Review Article

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# Effectiveness of coma arousal therapy on patients with disorders of consciousness – A systematic review and meta-analysis

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**Abstract:**

**BACKGROUND:** Disorders of consciousness (DOC) incorporate stages of awareness and arousal. Through coma arousal therapy sensory deprivation experienced by patients with DOC can be mitigated. Nevertheless, consensus concerning its effectiveness on these patients is still fractional.

**PURPOSE:** This review aims to investigate the effectiveness of coma arousal therapies on patients with DOC.

**METHODS:** A meta-analysis was performed by searching electronic databases using search terms, the studies investigating the effect of coma arousal therapy in patients with DOC using the Coma Recovery Scale-Revised and Glasgow Coma Scale as outcome measures were included. The risk of bias was assessed, using Cochrane and Joanna Briggs Institute critical appraisal tools. Further, analysis was conducted for the included studies.

**RESULTS:** Out of 260 studies, 45 trials were reviewed and assessed for bias, with 31 studies included for analysis. The analysis demonstrates a significant difference in pre- and post - sensory stimulation, vagus nerve stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation. Sensory stimulation showed the greatest mean difference of −4.96; 95% CI = -5.76 to - 4.15. The patients who underwent intervention after 3 months of illness showed significant improvement.

**CONCLUSION:** The result shows that sensory stimulation, transcranial magnetic stimulation, and transcranial direct stimulation can improve behavioral outcomes of patients with DOC, wherein sensory stimulation is found to be more effective.

**Keywords:**

Coma arousal therapy, coma recovery scale-revised, disorders of consciousness, meta-analysis

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## Introduction

"Consciousness is the state of awareness of the self and environment", defined by Plum and Posner.[1] Conscious behavior requires adequate wakefulness and awareness of sensory, cognitive, and affective experiences.[2] The major brain states of disorder of consciousness (DOC) are coma, unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS).[1] Coma is a transient state, characterized by loss of arousal and awareness. UWS is described as the presence of arousal and absence of awareness whereas in MCS, arousal and awareness are present but are minimal.[3] The worldwide prevalence of UWS/vegetative state (VS) is 0.2–6.1/100,000 inhabitants.[4] DOC occurs as a result of traumatic or nontraumatic factors (stroke [6%–54%], postanoxic coma [3%–42%], poisoning [<1%–39%], and



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metabolic causes [1%–29%]). It was seen that 5%–25% and 2.77% of patients remained in a chronic VS in nontraumatic and traumatic brain injury, respectively.[5,6] Multiple potential pathways are involved in DOC such as corticostriatal, thalamocortical, thalamostraital connections, and ascending reticular activating system. Postmortem diffused magnetic resonance imaging tractography showed extensive connectivity between brainstem nuclei and thalamic nuclei of the ascending arousal network in the control individual and complete disconnection in the patient having coma due to post - traumatic brain injury, thereby emphasizing the role of the ascending reticular system in the pathophysiology of DOC. Varied etiological factors elicit structural injury, cerebral edema, and electrical dysfunction in multiple pathways, involving cortical and subcortical areas and their connecting network. Disfacilitation comprehends to the reduction in neuronal firing rate which occurs due to structural loss or decreased neuronal input, which in turn lowers the synaptic transmission. As a result, it prevents the neurons from reaching the firing threshold, precipitating depression of the global cerebral activity.[7] In addition, the withdrawal of environmental stimuli can give rise to sensory deprivation.[8]

Extended hospital stays for DOC patients result in a range of negative outcomes for both the patient and family members, while the patient experiences many neurological, considered to be a sequela of the disease or injury such as spasticity, agitation, and non-neurological complications such as pneumonia, urinary tract infection, pressure ulcers, and venous thromboembolic events are the common adverse effects of DOC patients. Aforementioned, complications may lead to mortality in the long term.[9-12] Sensory stimulation is a rehabilitation approach for patients with DOC that is safe and economically feasible. Various coma arousal therapy techniques have been applied to improve the consciousness levels of patients with DOC. Multimodal stimulation,[13] unimodal stimulation, and noninvasive brain stimulation (NIBS)[14] are known to provide environmental enrichment thus abstaining from sensory deprivation[8] and promoting cortical plasticity,[15] respectively. There have been reviews focusing on coma arousal therapy in patients with DOC, are subjective to only unimodal coma arousal therapy, family-centered sensory stimulation, or have used a limited search strategy, thereby narrowing the study. A previous study conducted by Cheng *et al*.[16] stated that sensory stimulation might not be enough to bring back consciousness, on the contrary, Li *et al*.[17] determined that sensory stimulation appears to be a useful strategy for recovery. Since there have been conflicting opinions previously over the therapy's effects, a review study is required to understand the efficacy of coma arousal therapy. This review aims to provide a holistic perspective, on the efficacy of coma arousal therapy on patients with DOC, and be updated with the current state of research.

## Materials and Methods

This review was conducted in compliance with the guidelines in Preferred Reporting Items for Systematic Review and Meta-analysis[18] [Supplementary Table 1] The primary source of data was obtained by investigating electronic databases, PubMed, PEDro (Physiotherapy Evidence Database), Cochrane Library, Science Direct, Embase (Excerpta Medica Database), using predetermined keywords. Full-text articles published in English only between 2017 and 2022 were selected for the review. This review included articles with the following study types randomized controlled trials (RCTs), crossover trials, quasi-experimental, case studies, and case series. The studies selected comprised patients of all genders who were diagnosed with coma, UWS, and MCS and were intervened with coma arousal therapy. The patients were in the age group of 18 years and above. The outcome was evaluated with Coma Recovery Scale-Revised (CRS-R) as the primary outcome measure.[19] As compared to other scales, CRS-R has good interrater reliability and excellent content validity, as it entails the interpretative guidelines based on Aspen Workgroup consensus-based diagnostic classification for VS, MCS, and emerged the state of MCS.[20] Glasgow Coma Scale (GCS) as a secondary outcome measure.[21] The studies with any Chinese or Japanese therapy as their intervention were excluded, along with the grey literature, abstract-only studies, animal studies, conference papers, and editorial letters were also excluded. The search was performed on electronic databases, using a strategy built with the following words, using "multi-modal stimulation," "sensory stimulation," "transcranial magnetic stimulation," "transcranial direct current stimulation," "tilting," "vagus nerve stimulation," "non-invasive brain stimulation," "coma arousal therapy," "median nerve stimulation," "verticalization," "Coma," "minimally conscious state," "unresponsive wakefulness syndrome," "comatose," to obtain data along with Boolean operators, "AND," "OR" and above 2017 and only English, filters were used. The authors reviewed the title and abstract of the resulting studies. The pertinent studies were chosen, and complete versions of each were acquired. The authors S.K. (Sanjiv Kumar) and N.A. (Nupur Agarwal) reviewed the full-text papers and subjected them to selection criteria. Any disagreement regarding the approval or rejection of the studies was discussed during selection by addressing the matter between two reviewers. Data extraction, then, was performed using Microsoft Excel using study design, demographic data, type, and parameters of intervention. Authors were contacted if the information was not found in the full text.

### Quality assessment

Two authors independently evaluated the methodological quality of each trial using the Cochrane Collaboration's risk of bias instrument[22] and the Joanna Briggs Institute (JBI) tool.[23] In the JBI tool, the review evaluated the quality as yes or no, with a point of 1 for "yes" and 0 for "no." Using the JBI critical appraisal instrument, pilot studies, quasi-experimental studies, case series, and case studies were evaluated on a scale of 9, 9, 10, and 8, respectively. In addition, the Cochrane risk of bias tool was used to evaluate RCTs and crossover trials, classifying them into low risk, high risk, and some concerns in accordance with the criteria.

### Data analysis

The collected data were summarized using descriptive statistics: frequency, percentage; mean, and standard deviation. The pooled mean and standard deviation for quantitative data and the pooled proportion for qualitative data were computed with their 95% confidence intervals (CIs) to provide a summary of the demographic features. The fixed effect model was used to calculate the mean difference (MD) and 95% CI for the meta-analysis. To examine for heterogeneity, the Chi-square and $I^2$ statistics were utilized.[24] To evaluate the publishing bias, funnel plots were utilized. Data analytics were performed using the Review Manager Software (Rev Man 5, Cochrane Collaboration, Oxford, England).[25]

## Results

### Flow of trials

A literature search strategy turned up 260 potentially pertinent trials. Following the elimination of 80 studies, 180 studies were subjected to screening of title and abstract; 66 of these were excluded. The remaining 114 studies were categorized for retrieval, 96 full-text articles were retrieved and subjected to eligibility criteria, out of which 51 studies were excluded, and 45 studies were ultimately chosen for the review. Of these 14 studies included case studies or studies that presented the data in the form of median and interquartile deviation that could not be subjected to further analysis, due to which 31 studies were subjected to statistical analysis. In addition, five coma arousal therapy interventions were identified [Figure 1].[18]

### Characteristics of study

The characteristics of the 45 reviewed studies, which include the following: - Author's name and year of publication, type of study, intervention (i.e. repetitive transcranial magnetic stimulation [rTMS], transcranial direct current stimulation [tDCS], tilting, sensory stimulation, and vagus nerve stimulation [VNS] interventions), parameters (duration, sessions, intensity, and frequency of the intervention), and outcome measures [Table 1].

### Critical appraisal

The quality analysis, which used Cochrane risk of bias assessment, revealed that, out of 20 studies, 8 were at low risk, 7 were at high risk, and the remaining 5 had some concerns. The risk of bias in RCT and crossover trials is summarized using the Cochrane tool [Supplementary Figures 1 and 2]. The methods of randomization in the 6/20 study were not well stated,[26,27,29,37,44,47] and the allocation sequence concealment in the 10/20 trials is unclear.[26,27,29,30,37,44,55,56,59,60] The blinding of the outcome assessor is not explicitly mentioned in 5/20 examinations,[26,29,49,55,60] and the 2/20 research study indicated no blinding of the outcome assessor.[27,58] All crossover trials had adequate washout intervals before the evaluation of the outcome measure, which mitigated the likelihood of further possible bias. According to the JBI critical appraisal tool, the mean scores for the 7 pilot studies [Supplementary Figure 3], 12 pre–post [Supplementary Figure 4], 2 case series [Supplementary Figure 5], and 4 case studies [Supplementary Figure 6] are 6.91 ± 0.62, 6 ± 1, 9 ± 1.41, and 6.75 ± 0.25, respectively, indicating well appraisal. In addition, publication bias was evaluated for the 31 research that were included in the study, of these, 11 studies, including 5 rTMS and 6 sensory stimulation studies, were determined to exhibit publication bias. There is no publication bias in studies on tDCS, tilting, or VNS trials [Supplementary Figures 7-12].

### Demographic characteristics

Demographic data such as gender, etiology, and age reported in mean and standard deviation for intervention and control groups have been evaluated [Table 2 and Supplementary Table 2]. Etiology was grouped broadly into traumatic and non-traumatic brain injury, in which few of the causes were cancer, circulatory system disease, hemorrhage, ischemic stroke, aneurysm, cardiac arrest, and hypoxic-ischemic encephalopathy.

### Outcome measure

A total of 31 studies were included in the meta-analysis with a sample size of 574 for the intervention group and 19 studies with a sample size of 417 were analyzed for the control group. All the studies measure the behavioral response to coma arousal therapy by CRS-R, except six studies on sensory intervention, which examined the consciousness level by GCS. To gauge the efficacy of coma arousal therapies, we first compared CRS-R pre and post intervention. Regardless of the course of the intervention, the total effect size, i.e. improvement from pretest to posttest was significant for all interventions, except tilting. Sensory had the largest effect magnitude with a "$Z = 12.10$," $p < 0.00001$, and effect size of – 4.96;

95% CI = −5.76 to − 4.15, for the studies evaluated by CRS-R [Figure 2], and "$Z = 26.48$," $p < 0.00001$ and effect size of − 3.80; 95% CI = −4.08 to − 3.52 for the studies evaluated by GCS [Figure 3], followed by VNS, rTMS, and tDCS intervention. VNS showed an effect size of − 3.87; 95% CI = −6.46 to − 1.28 [Figure 4] rTMS and tDCS showed an improvement pre- to posttest with an effect size of − 3.19; 95% CI = −3.54 to − 2.84 [Figure 5] and − 1.59; 95% CI = −2.26 to − 0.92 [Figure 6], respectively. The cumulative effect size (−3.50; 95% CI = −10.45–3.45) of tilting was not significant with $P = 0.32$ [Figure 7].

