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An individual patient data meta-analysis on vagal nerve stimulation for recovery from disorders of consciousness

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Running Head: VNS for disorders of consciousness

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Abstract

Objectives: Disorders of consciousness (DoC), including vegetative state (VS), unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS), are characterized by impaired consciousness and have limited therapeutic options. We aimed to perform a systematic review and meta-analysis of individual participant data (IPD) on the efficacy of vagal nerve stimulation (VNS) for DoC.

Methods: A systematic literature search identified studies on the use of VNS in patients with DoC. IPD were extracted from included studies and pooled for analysis. The primary outcome was improvement in consciousness, assessed clinically using the Coma Recovery Scale-Revised (CRS-R).

Results: A total of 10 studies including 112 patients were identified. VNS was associated with significant improvements in consciousness, with a mean increase of 2.78 (95% CI 1.62 to 3.94) in CRS-R. 40.2% of patients improved in CRS-R score above the minimal clinically significant difference (MCID) of 3 or more. Patients in MCS improved more than those in coma or VS/UWS.

Conclusions: This IPD meta-analysis provides early evidence for the efficacy of VNS in improving consciousness in patients with DoC. Our results imply the need for high quality randomized controlled trials for both invasive and non-invasive VNS to better inform its role in DoC neuro-recovery.

Key Words:

Coma, disorders of consciousness, minimally conscious state, unresponsive wakefulness syndrome, vegetative state, vagal nerve stimulation

Abbreviations:

BAEP	brainstem auditory evoked potentials
CBF	cerebral blood flow
CRS-R	Coma Recovery Scale-Revised
DBS	deep brain stimulation
DMN	default mode network
DoC	disorders of consciousness
EEG	electroencephalogram
eMCS	emergence from a minimally conscious state (eMCS)
fMRI	functional magnetic resonance imaging
HIE	hypoxic-ischemic encephalopathy
IPD	individual participant data
iVNS	invasive vagus nerve stimulation
MCID	minimal clinically significant difference
MCS	minimally conscious state
rTMS	repetitive transcranial magnetic stimulation
SCS	spinal cord stimulation
SEP	somatosensory evoked potentials
taVNS	transcutaneous auricular VNS
TBI	traumatic brain injury
tDCS	transcranial direct current stimulation
UWS	unresponsive wakefulness syndrome
VNMM	vagus nerve magnetic modulation
VNS	vagal nerve stimulation

Introduction

Disorders of consciousness (DoC) are a group of conditions characterized by a prolonged state of decreased awareness or arousal.[1] It encompasses a spectrum of states ranging from coma, to vegetative state or unresponsive wakefulness syndrome (VS/UWS), to minimally conscious state (MCS) and, finally, to emergence from a minimally conscious state (eMCS).[2] Comatose patients are unable to open their eyes, in contrast to VS/UWS, in which there is spontaneous or stimulus-induced eye opening and return of sleep-wake cycles, albeit without awareness.[3] In MCS, patients exhibit arousal with minimal or fluctuating awareness. MCS can be further divided into MCS+ or MCS- based on the presence (+) or absence (-) of language abilities.[4,5] Finally, eMCS is achieved when patients demonstrate sustained and consistent abilities for functional communication or functional object use.[6] The Coma Recovery Scale-Revised (CRS-R) is a bedside clinical assessment tool most commonly used for assessing levels of consciousness.[6]

DoCs occur as a sequelae of cerebral insult secondary to a broad range of etiologies, commonly due to severe traumatic brain injury (TBI), stroke or hypoxic-ischemic encephalopathy (HIE). Studies have demonstrated impaired metabolism and functional disconnections within corticocortical and thalamo–cortical areas of the default mode network (DMN) in patients with DoC, suggesting the involvement of the DMN in DoC [Fig. 1].[7–10] Conventional treatment is largely supportive, and focuses on symptom management, prevention of complications such as spasticity, dystonia, paroxysmal sympathetic hyperfunction, nosocomial infections, venous thromboembolism, and contractures; these latter conditions are usually managed during the rehabilitation phase. Pharmacologic agents directed towards neurorecovery include Amantadine, Methylphenidate, Apomorphine or Zolpidem. These, together with other existing strategies such as sensory stimulation, hyperbaric oxygen therapy, and neuromodulation, all demonstrate limited efficacy and evidence.[11–13]

