment, the amount of the adjunctive therapy should be kept the same between the study intervention groups. In cases where the therapy is not equally distributed, we will exclude these studies from analysis to perform a sensitivity analysis.

Types of outcome measures

Primary outcomes

The primary aim of this review is to investigate the efficacy and the safety of the non-invasive brain stimulation methods. Therefore two primary outcomes are defined:

1.1 Change in level of consciousness

Most likely this aspect will be assessed by means of the Coma Recovery Scale revised (CRS-r) or the Disability Rating Scale (DRS), but we will also accept the Wessex Head Injury Matrix, the Coma Near Scale, the Sensory Modality Assessment and Rehabilitation Technique, and other validated scales used to assess the level of consciousness.

1.2 Frequency of any adverse events or serious adverse events

We will use an exploratory approach. That is, we will describe all reported adverse events and serious adverse events and seek to find categories to structure the reporting. Adverse events and serious adverse events may include, for example, epileptic seizures, skin problems, or signs of pain. We will report the frequency in relation to the number of participants included. We will report the number of participants in each group experiencing adverse events or serious adverse events as well as the total number of adverse events or serious adverse events in each group.

Secondary outcomes

2.1 Acceptability of the interventions

We will assess acceptability of the interventions by means of:

1. the proportion of eligible patients randomized; and
2. the rate of dropout from study participation during the intervention phase after randomization.

We will also analyze the reasons for rejection of participation and dropout, if reported. Acceptability in this context will refer primarily to acceptability to the participants' legal representatives or proxy decision-makers. In the unlikely event that a participant regains the ability to consent during a study, we will seek evidence on acceptability to participants.

Search methods for identification of studies

We will identify relevant studies through searching the electronic databases, trials registries, and other sources listed below.

Electronic searches

We will search ALOIS (www.medicine.ox.ac.uk/alois), Cochrane Dementia and Cognitive Improvement's specialized register.

ALOIS is maintained by the Information Specialists for Cochrane Dementia and Cognitive Improvement, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy older populations. The studies are identified through:

1. searching the Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
2. searching a number of major healthcare databases: MEDLINE, Embase, CINAHL and PsycINFO;
3. searching a number of trials registers: ClinicalTrials.gov; and the World Health Organization's (WHO) International Clinical Trials Register Platform (ICTRP), which covers ISRCTN; the [Chinese Clinical Trial Registry](http://www.clinicaltrials.gov); the [German Clinical Trial Register](http://www.clinicaltrials.gov); the [Iranian Registry of Clinical Trials](http://www.clinicaltrials.gov) and the [Netherlands Trials Register](http://www.clinicaltrials.gov), plus others;
4. searching grey literature sources: ISI Web of Science Core Collection.

To view a list of all sources searched for ALOIS on the ALOIS web site (www.medicine.ox.ac.uk/alois).

Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement and cognitive enhancement studies, can be viewed on the Cochrane Dementia and Cognitive Improvement Group's website: dementia.cochrane.org/searches.

We will run additional searches in MEDLINE, Embase, PsycINFO, Cinhal, LILACs, ClinicalTrials.gov and the WHO Portal/ICTRP to ensure that the searches for this review are as comprehensive and as up-to-date as possible. See [Appendix 1](#) for the search strategy that we will use for the retrieval of reports of studies from MEDLINE (via the Ovid SP platform).

We will perform the searches without language restriction.

Searching other resources

We will handsearch the reference lists of included studies and relevant review articles to identify further studies. We will also contact authors of identified RCTs to request further information.

Data collection and analysis

The two review authors, CK and AT, will independently identify studies for inclusion, extract study data and assess the risk of bias of included studies.

Selection of studies

The review authors will use the software [Covidence](#) for selection of relevant studies, which will automatically screen out duplicates. CK and AT will screen the remaining titles and abstracts again for duplicates and for potential eligibility according to the

PICOS (Participants, Intervention, Control, Outcome, Study design) criteria. CK and AT will then independently assess the full text of all potentially relevant studies for inclusion by means of the same PICOS criteria, resolving any disagreements by discussion. We will report each study identified as potentially eligible but subsequently excluded in the 'Characteristics of excluded studies' table. We will create a flow chart to describe process of study selection according to the PRISMA Statement ([Moher 2009](#)).

Data extraction and management

From each eligible study published in English, CK and AT will independently extract information on the following key characteristics using a data collection form.