The tDCS, VNS, and sensory intervention studies evaluated by CRS-R trials showed insignificant heterogeneity, while tDCS and VNS showed low and no heterogeneity, with $I^2$ = 18% and 0%,

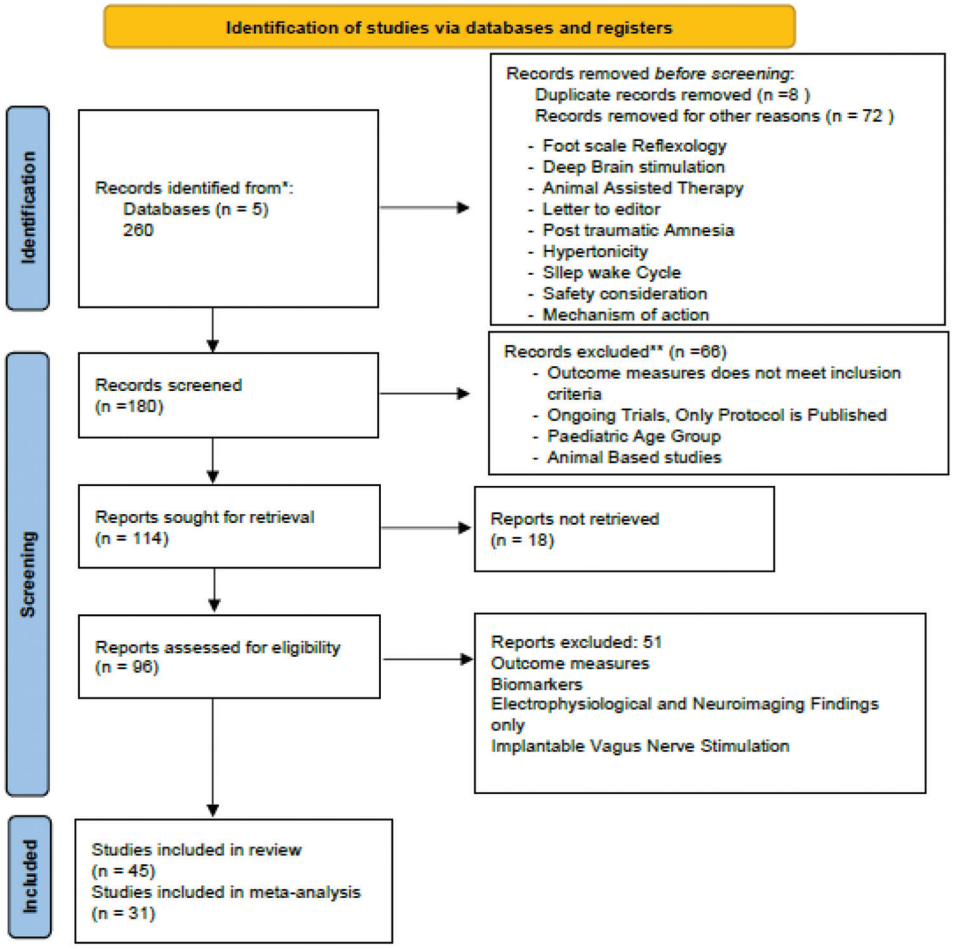


**Figure 1:** Selection process represented in a flow diagram

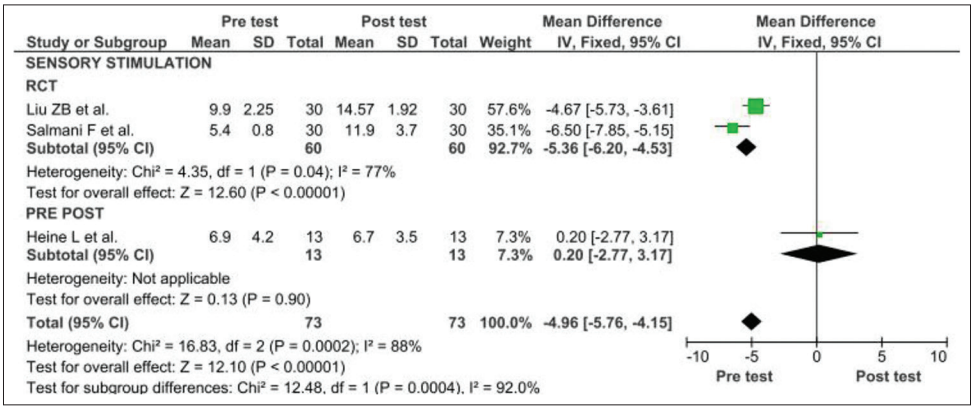


**Figure 2:** Pre–post Coma Recovery Scale-Revised score sensory stimulation represented through forest plot (intervention group). Sensory CRS-R: Sensory stimulation evaluated by Coma Recovery Scale-Revised, SD: Standard deviation, CI: Confidence interval

**Table 1: Study characteristics**

| Study | Study design | Sample size | Interv ention | Groups | Site of Stimulation | Parameters | Duration | Outcome, measure |
|---|---|---|---|---|---|---|---|---|
| He RH *et al*., 2021[26] | RCT | 50 | rTMS | rTMS, Sham | LDLPFC | Frequency -10 Hz Pulses - 1000 Intensity - 100% RMT | Sessions-10 Weeks – 2 | CRS - RSerum Estradiol |
| Zhang X *et al*., 2021[27] | RCT | 48 | rTMS | rTMS, Sham | LDLPFC | Frequency – 5 Hz Pulses - 1200 Intensity-80% RMT ITI – 2 sec | Sessions - 40 Weeks - 8 Duration – 20 mins | CRS-R EEG |
| Chen JM *et al*., 2022[28] | RCT | 50 | rTMS | rTMS, Sham | LDLPFC | Frequency – 10 Hz Pulse – 1000 Intensity - 90%RMT ITI - 60 sec | Sessions – 30 Weeks – 6 | CRS-R GCS BAEP |
| Liu M *et al*., 2022[29] | RCT | 58 | rTMS | rTMS, Sham | Thumb in motor area of cerebral cortex | Frequency - 0.5Hz Intensity - 80%RMT lasting for 10s | Weeks - 4 weeks Treatment- 5 day sRest – 2 days , once/day Session – 20 | CRS-R GCS BAEP |
| Liu X *et al*., 2018[30] | Cross over Trail | 7 | rTMS | rTMS, Sham | Left primary motor cortex | Frequency - 20 Hz Pulses - 1000 Lasting for 2.5s ITI - 28 sec, | Sham – 5 days Active – 5 days WOP – 1 Week | CRS-R fMRI |
| Ge X *et al*., 2021[31] | NRCT | 32 | rTMS | rTMS, Control | RDLPFC | Frequency – 10 Hz Intensity – 100% RMT ITI – 10 sec | Session – 20 Days – 20 Duration -20 mins 8 sec | CRS - RMEP Latency |
| He RH *et al*., 2020[32] | Pre – Post | 25 | rTMS | - | LDLPFC | Frequency – 20 Hz Pulses – 2000 Intensity – 100% RMT ITI – 20 sec | Sessions – 20 Weeks -4 | CRS-R EEG |
| Xia X *et al*., 2017[33] | Pre – Post | 16 | rTMS | - | LDLPFC | Frequency – 10 Hz Pulses – 1000 Intensity -90% RMT ITI -60 sec | Duration – 11 mins 40 sec Sessions – 20 Total days – 20 | CRS-R |
| Xia X *et al*., 2017[34] | Pre – Post | 18 | rTMS | - | LDLPFC | Frequency – 10 Hz Pulses – 1000 Intensity -90% RMT ITI -60 sec | Duration – 11 mins 40 sec Sessions – 20 Total days – 20 | CRS-R EEG |
| Jang SH *et al*., 2020[35] | Case Report | 1 | rTMS | - | RDLPFC | Frequency – 10 Hz Intensity – 80% RMT | Sessions – 7/week 8 min period 2 times/day | CRS-R |
| Martens G *et al*., 2020[36] | Cross over | 46 | tDCS | Active and Sham | Anode - 4( F3-F4, CP5-CP6 )Cathode - 4 ( Fp2-Fpz , O1-Oz) | Intensity - 1m A30-sec ramp up - down WOP – 48 hrs minimum | Sessions – 2 Duration - 20 mins WOP – 2-6 days | CRS-R EEG |
| Zhang Y *et al*., 2017[37] | RCT | 26 | tDCS | Real and Sham Group | Anode - LDLPFC, Cathode - Right Supraorbital region | Intensity - 2mA | Duration - 20 mins Sessions – 20 Total days – 10 | CRS-R |
| Zhang X *et al*., 2021[38] | NRCT | 105 | tDCS | Historical control, Experimental | PFA, LFTPC, RFTPC, LDLPC | Intensity - 2mA | 2 times/day5 days/week4 weeks –to target all 4 target Weeks - 8 Sessions - 80 sessions | CRS-R EEG |
| Zhang R *et al*., 2020[39] | Pre – Post | 35 | HD-tDCS | - | Anode - Precuneus ( Pz) Cathode - 4 (Cz , P3 , P4 ,POz) | Intensity - 2mA | Duration – 20 mins Sessions – 28 Total days – 14 | CRS-R EEG |

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**Table 1: Contd...**

| Study | Study design | Sample size | Interv ention | Groups | Site of Stimulation | Parameters | Duration | Outcome, measure |
|---|---|---|---|---|---|---|---|---|
| Han J *et al.*, 2022[40] | Pre – Post | 22 | HD- tDCS | - | Anode – LDLPFC (F3) Cathode - 4 electrodes (AFz , FCz , F7, C5 ) | Intensity - 2m A30 sec ramp up and down | Duration -20 mins Session - 10 Total days - 5 | CRS-R EEG |
| Han J *et.al.* 2022 [41] | Pre – post | 19 | HD - tDCS | - | Anode – LDLPFC (F3) Cathode - 4 electrodes (AFz , FCz , F7, C5 ) | Intensity - 2mA 30 sec ramp up and down | Duration -20 mins Session -10 Total days - 5 | CRS-R EEG |
| Martens G *et al.*, 2018[42] | Cross – Over Trial | 27 | tDCS/ Sha m | - | Anode - LDLPFC, Cathode - Right Supraorbital region | Intensity - 2m A5-sec ramp up - down | Duration – 20 mins Sessions – 20 Weeks -4 WOP – 8 weeks | CRS-R |
| Barra A *et al.*, 2022[43] | Cross – Over Trial | 12 | tDCS/tPCS/ Sham | - | TDCS :Anode - LPFC (F3) Cathode - Contralateral Orbitofrontal Area tPCS – bi-mastoids | Intensity - 2mA ( For both ) 30-sec ramp up and down tPCS – 6-10 Hz | Duration – 20 mins for each intervention Single session WOP – 5 days | CRS-R EEG |
| Carriere M *et al.*, 2020[44] | Cross – Over Trial | 13 | tDCS/Sham | - | Anode - DLPFC (F3) Cathode – Right supraorbital region | Intensity - 2mA 30 sec ramp up and down | Duration - 20 mins Sessions – 2 (1 sham, active)WOP - >48 hrs | CRS-R EEG |
| Bai Y *et al.*, 2017[45] | Cross – Over Trial | 17 | tDCS | - | Anode - LDLPFC, Cathode - Right Supraorbital region | Intensity - 2mA 30 sec ramp up and down | Duration - 20 mins Session - 2 sessions(1 sham, 1 Active) WOP – 3 days | CRS-R EEG |
| Thibaut A *et al.*, 2017[46] | Cross – Over Trial | 16 | tDCS | - | Anode - LDLPFC, Cathode - Right Supraorbital region | Intensity - 2m A5 sec ramp up and down | Duration - 20 mins 5 days for sham and 5days active WOP – 1 week | CRS-R |
| Estraneo A *et al.*, 2017[47] | Cross – Over Trial | 13 | tDCS | - | Anode - LDLPFC, Cathode - Right Supraorbital region | Intensity - 2mA 30 sec ramp up and down | Duration - 20 mins 5 days for sham and 5days active WOP – 1 week | CRS-R EEG |
| Peng Y *et.al.*, 2022[48] | Pilot Study | 11 | tDCS | - | Anode DLPFC(F3) , Cathode - Supraorbital area | Intensity - 2mA 30 sec ramp up and down | Duration - 20 mins Weeks -2 real tDCS 1 week Sham tDCS - 1 week | CRS-R ,fMRI |
| Martens G *et al.*, 2019[49] | Cross – Over Trial | 10 | tDCS | | Anode - C3 or C4 Cathode - Contralateral Supraorbital Area | Intensity -2mA | Sessions – 2 (1 active, 1 sham )Duration – 20 mins WOP – 24h | CRS-R |
| Straudi S *et al.*, 2019[50] | Pilot Study | 10 | tDCS | - | Anode – 2 Primary motor cortex (M1) bilaterally Cathode - nasion | Intensity - 2mA | Sessions – 10Weeks – 2 Duration – 40 mins | CRS-R EEG |
| Wang X *et al.*, 2020[51] | Pilot Study | 11 | HD - tDCS | - | Anode - Pre cuneus (Pz) Cathode – 4 (Cz , P3 , P4 , POz ) | Intensity - 2mA | Session – 28 Total Days - 14Duration – 20 mins | CRS-R |
| Guo Y *et al.*, 2019[52] | Pilot Study | 11 | HD - tDCS | - | Anode - Pre cuneus (Pz) Cathode – 4 (Cz , P3 , P4 , POz ) | Intensity - 2mA | Session – 28 Total Days - 14Duration – 20 mins | CRS-R EEG |
| Zhang Y *et al.*, 2019[53] | Pilot Study | 13 | tDCS | - | Anode - LDLPFC (F3) Cathode - Right Supraorbital Region | Intensity -2mA 30 sec ramp up and down | Duration – 20 mins Sessions – 20 Total Days – 10 | CRS-R |