Neuromodulation includes non-invasive techniques such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), as well as invasive methods like deep brain stimulation (DBS) and spinal cord stimulation (SCS), but the evidence is still unclear.[14–16] It also includes vagus nerve stimulation (VNS), which can be done both invasively, or non-invasively in the form of transcutaneous auricular VNS (taVNS) or vagus nerve magnetic modulation (VNMM). VNS is a neuromodulatory technique that has been commonly utilized to treat various medical conditions, including epilepsy and depression. New applications in heart failure and inflammatory conditions are being explored as well.[17–20] VNS has been postulated to work by activating brainstem centers involved in regulation of awareness such as the locus coeruleus and raphe nuclei, which in turn receive inputs from the afferent nucleus of the vagus nerve, the nucleus tractus solitarius [Fig. 1].[21] Early reports of VNS use for DoC also demonstrated promising results.[22–25] However, current evidence is limited to small studies and case reports, with no consensus established on the efficacy of VNS for DoC. A recent systematic review by Dong et al. qualitatively summarized the evidence available in the literature but did not quantitatively synthesize the existing data.[26]

VNS can be done invasively via surgical implantation of electrodes around the main cervical trunk of the vagus nerve, or non-invasively as in the case of taVNS or VNMM. Invasive VNS (iVNS) has shown efficacy in and is FDA-approved for multiple conditions such as epilepsy, depression, and stroke rehabilitation, but holds risks of surgery such as infection, vocal cord paresis, lower facial weakness and cardiac events.[27–29] Additionally, iVNS involves electrodes connected to an implantable stimulator, which works via a continuous on-off stimulation cycles that may cause adverse events as well such as voice alteration, cough, dyspnea, paresthesia, headache and pain.[30] To circumvent these risks, non-invasive methods of VNS were studied, including taVNS and VNMM. TaVNS works by stimulating the auricular branch of the vagus nerve by using external electrodes. VNMM has some early

evidence of efficacy, as another non-invasive method using magnetic fields to induce electrical currents in the vagus nerve. Both these non-invasive methods avoid the risks of surgery, and have been reported to have fewer adverse events.[31] However, evidence on their efficacy and applications in different conditions remain limited.[32] Only one study has evaluated the efficacy of VNMM for DoC, and further studies are required to validate its findings.[33]

To better understand the efficacy of VNS as a potential treatment for DoC, we aimed to conduct the first systematic review and meta-analysis of VNS for DoC, using individual patient data (IPD) in particular, to determine the current collective evidence on the topic and guide future interventional studies. The granularity of IPD meta-analysis allows us to determine patient-level correlations, which would not be possible with study-level data.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.[34] The study protocol was registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42024576384).

Systematic searches were performed on PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) up to July 30, 2024. The search terms included synonyms and concepts of DoC and VNS (Supplementary Materials). The search results from all three databases were first de-duplicated within the Zotero reference manager. Then, the data were exported into the Rayyan platform for screening.[35] Any two of six reviewers (JZ, ZZ, AW, ES, ML, YTL) worked individually and in a blinded fashion to review the fitness of the articles. Disagreements were resolved by discussion among the reviewers, and any remaining discrepancy resolved by senior author YTL. Level 1 (L1) screening evaluated articles through examination of titles and abstracts. From here, shortlisted articles went on to

Level 2 (L2) screening where full texts were reviewed. Reasons for rejection were documented clearly in accordance with the PRISMA Guidelines.

All studies reporting use of VNS for DoC were included in the meta-analysis. Inclusion criteria consisted of patients of all ages who underwent VNS (both invasive or non-invasive) for DoC secondary to any etiology, English or Chinese language studies, and reporting CRS-R. In view of the expected small number of studies, we placed no restrictions in sample size of study and included case reports and case series. Exclusion criteria included animal studies, meta-analysis/reviews, trial registrations or protocols, VNS use for DoC secondary to status epilepticus (as such cases of DoC are potentially reversible and occur via a different pathophysiology), and studies with non-clinical endpoints only (i.e., no report of CRS-R), such as neuroimaging or electrophysiological findings.

The following variables were extracted: study details, sample size of study, demographic characteristics of included patients such as age and sex, details of DoC such as etiology, duration and phase (coma, VS/UWS, MCS-, MCS+, eMCS), VNS details such as the type, model, duration, intensity, frequency and pulse width, baseline GCS, CRS-R scores at baseline, during and after treatment, and any other outcomes reported during the follow-up period and duration of follow-up.