1. General information: title, authors, year of publication, source of publication, country, declared conflicts of interest
2. Methods: study design, test of carry-over effect (for cross-over trials), duration of the study (intervention and follow-up), information relevant to 'Risk of bias' assessment (see below)
3. Participants: setting, recruitment method, number of eligible participants identified, number of participants randomised, withdrawal from study with reasons (specifically intervention-related dropout), relevant diagnostic details (e.g. type of brain injury, location of brain injury, severity level of disorders of consciousness, etc.), age, sex, subgroup allocation, time since injury
4. Intervention: overall duration, number of sessions, session frequency, type of intervention, device, electrode/coil positions, electrode/coil shape, focused brain area, stimulation parameter, stimulation intensity, concomitant therapy, patient position, user, user qualifications
5. Outcomes: primary and secondary outcomes, nature and frequency of adverse events and serious adverse events (number of participants with and total number of adverse events and serious adverse events, whether adverse events and serious adverse events were collected systematically, measurement time points, intention-to-treat analysis, amount of and reason for missing data, imputation method (when applicable)).

We will seek study protocols in order to inform our assessments of selective reporting bias.

In case of any disagreements in data extraction, we will attempt to resolve them by discussion, contacting the study authors for further information if necessary. If this still does not lead to an agreement, we will ask a member of Cochrane Dementia and Cognitive Improvement to adjudicate and we will report the disagreement in the 'Characteristics of included studies' tables. We will keep the data collection form under review throughout the process of data extraction, adding any further categories of data that appear to be relevant.

For data extraction of studies published in French, German, Greek, Italian, Russian and Spanish, we will include native speakers who are familiar with reading scientific papers in the topic of severe disorders of consciousness. For other languages we will find suitable translators with the help of the Cochrane Dementia and Cognitive Improvement editorial office.

We will enter the data that we have collected into a 'Characteristics of included studies' table. If characteristics are unreported or

unclear, we will contact authors of those studies directly for further information.

We will use Review Manager 5 (RevMan 5) to enter and organize data and citations ([Review Manager 2014](#)).

Assessment of risk of bias in included studies

CK and AT will independently assess the risk of bias in each included study using the 'Risk of bias' criteria described in the newest version available of the *Cochrane Handbook for Systematic Reviews of Interventions* at the time of evaluation, that is, version 6 ([Higgins 2019](#)), or higher.

We will assess potential risk of bias for the following domains: randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. We will make a judgement for each study whether there is a 'low risk of bias', 'high risk of bias' or if there are 'some concerns' and we will summarize our judgement in the 'Risk of bias' table. The two review authors will resolve any disagreements through discussion. If we are unable to reach an agreement, we will label the criterion under discussion with the highest category of risk of bias that was chosen by one of the review authors. In addition, we will judge cross-over trials to be at high risk of bias as there is a possibility of carry-over effects (see [Unit of analysis issues](#)).

Measures of treatment effect

For outcomes that are based on dichotomous data, we will enter the frequencies into RevMan 5 and calculate risk differences (RDs) with 95% confidence intervals (CIs). For outcomes that are based on continuous data, we will enter means and standard deviations (SDs) and calculate a pooled estimate of the mean difference (MD) with 95% CIs. We will handle outcome measures that are based on ordinal scale data as continuous data unless cut-off values are reported. We will use standardized mean differences (SMDs) when the outcome is measured by different scales in different studies.

Sometimes scales can be different in direction, that is, scales measured the same outcome but in some scales a higher value indicates better performance whereas in other scales a lower value indicates better performance. To ensure a consistent direction of the effect across all outcome measurements, where necessary we will multiply scores on the corresponding scales by -1 .

When data are extracted for the second primary outcome (adverse events and serious adverse events), we will count events that occurred during the study; if possible, we will count events per participant and the total number of events. We will analyze the number of deaths separately from other adverse events. When we extract data for the secondary outcome (non-participation or dropout rate), we will count the number of participants.

For all statistical comparisons we will use RevMan 5 in its current version ([Review Manager 2014](#)).

Unit of analysis issues

Cross-over trials

It is possible that we will identify cross-over trials. Where possible, we will analyze the data of both phases of the cross-over trials using effect estimates from paired analyses. When effect estimates from

paired analyses are not reported, we will contact study authors and ask them for the relevant information. If no paired data are available, we will use unpaired data from both treatment phases, recognising that this will reduce the weight of the study in the meta-analysis. If only first-phase data are available, then we will include these. We will not define an appropriate washout period as there is no published guidance available. However, we will look for information within study reports about any evaluation of carry-over effects. If a carry-over effect is reported, or if no analysis of possible carry-over is mentioned but only first-phase data are available, then we will include first-phase data from these studies but will consider them to be at high risk of bias. If no analysis of possible carry-over is mentioned, but only unpaired data from both trial phases are available, then we will consider the risk of bias to be unclear.