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**Table 1: Contd...**

| Study | Study design | Sample size | Interv ention | Groups | Site of Stimulation | Parameters | Duration | Outcome, measure |
|---|---|---|---|---|---|---|---|---|
| Lin Y *et al.*, 2019[54] | Case Study | 2 | Simultane ous tDCS and rTMS | - | Simultane ous tDCS, HF-rTMS | tDCS Intensity - 1.5 mA Anodal -P4 – Left\|P3 – RightCathodal - T3 rTMSP4 – Left\|P3 – Right Pulses –5000<br>Frequency -5Hz Intensity – 70%RMT ITI – 55 sec Duration -20 mins each hemisphere 10 s Ramp up 10 s ramp down | Duration – 40 mins Sessions – 14 Weeks – 2 | CRS-R GCS EEG fMRI |
| Liu ZB *et al.*, 2022[55] | RCT | 90 | Music Therapy | 2Experiment al Group, 1 controlgroup | | Favorite song+Alpha beat music+HBOT | Duration - 20-30 minSession – 60 Total days – 30 | CRS-R GCS BAEP EEG |
| Adineh M *et al.*, 2022[56] | RCT | 66 | Multi - Sensory Stimulation by family | Intervention, Control group | MULTISENSORY | SSP - By family members, Visual, Aroma, Tactile, Motor Stimulation in steps | Duration - 1 Hour/Day Sessions – 7 Total days – 7 | GCS |
| Ahmed FR *et al.*, 2022[57] | Quasi – Experimenta l Design | 60 | Auditory and Tactile stimulation by Family | Control Group, Study Group | | Family-centered organized auditory and tactile stimuli | Week – 2 Session – 14 Duration - 15 mins | GCS |
| Varghese R *et al.*, 2021[58] | RCT | 20 | Auditory Stimulation | Intervention group, Control Group | AUDITORY | Recorded Voice messages of their close relatives | Duration - 20 mins 3 sessions/day 5 days | GCS |
| Cevik K *et.al.*, 2018[59] | RCT | 60 | Auditory Stimulation | Intervention Group, Control Group | - | Male Nurse Voice Message Repeated - 3-4 times Message Lasted for 5 - 10 mins | Sessions - 20 , Total - 10 | GCS |
| Salmani F *et.al.*,2017[60] | RCT | 90 | Multisensory Stimulation | Placebo Control, Intervention group | Multisensory | Control Treatment + BY FAMILY - 4 steps - Auditory Stimulation, Sensory Stimulation, Kinetic Stimulation,Affective Conversation | Sessions - 14 Duration - 30 - 45 mins Total Days - 7 days | CRS-R GCS |
| Cheng L *et.al.*,2018[16] | Pre – post | 29 | Sensory Stimulation | - | ABAB Design , 4 weeks each phase | A - no SSP , comprehensive rehab ( physical therapy, respiratory therapy and speech therapy, nursing care) B - SSP = Visual , auditory , tactile, olfactory , gustatory each sensation administered bilaterally 3 times | Each phase lasted for 4 weeks A - 5 days per wek Duration - 3 hours B- 3 days / week Duration - 20 mins | CRS-R fMRI |
| | | | | | | Each sensation was administered bilaterally 3 times | B – 3 days/week, Duration – 20 mins | |

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**Table 1: Contd...**

| Study | Study design | Sample size | Interv ention | Groups | Site of Stimulation | Parameters | Duration | Outcome, measure |
|---|---|---|---|---|---|---|---|---|
| Heine L *et al.*, 2017[61] | Pre – Post | 13 | Auditory and olfactory stimulation | - | Olfactory, Auditory | Preferred\|Neutral\|16 stimulation items combinations were presented to each patient, the order of stimuli and items was randomized both with and between patients | Sessions - 4 separated by 3-7 days, 5 min presentation of each stimulus | CRS-R |
| Wu M *et al.*, 2021[62] | Pilot Study | 14 | Music Stimuli, Subjects own name,White Noise | - | Auditory | Music Stimuli, Subjects own name, White NoiseStimuli sequence random | Duration - 5 mins each stimulusWashout - 2 mins | CRS-R EEG |
| De Luca R *et al.*, 2021[63] | Case Report | 1 | Audio-visual stimulation | - | | Standard physiotherapy with audio–visual stimulation – 15 days rest – then --- Integrated system – Neurowave Emotional stimulation (NES) | Conventional:2 months Duration – 60 minsNES Sessions - 6 Weeks - 24 Duration - 60 mins | CRS-R |
| Hakon J *et al.*, 2020[64] | Case Series | 5 | Trans auricular Vagus Nervestimulation | - | Left cymba conchae | Frequency - 25 Hz 30 sec on/30 sec off Intensity - 0.5 mA first 3 days, 1mA - 8 week period | Weeks - 8 weeks Daily Duration - 4 hours/day | CRS-R |
| Wang L *et al.*, 2022[65] | Pre – Post | 17 | Vagus Nerve Magnetic Stimulation | - | Left mastoid | Frequency - 10 Hz Intensity - 100%RMT | Frequency - 5 days/week Session - 20 Duration - 20 mins | CRS-R GCS BAEP |
| Osinska A *et.al*,2022[66] | Case Study | 1 | Non Invasive taVNS - | - | Intra-auricular epidermic electrode Contact Point - cymba concha | Frequency - 25 Hz Voltage - 25 V ON - 30 s , OFF - 30 s Intensity - 0.2 mA with increasing 0.1mA every week up to 1.5 mA | 4 hours /day - 6 months | CRS-R, EEG |
| Riberholt CR *et al.*, 2021[67] | RCT | 38 | Tilting with Stepping | Intervention and Control Group | Tilt Table with stepping | 70° head-up tiltStepping Frequency - 50-60steps/min | Session - 28 Weeks - 4 Duration - 20 mins | CRS-R |
| William K *et al.*, 2019[68] | Case Series | 4 | Robotic-assisted Gait Training | - | Lokomat Walking, BWS provided by overhead harness | BWS at 100%,Initial speed - 1.0 km/hrGoal was to progress to 70% BWS | 1.5 hr session (routine) + 1hr (trial session), 2sessions/week | CRS-R |
| De Luca R *et al.*, 2022[69] | Pilot Study | 16 | Robotic Verticalization Plus Music Therapy | Experiment al group and Control Group | Robotic Verticalization Plus Music Therapy | Gradually increasing the table inclination from 45 to 90 Stepping Frequency – patient Tailored | Frequency - 3 times/8 week Session - 24 days Duration - 45 mins | CRS-R |

WOP – Wash Out Period, RMT – Resting Motor Threshold, ITI – Inter Train Interval, BWS – Body Weight Support GCS – Glasgow Coma Scale, CRS -R- Coma Recover Scale -Revised, tDCS – Transcranial direct current stimulation, TMS – Repetitive Transcranial Magnetic stimulation , EEG – Electroencephalography, DLPFC – Dorsolateral Prefrontal Cortex, LDLPFC – Left DLPFC, RDLPFC – Right DLPFC, RCT -Randomized Controlled Trial , NRCT – Non -Randomized Controlled Trial, HD-tDCS – High Definition tDCS, fMRI -Functional Magnetic resonance Imaging, MEP – Motor Evoked Potential, BAEP – Brainstem Auditory Evoked Potential

**Table 2: Demographic characteristics of the intervention group**

| Demographic – intervention group | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Intervention** | **Age** | | | | **Gender** | | | | | **Etiology** | | | | |
| | ***n*** | **Mean** | **SD** | **95%CI** | ***n*** | **Male %** | **95%CI** | **Female %** | **95%CI** | ***n*** | **NTBI %** | **95%CI** | **TBI %** | **95%CI** |
| tDCS | 283 | 48.12 | 14.84 | 46.4-49.9 | 356 | 64.32 | 59.1-69.3 | 35.67 | 30.7-40.89 | 356 | 60.39 | 55.1-65.5 | 39.61 | 34.4-44.9 |
| rTMS | 148 | 50.32 | 11.38 | 48.5-52.1 | 149 | 71.81 | 63.9-78.9 | 28.18 | 21.1-36.1 | 161 | 54 | 46.0-61.9 | 45.9 | 38.0-53.9 |
| Sensory stimulation | 149 | 50.80 | 13.37 | 48.6-52.9 | 220 | 68.63 | 62.0-74.7 | 31.36 | 25.2-37.9 | 220 | 48.18 | 41.4-55.0 | 51.81 | 45.0-58.5 |
| TILTING | 12 | 40.67 | 10.89 | 34.5-46.8 | 31 | 70.96 | 51.9-85.7 | 29.03 | 14.2-48.04 | 31 | 0 | 0.0-11.2 | 100 | 88.7-100 |
| VNS | 22 | 57.50 | 17.1 | 50.4-64.7 | 23 | 69.56 | 47.0-86.7 | 30.43 | 13.2-52.9 | 23 | 52.17 | 30.5-73.18 | 47.82 | 26.8-69.4 |

tDCS- Transcranial direct current stimulation, rTMS – repetitive Transcranial Magnetic Stimulation, VNS – Vagus nerve stimulation, NTBI – Non-Traumatic Brain Injury, TBI – Traumatic Brain Injury, *n* - sample size, CI - Confidence Interval