The primary outcome measure used is the change in the CRS-R. The CRS-R is a behavioral test that quantifies levels of consciousness and ranges from 0 (deep coma) to 23 (able to follow commands and functionally handle objects).[6] Secondary outcomes included potential adverse events, such as changes in heart rate, blood pressure, respiratory rate, and/or saturation.

Statistical Analysis

For meta-analyses of primary and secondary endpoints, the random effects model was used to account for variance across studies.[36,37] Pooled mean differences were calculated with the inverse variance method.[38] 95% confidence intervals (CI) were computed using the Wilson Score confidence interval method with continuity correction. The I^2 statistic was adopted to gauge between-study heterogeneity, where I^2 ≤30%, between 30% and 50%, between 50% and 75%, and ≥75% suggested low, moderate, substantial, and considerable heterogeneity, respectively. P values for the I^2 statistic were derived from the chi-squared distribution of the Cochran Q test.

Individual patient data (IPD) are analyzed as a single cohort to quantify the change in CRS-R over time, taking into account the chronicity of the DoC. The recovery trajectories were described as line plots. Subgroup analyses related to coma etiology and the type of VNS (transauricular VNS, implanted VNS or vagal nerve magnetic stimulation) were performed. Correlation between age and chronicity of DoC with changes in CRS-R were quantified through Pearson's correlation. We also investigated the changes in DoC categories (UWS/VS, MCS-, MCS+ and eMCS) as reported by the study. For studies that did not subdivide the MCS into MCS+, MCS- or eMCS, we imputed the most likely clinical classification based on the distribution of CRS-R from the other studies [Fig. S1]. Both the actual and the imputed DoC categories were reported.

Publication bias was evaluated visually using funnel plot symmetry as well as quantitatively using Egger's and Begg's regression tests. Risk of bias (RoB) for the included studies was assessed using the National Institute of Health (NIH) Quality Assessment Tool. The RoB for each study was assessed individually by two authors and disagreements were resolved after consultation with a senior author (YTL).

Statistical analyses were performed using Python 3.9.13 and R version 4.2.3. P-values less than 0.05 were considered statistically significant.

Results

Study characteristics

Our search identified 616 unique publications. After screening of titles and abstracts, 15 articles were reviewed in full text. Ten papers were eventually included,[22–25,33,39–43] with 9 of these having data sufficient for IPD meta-analysis [Fig. 2]. Three papers were case reports, and seven remaining papers were interventional studies.

A total of 112 patients were reported across the 10 included studies. Of these, 87 patients had reported IPD. Among patients with IPD, 36 had DoC secondary to TBI, 19 were secondary to intraparenchymal hemorrhage, 18 were secondary to ischemic stroke, and 14 were secondary to HIE. There were 53 males and 34 females. Pooled mean age of included patients with IPD was 49.9 (16.5) years. Pooled mean duration of DoC was 175 (258) days. Pooled baseline CRS-R score was 8.5 (3.5). All except one of the included studies (Wang et al.) reported a single baseline CRS-R value before the start of VNS. In the study by Wang et al., the highest CRS-R score among three measurements taken within a week was used as the baseline CRS-R score. State of DoC at baseline comprised 14 eMCS, 50 MCS (4 MCS+, 21 MCS- and 25 unspecified), and 23 VS/UWS or coma. With regard to interventions, 11 patients underwent iVNS from 2 studies[22,40], 60 underwent taVNS from 8 studies, and 17 underwent VNMM from a single study[33] (**Table 1**).

The majority of studies implemented taVNS for 4 weeks, with the exception of Osińska et al., who implemented iaVNS for 6 months (Table 1). For iVNS, which was meant to provide long-term continuous stimulation, both studies tracked CRS-R over 6 months of implantation.[22,40]

Stimulation protocol

TaVNS and iVNS stimulation protocol differed significantly. For taVNS, treatment was administered for a defined period of time per day, either twice daily (for 30 minutes per session), or once daily (for four hours). For iVNS, stimulations were continuous, with a 30-s on / 5-min rest cycle akin to that used in epilepsy treatment. Details on stimulation parameters used across studies are summarized in Table 2.

Overall extent of recovery

Seven studies had sample sizes larger than 3 and were pooled using study-level meta-analysis. Pooled improvement in CRS-R was 2.78 across these 7 studies (95% CI: 1.62 - 3.94, I^2 = 86% [$p < 0.01$]) [Fig. 3].