Multiple treatment groups

In the case of studies comparing multiple interventions relevant to a meta-analysis, we will select one pair of interventions for all outcomes and exclude the others. If there are multiple NIBS protocols for the same NIBS method within one study, we will use the data from the protocol with the highest amount of therapy in our primary analyses. We will perform sensitivity analyses to investigate the effect of our decision on which multiple treatment protocols to include in the meta-analysis. When studies investigated more than one NIBS protocol, we will add a comparison of high versus low dose of the intervention. In the case of studies including multiple comparators, we will favour sham stimulation over treatment as usual. We will analyze active comparators in a separate meta-analysis.

Multiple observations

We are expecting to find studies with repeated measurements during the intervention phase (pre- and post-intervention), and during a follow-up period. We will pool data from the end of the treatment phase, regardless of the amount of therapy. We will analyze follow-up data collected after the end of the intervention period separately.

Dealing with missing data

We will report the percentage of participants who received the interventions per protocol (full amount of sessions/duration). We will report the percentage of missing data for each study and each intervention group for all time points and the reasons why data were missing. When study authors imputed missing data, we will report the method used and discuss the consequences on the meta-analysis. Where possible, we will use intention-to-treat data in the meta-analyses.

Assessment of heterogeneity

We will use I^2 statistics ([Higgins 2003](#)), to assess heterogeneity, considering I^2 greater than 50% as substantial heterogeneity ([Deeks 2019](#)). Where we identify substantial heterogeneity, we will consider and discuss possible clinical reasons for this. If substantial heterogeneity is identified, we will downgrade the certainty of the evidence for inconsistency.

Assessment of reporting biases

Where an individual meta-analysis contains at least 10 studies, we will create funnel plots that we will visually assess for skewness of data.

Data synthesis

We will analyse the data using RevMan 5 ([Review Manager 2014](#)).

We will perform a meta-analysis or subgroup-analysis whenever we are able to include data from at least two studies.

We will perform separate analyses for each NIBS method versus sham stimulation or treatment as usual, and versus active comparator(s). Where data allow, we will also compare higher versus lower dose for each NIBS method.

We will use a random-effects model, regardless of the level of heterogeneity.

For adverse and serious adverse events, we will only include in meta-analyses data from those studies that used a systematic method to monitor adverse events and serious adverse events.

Subgroup analysis and investigation of heterogeneity

Data permitting, we will perform subgroup analysis separating the different age groups (i.e. children, adults) and different levels of disorders of consciousness (i.e. UWS, MCS). We will also perform a subgroup analysis based on time since injury (i.e. disorder of consciousness persisting less than or more than 28 days since injury). If heterogeneity is not explained by these aspects, we will search for additional characteristics that could explain it, including different treatment protocols.

Sensitivity analysis

We will perform sensitivity analyses to evaluate the impact of study quality on the robustness of the conclusions drawn. In the sensitivity analysis we will examine the robustness of the

estimates by removing studies at high risk of bias from the meta-analyses. For the sensitivity analysis we will also exclude studies with a cross-over design if a carry-over effect is reported, or if no analysis of possible carry-over is mentioned but only first-phase data are available. If no analysis of possible carry-over is mentioned, but only unpaired data from both phases are available, then we will use sensitivity analyses to explore the effect of including unpaired data from both treatment phases or first-phase only data. We will perform sensitivity analyses excluding any studies in which adjunctive therapies given with the NIBS are not applied equally to both intervention groups. We will also perform sensitivity analyses to investigate the effect of a decision on which of multiple treatment groups to include, for example, the highest-dose protocol or the protocol most similar to others in the meta-analysis.

Summary of findings and assessment of the certainty of the evidence

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for all outcomes. For each comparison and each outcome, we will rate the certainty of the evidence as high, moderate, low or very low. We will use the [GRADEpro GDT](#) software to construct 'Summary of findings' tables for each comparison. For each NIBS approach there will be up to three comparisons (highest reported dose protocol versus sham stimulation or treatment as usual; highest reported dose protocol versus active comparators; higher dose versus lower dose). We will include all review outcomes in each 'Summary of findings' table.

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APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Craniocerebral Trauma/

2 exp Brain Edema/

3 Brain Diseases/

4 exp Unconsciousness/

5 exp Cerebrovascular Trauma/

6 ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) adj3 (injur* or trauma* or damag* or wound* or fracture* or contusion*)).ab,ti.

7 ((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) adj3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)).ti,ab.

8 ("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.

9 ((brain or cerebral or intracranial) adj3 (oedema or edema or swell*)).ab,ti.

10 ((unconscious* or coma* or concuss* or "persistent vegetative state") adj3 (injur* or trauma* or damag* or wound* or fracture*)).ti,ab.

11 ((ischaemic or ischemic) adj2 brain injur*).ti,ab.