**Table 3: Summary of the finding for intervention group**

| Intervention group | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Intervention** | ***n*** | **Chi²** | **df** | **I²** | ***P***** | ***Z*** | ***P* (Test for overall effect)#** | **Mean difference (95%CI)** | **Rank** |
| tDCS | 168 | 14.64 | 12 | 18% | 0.26 | 4.66 | <0.00001 | -1.59 [-2.26, -0.92]* | 3 |
| rTMS | 144 | 73.44 | 7 | 90% | <0.00001 | 17.68 | <0.00001 | -3.19[-3.54, -2.84]* | 2 |
| SENSORY-CRS-R | 73 | 16.83 | 2 | 88% | 0.0002 | 12.10 | <0.00001 | -4.96 [-5.76, -4.15]* | 1 |
| SENSORY – GCS | 163 | 136.47 | 5 | 96% | <0.00001 | 26.48 | <0.00001 | -3.80 [-4.08, -3.52]* | 1 |
| TILTING | 4 | - | - | - | - | 0.99 | 0.32 | -3.50[-10.45,3.45] | |
| VNS | 22 | 0.46 | 1 | 0% | 0.50 | 2.93 | 0.003 | -3.87 [-6.46, -1.28] | |

tDCS – Transcranial direct current stimulation, rTMS – Repetitive transcranial magnetic stimulation, Sensory CRS-R – Sensory stimulation evaluated by CRS-R, Sensory -GCS - Sensory stimulation evaluated by Glasgow Coma Scale, VNS – Vagus nerve stimulation, ***P* value for heterogeneity, #*P* value for overall effect size, *P*<0.05 level of significance, *n* - sample size

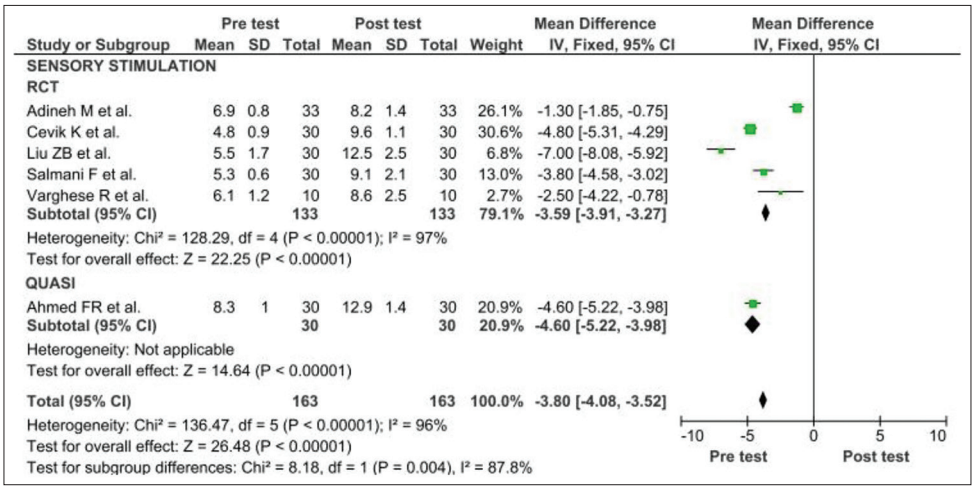


**Figure 3:** Pre–post Glasgow Coma Scale score sensory stimulation represented through forest plot (intervention group). Sensory–GCS: Sensory stimulation evaluated by Glasgow Coma Scale, SD: Standard deviation, CI: Confidence interval

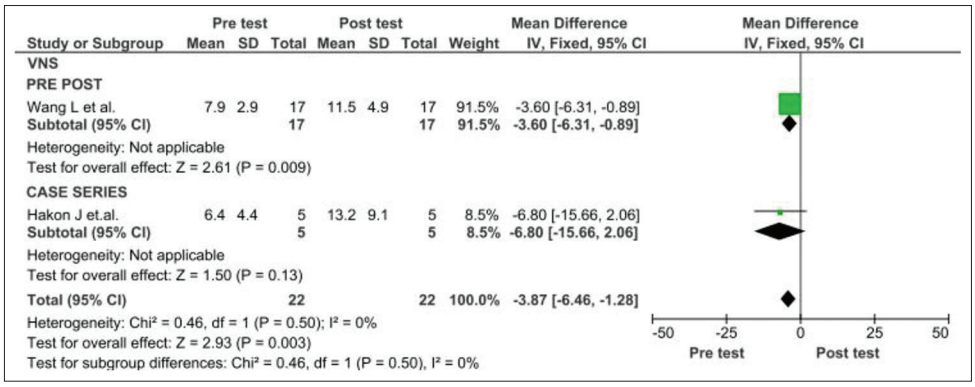


**Figure 4:** Pre-post Coma Recovery Scale-Revised score vagus nerve stimulation represented through forest plot (intervention group). VNS: Vagus nerve stimulation, SD: Standard deviation, CI: Confidence interval

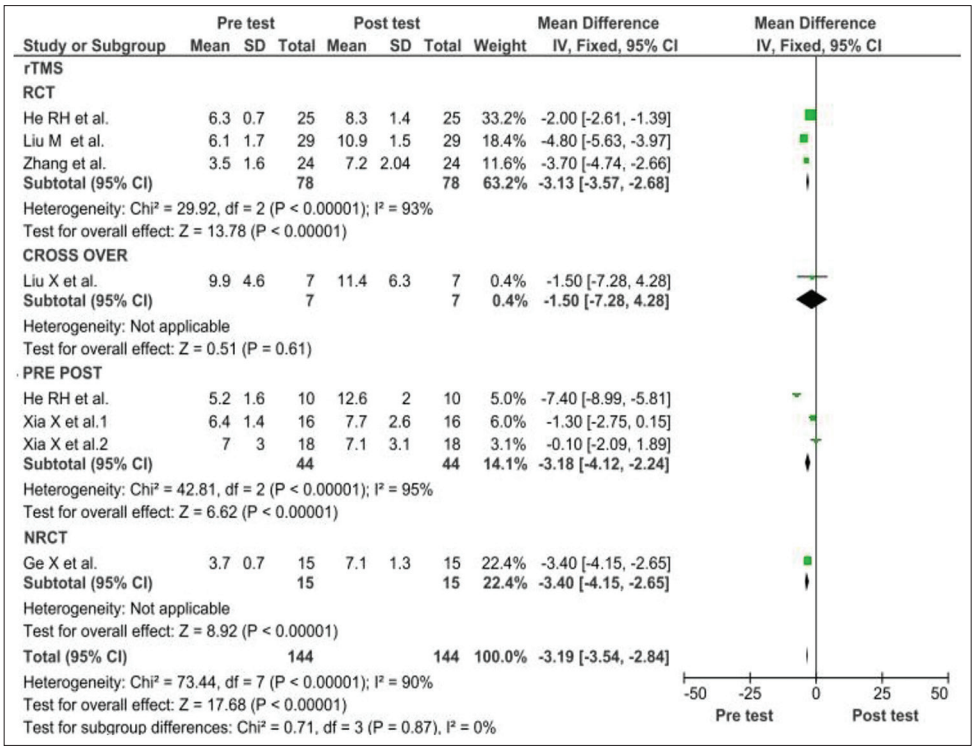


**Figure 5:** Pre–post Coma Recovery Scale-Revised score repetitive transcranial magnetic stimulation represented through forest plot (intervention group). rTMS: Repetitive transcranial magnetic stimulation, SD: Standard deviation, CI: Confidence interval

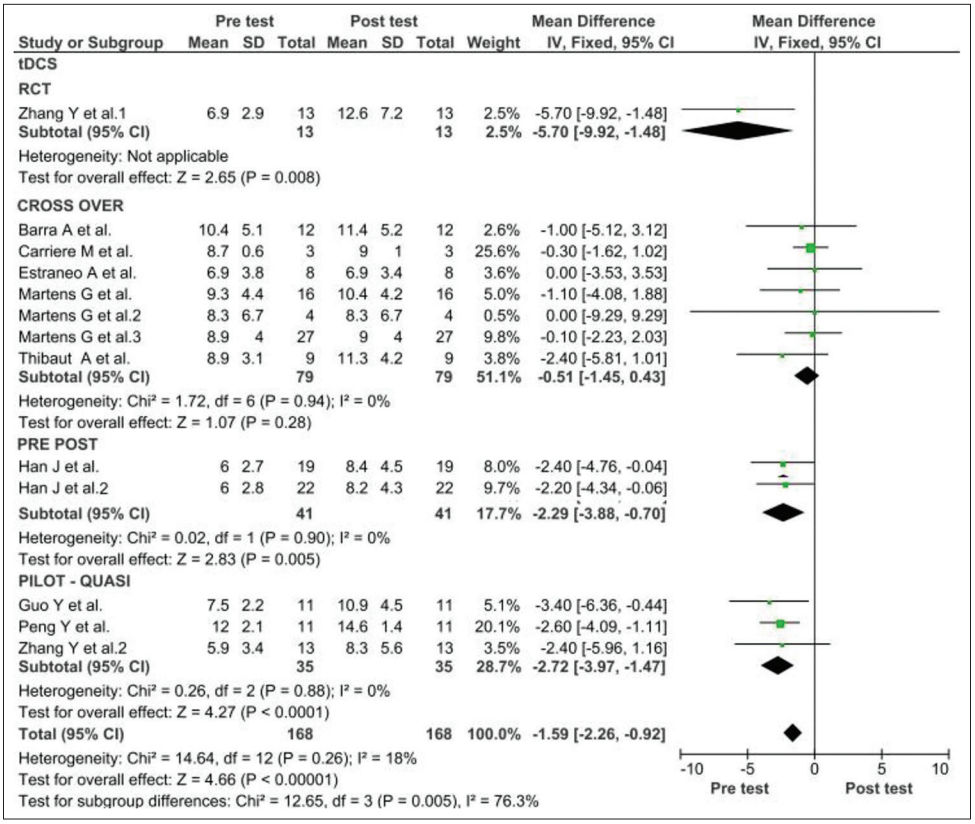


**Figure 6:** Pre–post Coma Recovery Scale-Revised score tDCS represented through forest plot (intervention group). tDCS - Transcranial direct current stimulation, SD: Standard deviation, CI: Confidence interval

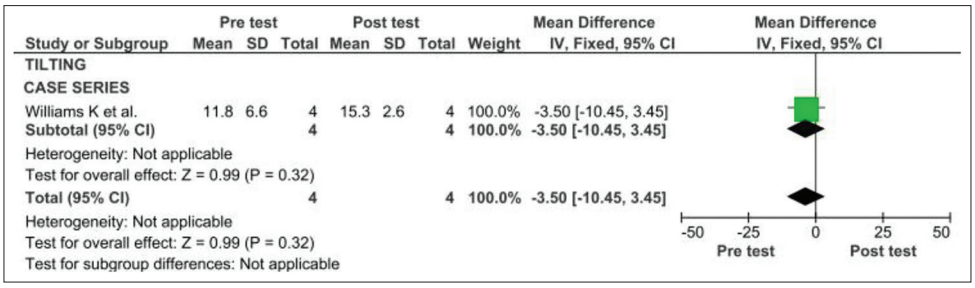


**Figure 7:** Pre–post Coma Recovery Scale-Revised score tilting represented through forest plot (intervention group). SD: Standard deviation, CI: Confidence interval

respectively [Figures 4 and 6]. Other interventions showed significantly high heterogeneity [Table 3].

For the control group of experiments, a forest plot was built using the available data to confirm the efficiency of the intervention. Data for rTMS, tDCS, and sensory stimulation were available. Except for tDCS and rTMS ($p$ = 0.67 and 0.0002, respectively), with an effect size of − 0.26; 95% CI = −1.43–0.92 [Supplementary Figure 13] and − 0.51; 95% CI = −0.78 to − 0.24 [Supplementary Figure 14], respectively, sensory intervention showed a significant result pre - post intervention. Where, sensory stimulation studies evaluated by CRS-R and GCS had the effect size of − 1.58; 95% CI = −2.20 to − 0.96 [Supplementary Figure 15], −1.30; 95% CI = −1.55 to − 1.06, respectively [Supplementary Figure 16], [Supplementary Table 3].