Individual patient data analyses

On pooled analysis of individual participant data, 35 (40.2%) of 87 patients (for whom change in CRS-R was reported) showed an improvement in CRS-R of 3 or more with VNS [Fig. 4a]. Notably, some patients with DoC duration longer than 1000 days showed CRS-R improvement after VNS (all were treated with taVNS). The type of VNS (iVNS versus taVNS versus VNMM) was not a significant factor predicting CRS-R improvement ($p = 0.572$) [Fig. 4c]. Similarly, etiology of DoC was non-predictive of CRS-R outcome ($p = 0.974$) [Fig. 4d]. Of note, iVNS was used for patients with longer DoC while taVNS and VNMM were used for patients with relatively shorter DoC.

Following VNS, 16% of all patients transitioned from coma or VS/UWS states to MCS, and another 16% upgraded from MCS to eMCS. Analysis of inferred MCS+ and MCS- categories demonstrated that 10% of patients improved from MCS- to MCS+ post-VNS. The inference of categories was done using imputation of CRS-R cut-off values from the studies that distinguished MCS+ (reported studies CRS-R range 13-14) and MCS- (reported studies CRS-R range 6-12) [Fig. 5]. For studies that did not make the distinction between MCS- and MCS+ (i.e., reported simply as MCS), we reassigned MCS with CRS-R score of 13 and above as MCS+, and those below 13 as MCS-.

Patients with longer DoC were found to have higher CRS-R at baseline ($r = 0.240$, $p = 0.025$) and a greater increase in CRS-R post-VNS ($r = -0.268$, $p = 0.013$) [Fig. 6]. Age was not significantly associated with baseline CRS-R or change in CRS-R score ($p = 0.304$ and 0.962 respectively).

Publication bias

A funnel plot was constructed to evaluate for any publication bias among included studies that involved 10 or more subjects. While there was some visually estimated funnel plot asymmetry, this was not statistically significant on Egger's ($t = 1.75$, $df = 4$, $p = 0.156$) and Begg's tests ($z = -0.19$, $p = 0.851$) [Fig. 7].

Risk of bias assessment

Risk of bias was assessed for studies involving 5 or more participants using the NIH Quality Assessment Tool. Among 7 studies evaluated, 2 had low risk of bias, 4 had moderate risk of bias and 1 had high risk of bias (Fig. 8).

Discussion

In this first systematic review and meta-analysis using IPD reporting on VNS for DoC recovery in 112 patients, most studies were uncontrolled with only 2 out of 10 studies being RCTs. Pooled improvement in CRS-R score after VNS by traditional meta-analysis was 2.78 (95% CI: 1.62 to 3.94). An improvement in CRS-R of 3 or more was observed in 40.2% of patients, and 32% of patients improved to the next best state of DoC as compared to baseline. In our relatively small sample of patients analyzed, the type of VNS and etiology of DoC were not significant determinants of DoC recovery. Age was not significantly associated with baseline CRS-R or change in CRS-R score post-intervention. Of note, among the 10 studies included and analyzed, only two were considered at low risk of bias, due to their randomized, double-blinded sham-controlled study design.

VNS is postulated to alter brain activities via pathways arising from brainstem areas that regulate cortical activities.[44] While the exact neurophysiology remains vague, there is some evidence that VNS works by first activating the nucleus tractus solitarius in the brainstem.[45] Then, these nuclei project directly to the locus coeruleus in the upper brainstem and indirectly via the nucleus paragantocellularis to the raphe nuclei.[46–48] The activation of the locus coeruleus, a major center for regulating awareness, leads to widespread norepinephrine release through the brain to alter sensorimotor responses and prefrontal activities. This enhances cognitive abilities such as attention, emotion, decision-making, motivation, learning and memory.[49–56] Activation of the raphe nuclei also promotes serotonin release, which also acts on multiple areas in the brain to upregulate DMN activity and downregulate activity in the sensorimotor network.[57–59] Functional MRI studies have also demonstrated positive responses in the thalamus and cortical areas such as the left prefrontal cortex, the right and the left postcentral gyrus, the left posterior cingulate gyrus and the left insula during VNS, suggesting possible involvement of these areas in modulating wakefulness for

patients with DoC.[60,61] The observation that VNS benefits those in MCS more than those in VS/UWS suggests that some residual functionality in the above network is likely necessary to support consciousness recovery.