12 or/1-11

13 exp Electric Stimulation/

14 exp Transcranial Magnetic Stimulation/

15 exp Magnetic Field Therapy/

16 exp Electromagnetic Fields/

17 "brain stimulation*".ti,ab.

- 18 "transcranial magnetic stimulation".ti,ab.
- 19 TMS.ti,ab.
- 20 rTMS.ti,ab.
- 21 "theta burst stimulation*".ti,ab.
- 22 TBS.ti,ab.
- 23 "transcranial direct current stimulation*".ti,ab.
- 24 tDCS.ti,ab.
- 25 "cranial electrotherapy stimulation*".ti,ab.
- 26 CES.ti,ab.
- 27 ("non-invasive cortical electrostimulation*" or RINCE).ti,ab.
- 28 NIBS.ti,ab.
- 29 Vagal nerve stimulation.ti,ab.
- 30 VNS.ti,ab.
- 31 auricular stimulation.ti,ab.
- 32 taVNS.ti,ab.
- 33 LIFUP.ti,ab.
- 34 "thermal current*".ti,ab.
- 35 ultrasound puls*.ti,ab.
- 36 "Galvanic vestibular stimulation".ti,ab.
- 37 "Caloric stimulation".ti,ab.
- 38 or/13-37
- 39 12 and 38
- 40 randomized controlled trial.pt.
- 41 controlled clinical trial.pt.
- 42 randomized.ab.
- 43 placebo.ab.
- 44 drug therapy.fs.
- 45 randomly.ab.
- 46 trial.ab.
- 47 groups.ab.
- 48 or/40-47
- 49 exp animals/ not humans.sh.
- 50 48 not 49
- 51 39 and 50

Appendix 2. Glossary

CRS-r	Coma Recovery Scale revised; assessment to characterise and monitor functions in patients with severe disorders of consciousness. It consists of 25 items that comprise 6 subscales addressing auditory visual, motor, oromotor, communication, and arousal processes.
DRS	Disability Rating Scale; DRS can track an individual from coma to community. It includes 8 items including eye opening, communication ability, motor response, feeding, toileting, grooming, level of functioning, and employability.
LIFUP	low-intensity focused ultrasound pulse; a technology that exploits low intensity and pulse mechanical waves in order to induce regenerative and anti-inflammatory effects on biological tissues.
MCS	minimally conscious state; MCS is a specific state to describe the severity of the disorder of consciousness. Patients in the MCS recover some small signs of consciousness (e.g. visual pursuit following commands, localization to painful stimulus, contextualised smiles or tears) without being able to communicate.
MCS-minus	minimally conscious state-minus; MCS-minus describes patients with non-reflexive behaviours such as visual pursuit or fixation-oriented movements and localisation to pain but no language-related behaviours.
MCS-plus	minimally conscious state-plus; MCS-plus characterises patients who recover command-following, intelligible verbalisation, and/or intentional communication.
NIBS	non-invasive brain stimulation; NIBS encompasses several different techniques that aim to stimulate the brain in a non-invasive way using electrical magnetic or thermal currents, or ultrasound.
rTMS	repetitive transcranial magnetic stimulation; a brain stimulation technique used to induce focalised neural depolarization and firing. An electromagnetic coil is placed against or close to one's scalp in order to deliver magnetic (painless) pulses that stimulate nerve cells in a target brain region.
taVNS	transcutaneous auricular vagal nerve stimulation; 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, alters the firing rate of the vestibular nerve. This technique is thought to stimulate basal forebrain/brainstem projections through central thalamus and hypothalamus, in distal fronto-parietal and striatal networks.
tDCS	transcranial direct current stimulation; a neuromodulation technique modulating cortical excitability through the application of a weak (usually ≤ 2 mA) direct current through the brain between two electrodes, mainly one anode to one cathode, although new devices offer multichannel montages with multiple anodes and multiple cathodes. Physiologically, the establishment of long-lasting effects depends on membrane potential changes as well as modulations of N-methyl-D-aspartate receptor efficacy, which can induce long-term potentiation and long-term depression-like effects.
UWS	unresponsive wakefulness syndrome; UWS is a specific state to describe the severity of the disorder of consciousness. Patients in the UWS recover the ability to open their eyes, in contrast to patients in coma, but they do not express any signs of consciousness of themselves or of their environment.
VNS	vagal nerve stimulation; a medical treatment that involves delivering electrical impulses to the vagus nerve.
VS	vegetative state; a term that was formerly used for UWS.

CONTRIBUTIONS OF AUTHORS

1. Conception and design of the protocol: CK and AT contributed to all aspects.
2. Drafting the protocol: AT was mainly responsible for drafting the Background, and CK was mainly responsible for drafting the Methods.
3. Final approval of the document to be published: CK and AT gave final approval.

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Carmen Krewer: none declared

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