To determine the impact of the duration of injury on the efficiency of the intervention, the time as a variable was also examined. It was divided into periods above and below 3 months. Studies including participants affected longer than 3 months outnumbered those lasting <3. Except for the tilting intervention, which lacked research with sufficient data for analysis, the overall effect sizes of tDCS, rTMS, sensory stimulation, and VNS over 3 months showed significant results in improvement pre - post intervention with an effect size of − 1.56 [Supplementary Figure 17], −3.14 [Supplementary Figure 18], −4.70 [Supplementary Figure 19], −3.60 [Supplementary Figure 20], [Supplementary Table 4], respectively. Only 4 studies, each with a different intervention (rTMS, tDCS, tilting, and VNS) were analyzed for < 3 months, in which, a significant effect size, was shown by the rTMS study ($Z$ = 6.39, $p$ < 0.00001) with an effect size of − 2.00; 95% CI = −2.61 to − 1.39 [Supplementary Figure 21], [Supplementary Table 5].

## Discussion

An array of coma arousal therapy interventions is applied to enhance the level of consciousness in DOC patients. Previous systematic reviews and meta-analyses focused on a single intervention. The current study compiles the data and assesses numerous trials of various coma arousal therapies. Evaluating these interventions allows objective comparison of the overall effects of distinct coma arousal interventions. The results of the current meta-analysis have found sensory stimulation to be most effective, in improving the CRS-R and GCS scores. In addition, rTMS and tDCS were also found to be competent, which is consistent with prior systematic reviews and meta-analyses.[13,14,70] Analysis was conducted on 31 articles, accounting for a total of 574 patients with DOC, and showed a substantial improvement in CRS-R scores favoring the rTMS, tDCS, and sensory stimulation. However, examining the control group of sensory stimulation intervention studies show a significant improvement as assessed by GCS before and after the intervention. Out of the six, controlled trials assessed by GCS , showed a larger MD. In this study, in addition to conventional therapy, tDCS, median nerve stimulation, and hyperbaric oxygen therapy were administered for the control group, and auditory stimulation with biaural beat therapy and hyperbaric oxygen therapy for the experiment group,which could have led to a larger MD.[55]

Sensory intervention approaches resort to variations of multisensory stimulation and unimodal stimulation. In the present study, 10 studies were included in which 6 intervened multimodal stimulus[16,56,57,60,61,63] and 4 employed unimodal stimuli.[55,58,59,62] Multisensory stimulation included visual, tactile, gustatory, olfactory, and auditory stimuli. Auditory stimulation was the most commonly intervened as a unimodal or a part of the multimodal intervention, in the form of voice recording, preferred music, subjects' own name, or alpha beat frequency music stimulation.

According to Salmani *et al*., sensory stimulation also activates the limbic cortex. In addition, sensory stimulation also causes sensory enrichment, autonomic nervous system activation, and modulation of multiple cortical pathways through its connection to the thalamus.[60,71] The limbic cortex and hippocampus are stimulated in response to an affective stimulus. Six out of ten studies analyzed, in this review, administered stimuli that evoke an emotional response or recalled memory.[55-58,60,61] Under normal circumstances, neurogenesis occurs solely in two areas of the adult brain, one of which being the dentate gyrus of the

hippocampus,[72] if neurogenesis, is present in DOC patients, the likelihood of optimized behavior responses is higher with sensory stimulation, which may be of greater advantage over other treatments like NIBS, wherein NIBS works on mesocircuit model, by modulating cortical excitability and inducing neuroplastic changes, strengthening the functional neural connectivity, restoring corticothalamic networks, and activating the reticular activating system through the thalamocortical pathway for raising alertness and awareness,[7,15,28,40] it may not stimulate the limbic cortex as profoundly as sensory stimulation as it lacks affective component. However, a study conducted by Heine *et al*., suggested that various forms of stimulation were necessary in addition to an organized sensory program to raise arousal levels.[16]

In the analysis, VNS and tilting have also been evaluated. VNS has been shown to modulate cortical excitability by stimulating the release of non-adrenaline.[73] The effect size is insignificant in the VNS finding, as there was a lack of evidence, definitive inference cannot be drawn from it. A study conducted by Wang L *et al*., on VNS, suggests that vagus nerve magnetic modulation (VNMM) has a greater advantage over rTMS, one of them being the modulation of the superior reticular activating system by VNMM.[65] On another note, the results of tilting were not significant as there were only 3 studies, despite the fact that the effectiveness of tilting or tilting combined with stepping can increase the conscious level by causing multisensory stimulation-proprioceptors, pressure, touch, and change in position also stimulates the vestibular system, in addition, it has also shown to lower the intracranial pressure assisting in improving the cerebral blood flow.[74,75] Therefore, further research is warranted to confirm the effectiveness of VNS and tilting.

In addition to these interventions, median nerve stimulation is an effective intervention to enhance awareness suggested by a meta-analysis conducted by Wang P *et al*.[76] although the intervention was excluded from the study due to a lack of literature.

The effectiveness of the intervention was also evaluated concerning time since the onset of illness; it was broadly divided into above and below 3 months. The studies for below 3 months were comparatively fewer; it could be to avoid the bias of spontaneous recovery during the early phase of illness or to allow the patient to be hemodynamically stable to prevent complications.

In terms of safety, there were only 22 studies out of 45 trials that evaluated side effects, and 4 of those reported adverse effects such as local redness under the tDCS electrode[38,42,50] and another study noted pain brought by the placement of the harness in robotic-aided gait training,[68] while the remaining studies reported no side effects. The investigation done through the review has proven that coma-stimulating therapy is safe and effective as a whole.

## Strengths and limitations

Our meta-analysis brings new information regarding the effectiveness of coma arousal therapies on patients with DOC and suggests the most effective therapy. However, this study has some limitations, the first of which is the possibility of heterogeneity as a result of the inclusion of several study types in the analysis. Second, due to the variability in neurophysiological parameters used for evaluation in the studies, investigations of effectiveness solely relied on neurobehavioral evaluations, and CRS-R scores and excluded electrophysiological testing such as electroencephalography and brainstem auditory evoked potential, which provide an objective assessment of the patient's level of consciousness. Furthermore, only a small number of studies had information regarding the pre- and poststates of consciousness, as a result, stratified comparisons of coma, UWS, and MCS were not possible. Due to data being presented as a median and interquartile range, the effect size of a few studies could not be estimated.

## Ethics

When diagnosing and treating DOC patients require extended hospital stays, clinicians encounter several ethical difficulties. It is critical to determine who could benefit from rehabilitation as failing to do so could lead to unrealistic expectations. Errors can be minimized by employing valid, reliable, feasible, and economical procedures for evaluation and reassessment at the right intervals.[77] The GCS is a commonly used assessment tool that is devoid of behavioral response evaluation, lacks the ability to distinguish between various DOC states, and lacks standardization in subscale delivery.[78] A more precise diagnosis may result in better functional outcomes; on the other hand, an over or underestimation of brain function may lead to highly consequential management decisions. These limitations can be overcome using electrophysiologic testing and recurrent functional neuroimaging can be utilized to identify brain activity even when the patient shows no command following behavior (i.e. cognitive motor dissociation).[7,79]

## Future scope

There is a need for future research to conduct more RCTs that can improve the methodological quality of the trials. Conduct a study on a large sample size with long-term follow-up and assess the impact of the intervention on patients with the same etiology of DOC. Future trials should assess the level of consciousness with objective measures. Data should be presented in the form of mean and details for the number of coma, UWS, and MCS patients pre - post intervention should be provided.

Despite, the limitations of available evidence, this review suggests that interventions such as sensory stimulation,

rTMS, and tDCS are effective in improving the level of consciousness. However, the effectiveness of tilting and VNS could not be determined in this review.

## Conclusion

Our meta - analysis conducted on effectiveness of patients with DOC, coma arousal therapies such as sensory stimulation, rTMS, and tDCS have shown to ameliorate the consciousness level. Sensory stimulation is determined as the most effective intervention to improve the behavioral response of the patients. Subsequently, NIBS therapies such as rTMS, and tDCS can enhance the patient's conscious level. Further, VNS and Tilt have limited evidence to establish its efficacy. To strengthen the findings, a more rigorous research methodology should be adopted in future investigations. This entails conducting more controlled trials with larger samples and follow-up studies to know the long-term effect of the interventions. In addition, the pre–post behavioral state of DOC patients needs to be evaluated by objective measures and in terms of coma, UWS, and MCS.

### Author contributions

S.K and N.A independently conducted study that includes the selection process, and data extraction. N.A wrote the manuscript and S.K. contributed to the conception of the idea, data interpretation, and manuscript revision. Sanal T.S. conducted the analysis of the extracted data and its interpretation.

### Ethical statement

The study was approved by the ethical committee of the KLE Institute of Physiotherapy, a Constituent unit of KLE Academy of Higher Education and Research (SL. No 804, dated on 22/12/22).

### Declaration of Helsinki

Not applicable.

### Data availability statement

All data generated and/or analyzed during this study are included in this published article [and its supplementary information files].

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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| AUTHOR, YEAR | Risk of bias arising from the randomization process | Risk of bias due to deviations from the intended interventions | Missing outcome data | Risk of bias in measurement of the outcome | Risk of bias in selection of the reported result | OVERALL RISK OF BIAS |
|---|---|---|---|---|---|---|
| Liu M et.al.,2022 | ! | + | + | ! | ! | - |
| He RH et.al. ,2021 | ! | + | + | ! | ! | - |
| Zhang et.al. ,2021 | ! | + | + | ! | + | - |
| Chen JM et.al. ,2022 | + | + | + | + | + | + |
| Adineh M et.al. ,2022 | ! | + | + | + | + | ! |
| Varghese R et.al.,2021 | + | + | + | ! | + | ! |
| Cevik K et.al.,2018 | ! | + | + | ! | ! | - |
| Liu ZB et.al. ,2022 | ! | + | + | ! | ! | - |
| Salmani F et.al.,2017 | ! | + | + | + | + | ! |
| Riberholt CR et.al.,2021 | + | + | + | + | + | + |
| Zhang Y et.al.,2017 | ! | + | + | + | ! | - |
| De Luca R et.al., 2022 | + | + | + | + | ! | ! |

**Supplementary Figure 1:** Critical appraisal (randomized controlled trial). +: Low risk, !: Some concerns, -: High risk, RCT: Randomized controlled trial

| DOMAINS | Marten G et.al., 2020 | Martens G et.al.,2018 | Barra A et.al., 2022 | Carriere M et.al.,2020 | Thibaut A et.al., 2017 | Estraneo A et.al., 2017 | Martens G et.al., 2019 | Liu X et.al., 2018 |
|---|---|---|---|---|---|---|---|---|
| Risk of bias arising from the randomization process | + | + | + | + | + | ! | + | + |
| Risk of bias arising from period and carryover effects | + | + | + | + | + | + | + | + |
| Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | + | + | + | + | + | + | + | + |
| Risk of bias due to missing outcome data | + | + | + | + | + | + | + | + |
| Risk of bias in measurement of the outcome | + | + | + | + | + | + | + | + |
| Risk of bias in selection of the reported result | + | + | + | + | + | ! | + | ! |
| **OVER ALL RISK OF BIAS** | + | + | + | + | + | - | + | ! |

**Supplementary Figure 2:** Critical appraisal (cross-over trials). +: Low risk, !: Some concerns, -: High risk

| | Straudi S et al, 2019 | Wang X et al, 2020 | Guo Y et al, 2019 | Zhang Y et al, 2019 | Bai Y et.al., 2017 | Wu M et.al., 2021 | Peng Y et.al., 2022 |
|---|---|---|---|---|---|---|---|
| "Cause" and "effect" is clear | + | + | + | + | + | + | + |
| Participant comparisons are homogenous | + | + | + | + | + | + | + |
| Received similar treatment/care other than the exposure or intervention of interest | + | + | + | + | + | + | + |
| Control group included | - | - | - | - | - | - | - |
| Pre- and postintervention/exposure with multiple measurements | + | + | + | - | - | - | + |
| Follow-up reported | + | - | - | - | - | - | - |
| Outcomes measured uniformly for comparisons | + | + | + | + | + | + | + |
| Measurements were reliable | + | - | - | + | - | - | - |
| Appropriate statistical analysis was used | + | + | + | + | + | + | + |
| TOTAL | 8 | 6 | 6 | 6 | 5 | 5 | 6 |