Our meta-analysis demonstrated a pooled CRS-R improvement of 2.78. However, the prediction interval crossed zero, suggesting reduced confidence in this CRS-R improvement estimate. Furthermore, the I^2 statistic is 86%, indicating considerable heterogeneity in the included studies. This heterogeneity stems from differences in intervention types, patient populations, durations of treatment, and protocols, thus limiting the generalizability of our study's findings for VNS in all cases of DoC. Nonetheless, the clinical significance of an estimate of 2.78 improvement in CRS-R needs further clarification as the CRS-R demonstrates good criterion validity for detecting differences in transitions of behavioral states, e.g. from UWS to MCS. Using a probabilistic approach, Monti et al. proposed the use of a 2-point improvement in CRS-R as the MCID to suggest the success of an intervention.[62] For example, a 2-point change in the CRS-R score indicates more than an 80% likelihood of reaching a new threshold behavior for patients in VS or MCS-, whereas a similar change is associated with only a 40% chance for those in the MCS+ category.

In our analysis, 32% of the patients had an improvement in DoC category after VNS treatment (Fig. 4). With regards to intervention-specific adverse events, both iVNS and taVNS studies did not highlight any serious adverse events.[22,40] For taVNS, only local side effects were reported (e.g. itching of ear),[25] while anticipated changes in physiologic parameters like heart rate or blood pressure were often not reported.[24,25]

Nonetheless, improvements in DoC category after VNS should be interpreted with the caveat that the included studies were mostly single-arm observational studies with no control groups. Therefore, the benefit of VNS on the natural history of DoC remains to be elucidated.

Limitations

There are several limitations of this systematic review and meta-analysis. First, most included studies are case series, which provide low quality evidence and are prone to bias due to their non-randomized observational nature. The current analyses should prompt the need for rigorous prospective studies and randomized controlled trials (RCTs) to determine the efficacy and long-term safety of iVNS and taVNS. Second, the absence of control groups in most studies raises the possibility that some degree of coma recovery could be attributed to the natural course of recovery, rather than the effect of VNS, especially for those applying VNS at early stages of the study. Third, many studies involved unselected cohorts. Better prognostication and patient selection in the future might have produced a more pronounced effect. Fourth, follow-up durations in these studies were short, thereby limiting our understanding of long-term outcomes at this juncture. Finally, while knowing which components of the CRS-R improved is valuable, this information is often not reported, further constraining the interpretation of results. On a related note, in many studies MCS was not further subdivided into MCS-, MCS+ and eMCS. These would add ambiguity to data analysis, and the use of imputation to infer the likely categories could introduce bias in that part of the analysis. Future trials should provide more fine-grained division in these DoC categories.

Future directions

Future directions in the management of DoC include the use of prognostic biomarkers such as cognitive motor dissociation (CMD) for better patient selection for neuromodulation.[63,64] Exploring alternative interventions like deep brain stimulation (DBS) and repetitive transcranial magnetic stimulation (rTMS) could also add to the physician's armamentarium in managing patients with DoC. Future studies can also consider the efficacy of using multimodal treatment approaches for maximal patient benefit. There is a dearth of studies that combine rehabilitation interventions with such neuromodulation treatment.

Equally important to consider are the burden of care and the sociopsychological impacts on caregivers and families of patients with DoC, which are crucial areas for exploration.[65] While recognizing the challenges, it is prudent to adopt an optimistic outlook, as advancements in multimodal treatment can lead to meaningful improvements in patient care and quality of life.

Conclusions

Findings from our IPDA indicate that VNS offers a promising modality, with small but significant gains of CRS-R of 3 or more in 40.2% of patients across various levels of DoC states. The change in CRS-R post VNS appeared independent of age and etiology, though with some evidence that greater improvement may be seen in those with short-duration or less severe DoC. The risk of bias was moderate; hence these findings should be interpreted with caution. In addition, taVNS offers a portable home-based modality which could be used over prolonged durations with potential to reduce direct costs in DoC management. Our study findings further highlight the urgent need for further larger, prospective randomized controlled studies to better clarify the efficacy and role of VNS for DoC. The lack of mental capacity in DOC survivors

raises ethical questions about VNS treatment, hence the urgency for more research to educate practitioners about the efficacy, quality of life, health economics and longevity of the effects of iVNS or taVNS.