**Supplementary Figure 3:** Critical appraisal – pilot study

| | He RH et al, 2020 | Xia X et al, May ,2017 | Xia X et al, August ,2017 | Ge X et al, 2021 | Han J et al, August, 2022 | Han J et al, May, 2022 | Zhang R et al, 2020 | Zhang X et al, 2021 | Cheng L et al, 2018 | Ahmed FR et al, 2022 | Heine L et al, 2017 | Wang L et al, 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| "Cause" and "effect" is clear | + | + | + | + | + | + | + | + | + | + | + | + |
| Participant comparisons are homogenous | + | + | + | + | + | + | + | + | + | + | + | + |
| Received similar treatment/care other than the exposure or intervention of interest | + | + | + | + | + | + | + | + | + | + | + | + |
| Control group included | - | - | - | + | - | - | - | + | - | + | - | - |
| Pre- and postintervention/exposure with multiple measurements | - | + | + | - | + | + | + | + | + | + | - | + |
| Follow-up reported | - | + | - | - | + | - | - | + | - | - | - | - |
| Outcomes measured uniformly for comparisons | + | + | + | + | + | + | + | + | + | + | + | + |
| Measurements were reliable | + | - | - | - | + | + | + | - | + | - | + | - |
| Appropriate statistical analysis was used | + | + | + | + | + | + | + | + | + | + | + | + |
| TOTAL | 6 | 7 | 6 | 6 | 8 | 7 | 7 | 8 | 7 | 7 | 6 | 6 |

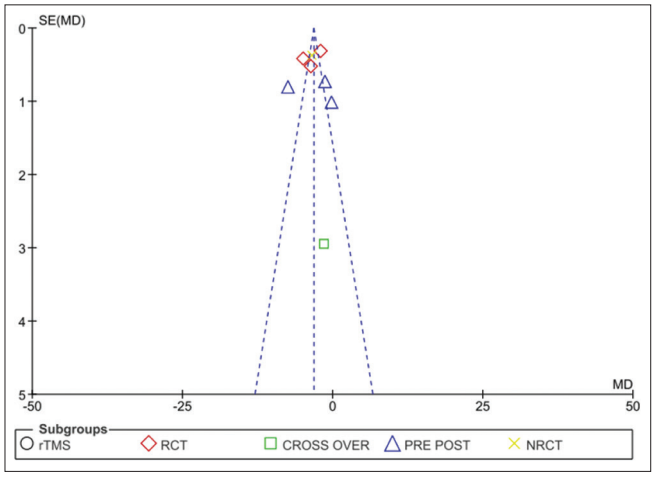
**Supplementary Figure 4:** Critical appraisal – pre–post study

| | William K et.al., 2020 | Hakon J et.al., 2020 |
|---|---|---|
| Clear criteria for inclusion | + | + |
| Condition measured in a standard, reliable way | + | + |
| Were valid methods used for identification of the condition | - | + |
| Consecutive inclusion of participants | + | + |
| Complete inclusion of participants | + | + |
| Clear reporting of the demographics | + | + |
| Clear reporting of clinical information | + | + |
| Outcomes or follow up results of cases clearly reported? | + | + |
| Clear reporting of the presenting site(s)/clinic(s) demographic information? | + | + |
| Statistical analysis appropriate? | - | + |
| TOTAL | 8 | 10 |

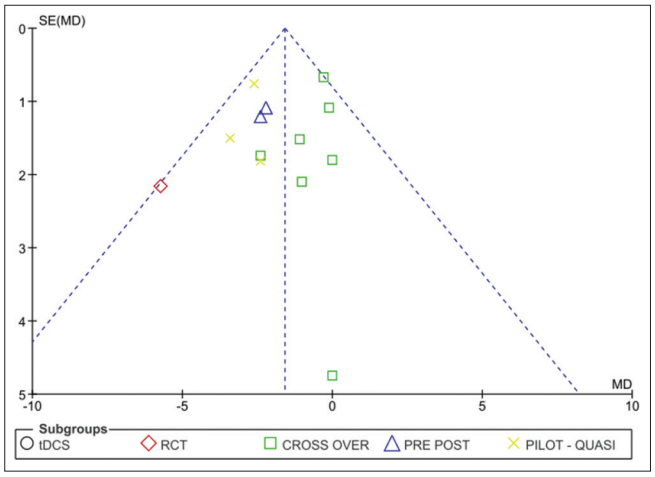
**Supplementary Figure 5:** Critical appraisal (case series)

| | Jang HS et. al., 2020 | Luca DR et al, 2021 | Lin Y et al, 2019 | Osinska A et.al., 2022 |
|---|---|---|---|---|
| Demographic characteristics clearly described | + | + | + | + |
| History clearly described and presented as a timeline | + | - | + | + |
| Current clinical condition of the patient on presentation clearly described | + | + | + | + |
| Diagnostic tests or assessment methods and the results clearly described | + | + | + | + |
| Intervention(s) or treatment procedure(s) clearly described? | + | + | + | + |
| Post-intervention clinical condition clearly described? | + | + | + | + |
| Adverse events or unanticipated events identified and described? | - | - | - | - |
| Takeaway lessons | + | + | + | + |
| TOTAL | 7 | 6 | 7 | 7 |

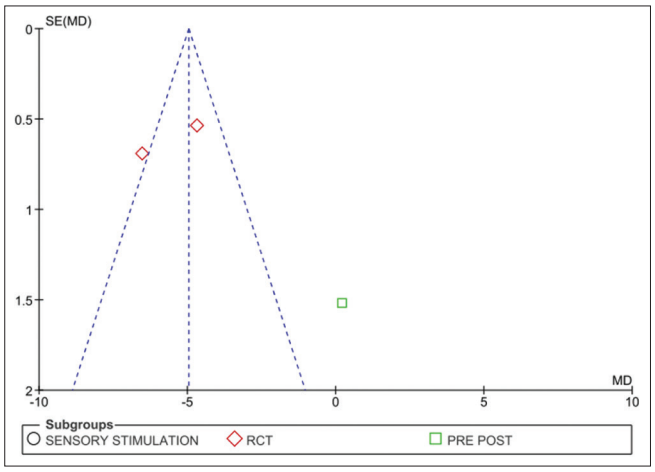
**Supplementary Figure 6:** Critical appraisal (case study)



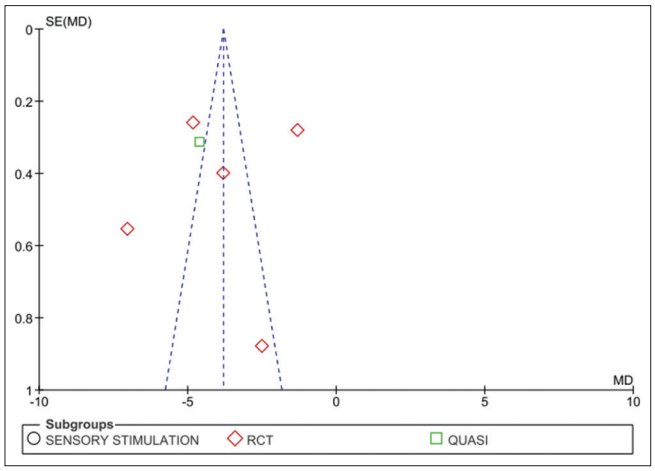

**Supplementary Figure 8:** Repetitive transcranial magnetic stimulation. rTMS: Repetitive transcranial magnetic stimulation



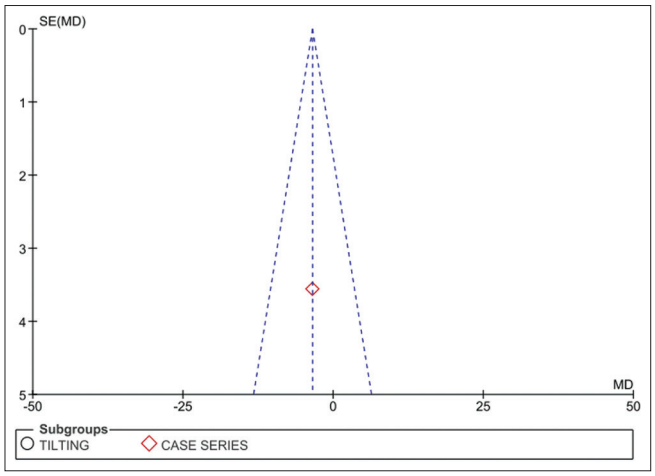

**Supplementary Figure 7:** Transcranial direct current stimulation. tDCS: Transcranial direct current stimulation



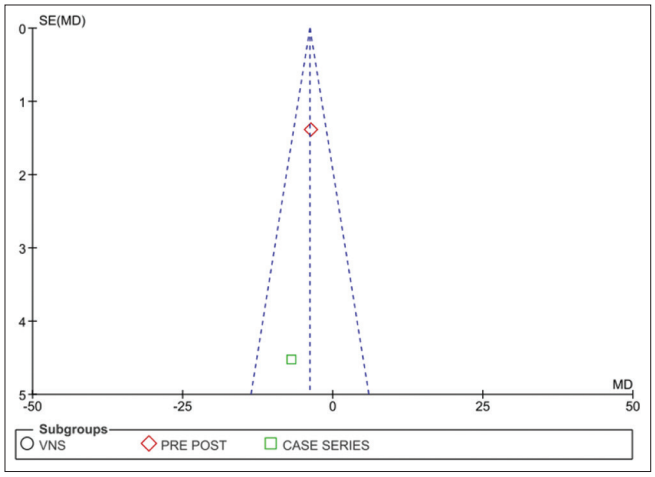

**Supplementary Figure 9:** Sensory stimulation-Coma Recover Scale - Revised. CRS-R: Coma Recover Scale – Revised



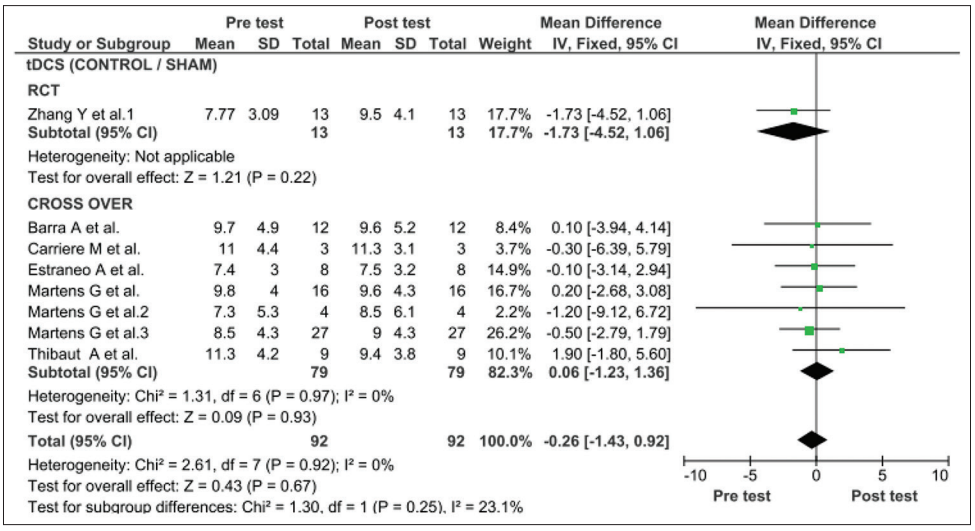

**Supplementary Figure 10:** Sensory stimulation-Glasgow Coma Scale. GCS: Glasgow Coma Scale



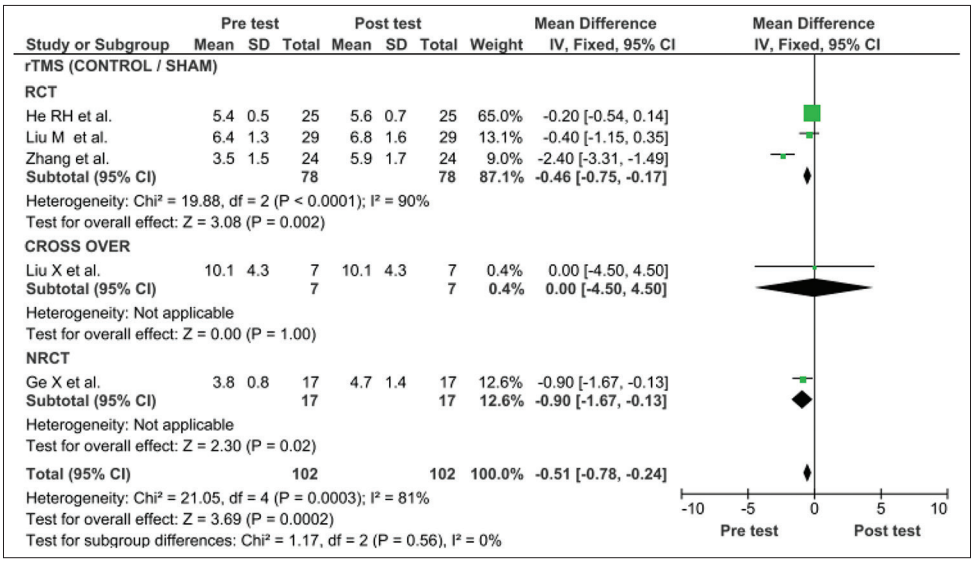

**Supplementary Figure 11:** Tilting



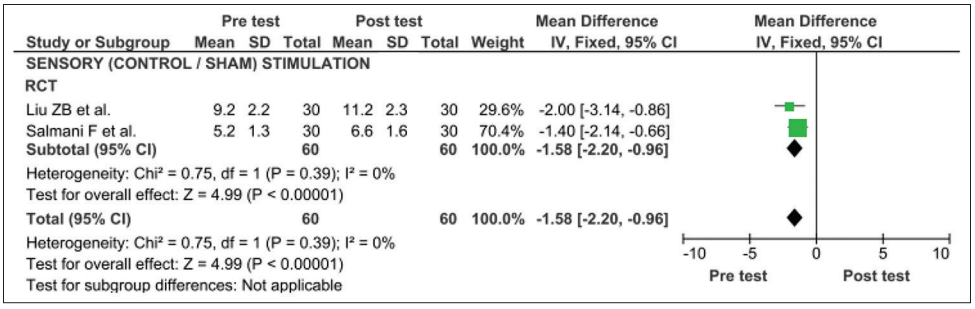

**Supplementary Figure 12:** Vagus nerve stimulation. VNS: Vagus nerve stimulation



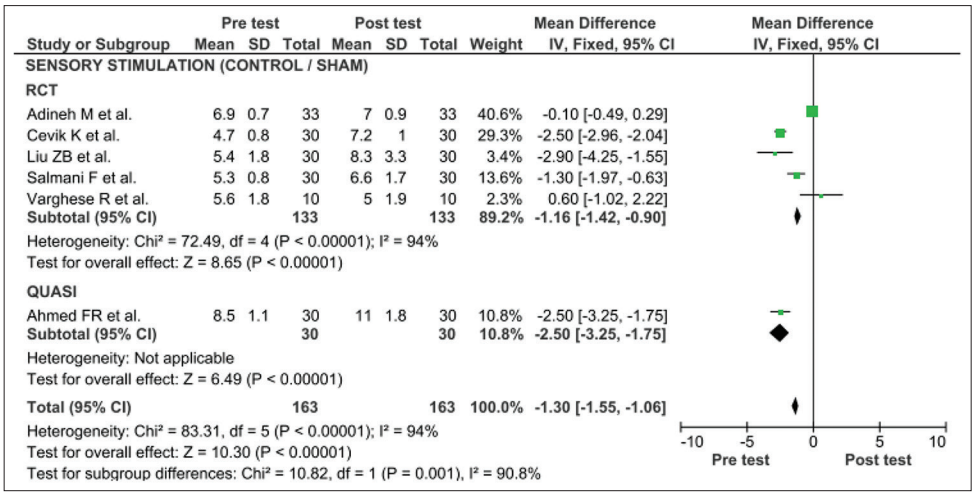

**Supplementary Figure 13:** Pre–post Coma Recovery Scale-Revised score Transcranial direct current stimulation representation of (control group). tDCS: Transcranial direct current stimulation, SD: Standard. deviation, CI: Confidence interval



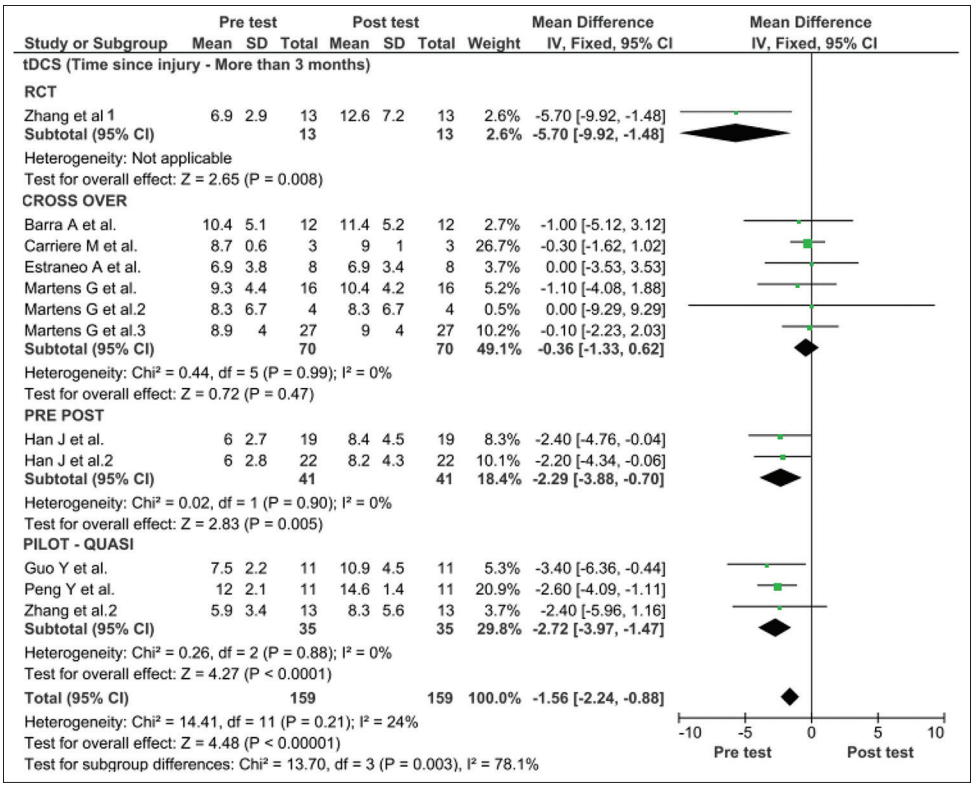

**Supplementary Figure 14:** Pre–post Coma Recovery Scale-Revised (CRS-R) score Repetitive transcranial magnetic stimulation (control group). rTMS: Repetitive transcranial magnetic stimulation, SD: Standard deviation, CI: Confidence interval



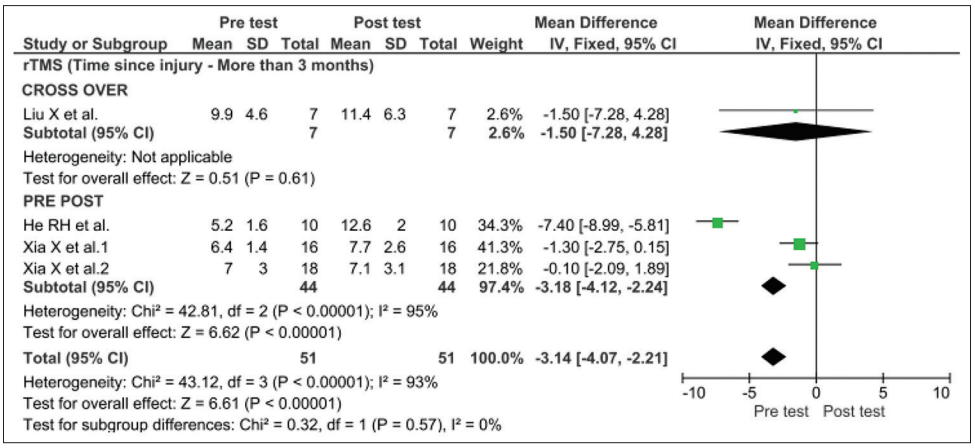

**Supplementary Figure 15:** Pre–post Coma Recovery Scale-Revised score sensory stimulation represented through forest plot (control group). CRS-R: Sensory stimulation evaluated by Coma Recovery Scale-Revised, SD: Standard deviation, CI: Confidence interval



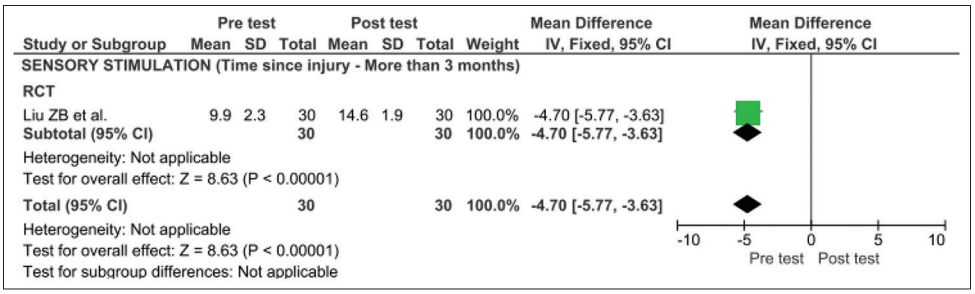

**Supplementary Figure 16:** Pre–Post Glasgow Coma Scale score sensory stimulation represented through forest plot (control group). Sensory – GCS: Sensory stimulation evaluated by Glasgow Coma Scale, SD: Standard deviation, CI: Confidence interval



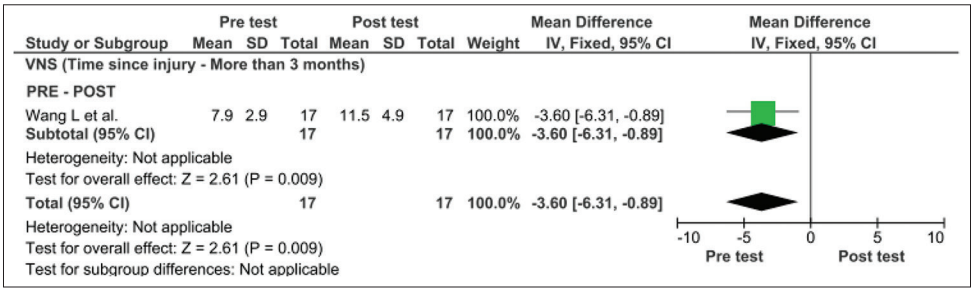

**Supplementary Figure 17:** Pre–post Coma Recovery Scale-Revised Score transcranial direct current stimulation (time since injury – more than 3 months) represented through forest plot. SD: Standard deviation, CI: Confidence interval



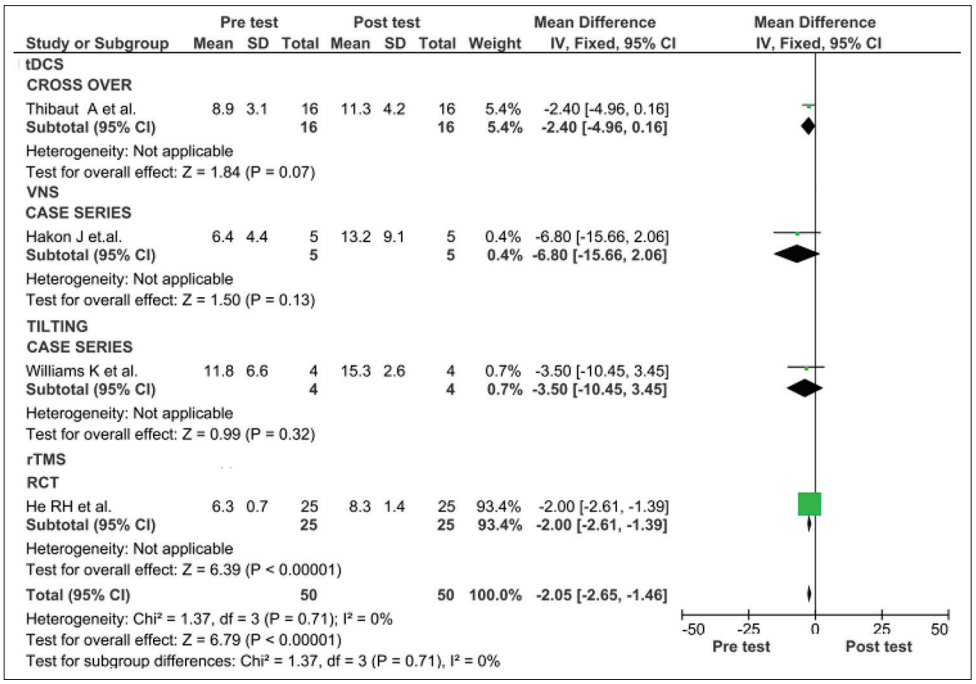

**Supplementary Figure 18:** Pre–post Coma Recovery Scale-Revised score rTMS (time since injury – more than 3 months) represented through forest plot. SD: Standard deviation, CI: Confidence interval