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Data Availability

The data used for analysis in this paper are all publicly available from the included studies. There is no additional data used available for sharing. For data enquiry and requests, please contact the corresponding author.

Figure Legends

Figure 1. Proposed pathway involved in consciousness recovery following vagal nerve stimulation.

Figure 2. PRISMA flowchart.

Figure 3. Forest plots for studies with n>3 only, sorted by the maximum change in CRS-R during the study and follow-up period.

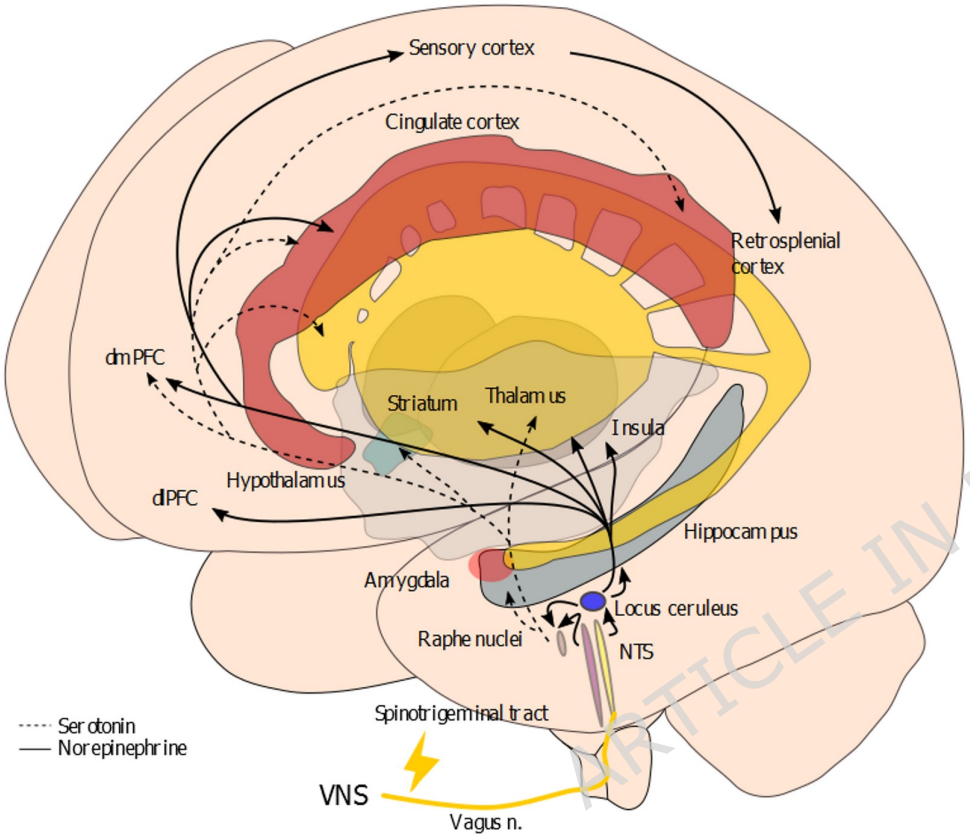
Figure 4. (a) Waterfall plot for CRS-R recovery. (b) Changes in CRS-R for each individual patient, grouped by the initial DoC categories (imputed categories) (c), by responders vs non-responders (d), by type of VNS (iVNS, taVNS and VNM) (e), and by etiology (TBI, HIE, or stroke) (f).

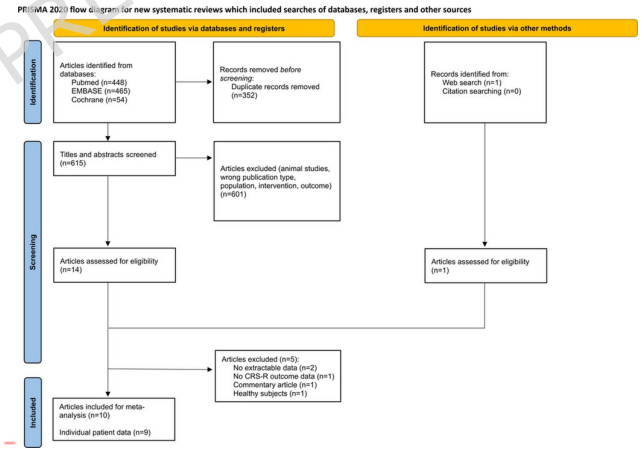
Figure 5. Sankey diagrams showing the change in DoC category. (a) The actual reported categories. As some studies did not subdivide MCS into MCS- and MCS+, the latter two were merged into a single MCS category. (b) Imputed DoC categories based on reassignment from CRS-R cut-off values from the other studies that separated out MCS- from MCS+ (see Figure S1 for details of imputation).