**Supplementary Figure 19:** Pre–post Coma Recovery Scale-Revised score sensory stimulation (time since injury – more than 3 months) represented through forest plot. SD: Standard deviation, CI: Confidence interval




**Supplementary Figure 20:** Pre–post Coma Recovery Scale-Revised Score vagus nerve stimulation (time since injury – more than 3 months) represented through forest plot. SD: Standard deviation, CI: Confidence interval




**Supplementary Figure 21:** Pre–post Coma Recovery Scale-Revised - time since injury (<3 months) represented through forest plot. SD: Standard deviation, CI: Confidence interval

**Supplementary Table 1: Preferred reporting items for systematic review and meta-analysis 2020 main checklist**

| Topic | *n* | Item | Location where item is reported |
|---|---|---|---|
| Title | | | |
| Title | 1 | Identify the report as a systematic review | In the title |
| Abstract | | | |
| Abstract | 2 | See the PRISMA 2020 for abstracts checklist | |
| Introduction | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge | Introduction, last paragraph |
| Objectives | 4 | Provide an explicit statement of the objective (s) or question (s) the review addresses | Introduction, last paragraph |
| Methods | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses | Methodology |
| Information sources | 6 | Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted | Methodology |
| Search strategy | 7 | Present the full search strategies for all databases, registers, and websites, including any filters and limits used | Methodology |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process | Methodology |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process | Methodology |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect | Methodology |
| | 10b | List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information | Methodology |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process | Quality assessment |
| Effect measures | 12 | Specify for each outcome the effect measure (s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results | Data Analysis section |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item 5]) | Methodology |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling missing summary statistics, or data conversions | PRISMA flow chart |
| | 13c | Describe any methods used to tabulate or visually display the results of individual studies and syntheses | Data Analysis section |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used | Data Analysis section |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression) | Not performed |
| | 13f | Describe any sensitivity analyses conducted to assess the robustness of the synthesized results | Not performed |
| Reporting bias assessment | 14 | Describe any methods used to assess the risk of bias due to missing results in a synthesis (arising from reporting biases) | Not included studies with incomplete data |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome | Not performed |

*Contd...*

**Supplementary Table 1: Contd...**

| Topic | *n* | Item | Location where item is reported |
|---|---|---|---|
| Results | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram | Flow of trials |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded | Not done |
| Study characteristics | 17 | Cite each included study and present its characteristics | Characteristics table |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study | Critical Appraisal section |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) Summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots | Outcome measure results, summary tables for intervention and control group |
| Results of syntheses | 20a | For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies | Critical Appraisal section |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect | Not done |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results | Result section and limitations |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results | Not done |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed | Not included studies with incomplete data |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed | Not done |
| Discussion | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence | First paragraph |
| | 23b | Discuss any limitations of the evidence included in the review | Limitations section |
| | 23c | Discuss any limitations of the review processes used | Limitations section |
| | 23d | Discuss the implications of the results for practice, policy, and future research | Future scope section |
| Other information | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered | Review was not registered |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared | Protocol was not prepared |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol | Not registered |
| Support | 25 | Describe sources of financial or nonfinancial support for the review, and the role of the funders or sponsors in the review | Nil |
| Competing interests | 26 | Declare any competing interests of review authors | Conflict of interest |
| Availability of data, code, and other materials | 27 | Report which of the following are publicly available and where they can be found: Template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review | No |

| Topic | *n* | Item | Reported? |
|---|---|---|---|
| Title | | | |
| Title | 1 | Identify the report as a systematic review | Yes |
| Background | | | |
| Objectives | 2 | Provide an explicit statement of the main objective (s) or question (s) the review addresses | Yes |
| Methods | | | |
| Eligibility criteria | 3 | Specify the inclusion and exclusion criteria for the review | Yes |
| Information sources | 4 | Specify the information sources (e.g., databases, registers) used to identify studies and the date when each was last searched | Yes |

*Contd...*

**Supplementary Table 1: Contd...**

| Topic | *n* | Item | Reported? |
|---|---|---|---|
| Risk of bias | 5 | Specify the methods used to assess the risk of bias in the included studies | Yes |
| Synthesis of results | 6 | Specify the methods used to present and synthesize results | No |
| Results | | | |
| Included studies | 7 | Give the total number of included studies and participants and summarize relevant characteristics of studies | Yes |
| Synthesis of results | 8 | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e., which group is favored) | Yes |
| Discussion | | | |
| Limitations of evidence | 9 | Provide a brief summary of the limitations of the evidence included in the review (e.g., study risk of bias, inconsistency, and imprecision) | No |
| Interpretation | 10 | Provide a general interpretation of the results and important implications | Yes |
| Other | | | |
| Funding | 11 | Specify the primary source of funding for the review | No |
| Registration | 12 | Provide the registered name and registration number | No |

PRISMA: Preferred reporting items for systematic review and meta-analysis

**Supplementary Table 2: Demographic characteristics of the control group**

| DEMOGRAPHIC – CONTROL GROUP | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Interevntion** | **Age** | | | | **Gender** | | | | | **ETIOLOGY** | | | | |
| | ***n*** | **Mean** | **SD** | **95%CI** | ***n*** | **Male %** | **95% CI** | **Female %** | **95%CI** | ***n*** | **NTBI %** | **95% CI** | **TBI %** | **95%CI** |
| tDCS | 50 | 45.6 | 13.94 | 41.7-49.5 | 63 | 74.6 | 62.0-84.7 | 25.39 | 15.2-37.9 | 64 | 59.37 | 46.3-71.4 | 40.62 | 28.5-53.6 |
| rTMS | 74 | 53.16 | 10.94 | 50.7-55.6 | 91 | 74.72 | 64.5-83.2 | 25.27 | 16.7-35.4 | 96 | 42.7 | 32.6-53.2 | 57.29 | 46.7-67.3 |
| Sensory stimulation | 93 | 55.04 | 11.6 | 52.7-57.4 | 163 | 64.41 | 56.5-71.7 | 35.58 | 28.2-43.4 | 130 | 45.38 | 36.6-54.3 | 54.61 | 45.6-63.3 |
| TILTING | 8 | 66 | 8.08 | 60.4-71.6 | 8 | 75 | 53.7-88.8 | 25 | 11.1-46.2 | 8 | 0 | 00.-12.7 | 100 | 87.2-10.0 |
| VNS | No groups | | | | | | | | | | | | | |

tDCS - Transcranial direct current stimulation, rTMS – repetitive Transcranial Magnetic Stimulation, VNS – Vagus nerve stimulation, NTBI – Non-Traumatic Brain Injury, TBI – Traumatic Brain Injury, *n* - sample size, CI -Confidence Interval

**Supplementary Table 3: Summary of the finding for control group**

| Control group | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Intervention** | ***n*** | **Chi²** | **df** | **I²** | ***P***** | ***Z*** | ***P* (Test for overall effect)#** | **Mean difference (95%CI)** | **Rank** |
| tDCS | 92 | 2.61 | 7 | 0% | 0.92 | 0.43 | 0.67 | -0.26[-1.43,0.92] | - |
| rTMS | 102 | 21.05 | 4 | 81% | 0.0003 | 3.69 | 0.0002 | -0.51[-0.78, -0.24] | - |
| SENSORY-CRS-R | 60 | 0.75 | 1 | 0% | 0.39 | 4.99 | <0.00001 | -1.58[-2.20, -0.96]* | 1 |
| SENSORY – GCS | 163 | 83.31 | 5 | 94% | <0.00001 | 10.30 | <0.00001 | -1.30[-1.55, -1.06]* | 2 |
| TILTING | NA | | | | | | | | |
| VNS | NA | | | | | | | | |

***P* value for heterogeneity, #*P* value for overall effect size, *P*<0.05 level of significance, tDCS – Transcranial direct current stimulation, rTMS – Repetitive transcranial magnetic stimulation, Sensory CRS-R – Sensory stimulation evaluated by CRS-R, Sensory -GCS - Sensory stimulation evaluated by Glasgow Coma Scale, VNS – Vagus nerve stimulation , *n* - sample size, NA – Not Applicable as there was no control group

**Supplementary Table 4: Summary of the finding for time since injury above 3 months**

| **Intervention** | ***n*** | **Chi²** | **df** | **I²** | ***P***** | ***Z*** | ***P* (Test for overall effect)#** | **Mean difference (95%CI)** | **Rank** |
|---|---|---|---|---|---|---|---|---|---|
| tDCS | 159 | 14.41 | 11 | 24% | 0.21 | 4.48 | <0.00001 | -1.56[-2.24, -0.88]* | 3 |
| rTMS | 51 | 43.12 | 3 | 93% | <0.00001 | 6.61 | <0.00001 | -3.14[-4.07, -2.21]* | 2 |
| SENSORY -CRS-R | 30 | | | NA | | 8.63 | <0.00001 | -4.70[-5.77, -3.63]* | 1 |
| SENSORY – GCS | NA | | | | | | | | |
| TILTING | NA | | | | | | | | |
| VNS | 17 | | | NA | | 2.61 | 0.009 | -3.60 [ -6.31, -0.89] | |

***P* value for heterogeneity, #*P* value for overall effect size, *P*<0.05 level of significance, tDCS- Transcranial direct current stimulation, rTMS – Repetitive transcranial magnetic stimulation, Sensory CRS-R – Sensory stimulation evaluated by CRS-R, Sensory -GCS - Sensory stimulation evaluated by Glasgow Coma Scale, VNS – Vagus nerve stimulation , *n* - sample size, NA – Not Applicable as there were no studies with sufficient information

## Supplementary Table 5: Summary of the finding for times since injury below 3 months

| Time since injury – below 3 months | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Intervention** | ***n*** | **Chi²** | **df** | ***I²*** | ***P***** | ***Z*** | ***P* (Test for overall effect)#** | **Mean difference (95% CI)** | **Rank** |
| tDCS | 16 | | NA | | | 1.84 | 0.07 | -2.40 [ -4.96, 0.16] | |
| rTMS | 25 | | NA | | | 6.39 | <0.00001 | -2.00 [-2.61, -1.39]* | 1 |
| SENSORY- CRS-R | | | | | | | NA | | |
| SENSORY – GCS | | | | | | | NA | | |
| TILTING | 4 | | NA | | | 0.99 | 0.32 | -3.50[-10.45, 3.45] | |
| VNS | 5 | | NA | | | 1.50 | 0.13 | -6.80[-15.66,2.06] | |

***P* value for heterogeneity, #*P* value for overall effect size, *P*<0.05 level of significance, tDCS - Transcranial direct current stimulation, rTMS – Repetitive transcranial magnetic stimulation, Sensory CRS-R – Sensory stimulation evaluated by CRS-R, Sensory -GCS - Sensory stimulation evaluated by Glasgow Coma Scale, VNS – Vagus nerve stimulation, *n* - sample size, NA – Not Applicable as there were no studies with sufficient information