Figure 6. Correlation plots between different variables and the associated statistical tests. Age had no significant associations with baseline CRS-R or their eventual change

Figure 7. Contour-enhanced funnel plot.

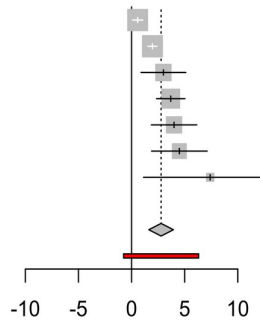
Figure 8. Bias / quality assessment for studies involving n≥5 participants.

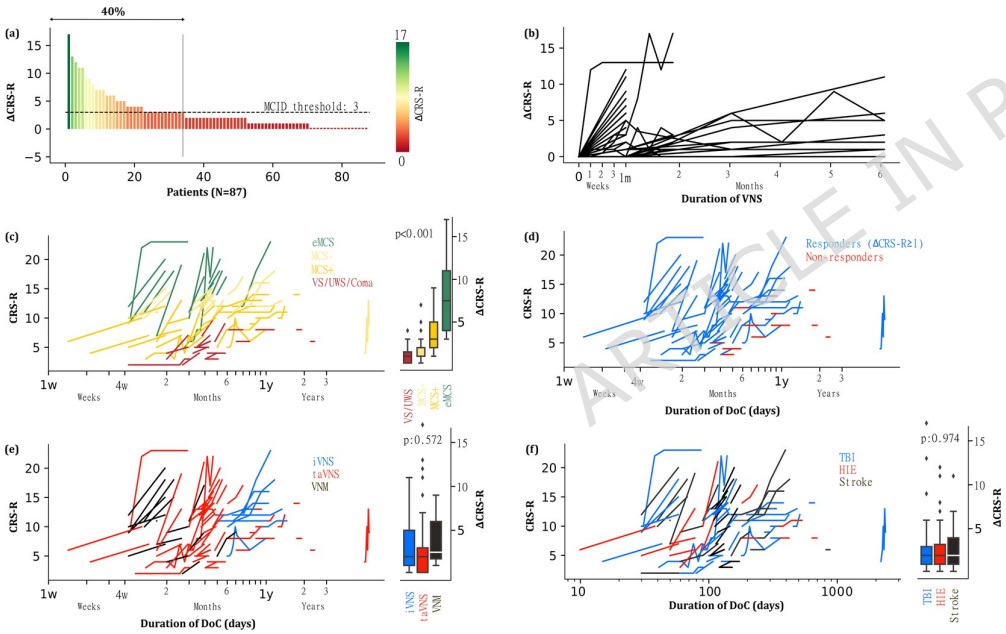


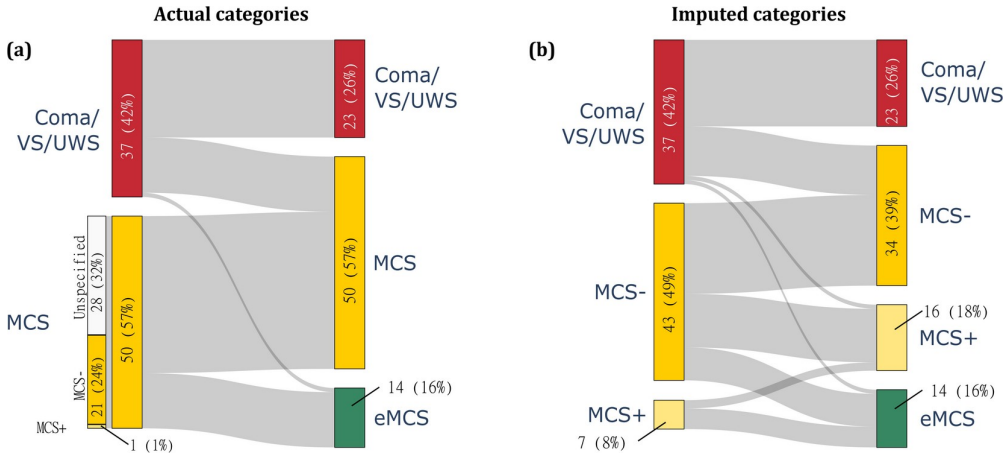


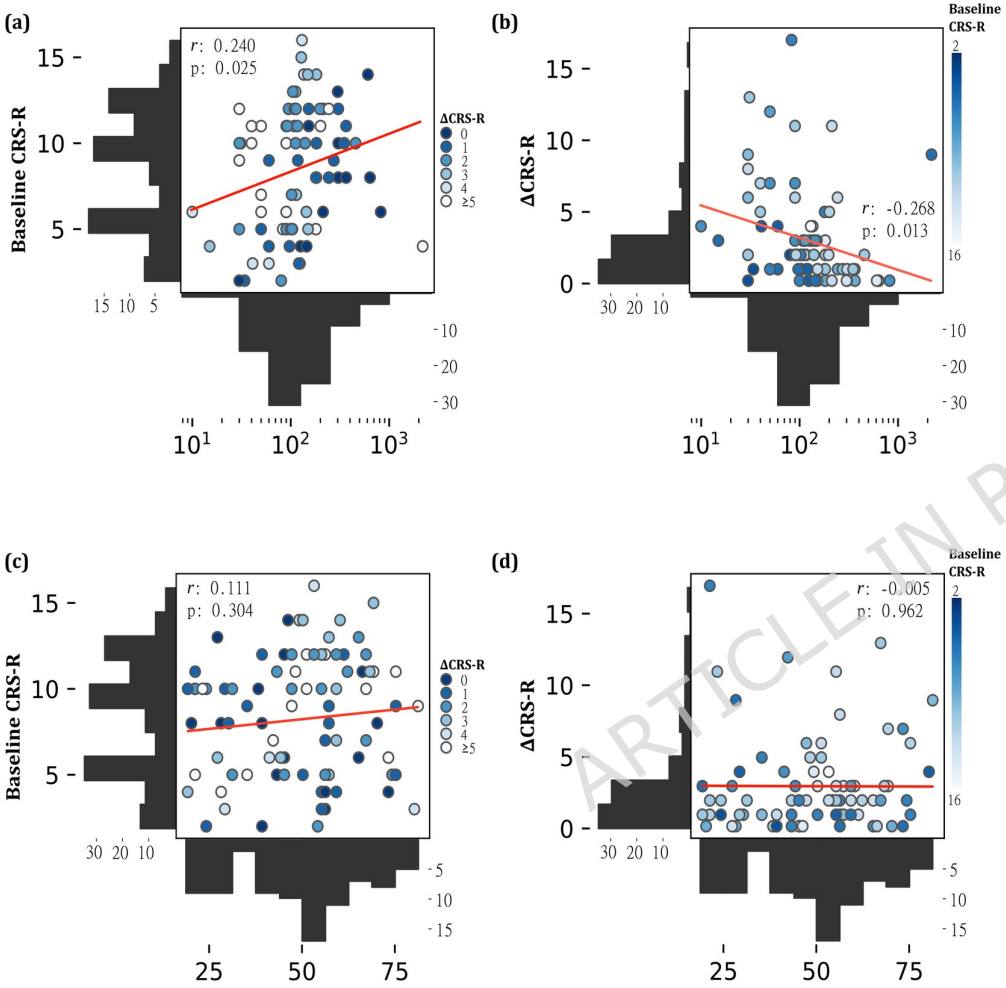
Author	g	n	SE	ΔCRS-R	ΔCRS-R	95%-CI	Weight
Noe, 2020	0.5710	14	0.2506		0.57	[0.08; 1.06]	21.7%
Zhou, 2023a	1.9643	28	0.2211		1.96	[1.53; 2.40]	21.9%
Xiang, 2020	3.0000	10	1.0750		3.00	[0.89; 5.11]	12.9%
Wang, 2022	3.6875	16	0.6814		3.69	[2.35; 5.02]	17.4%
Zhou, 2023b	4.0000	25	1.0902		4.00	[1.86; 6.14]	12.7%
Yu, 2021	4.5000	10	1.3354		4.50	[1.88; 7.12]	10.5%
Hakon, 2020	7.4000	5	3.2031		7.40	[1.12; 13.68]	2.9%
Random effects model					**2.78**	**[1.62; 3.94]**	**100.0%**
Prediction interval						**[-0.75; 6.31]**	

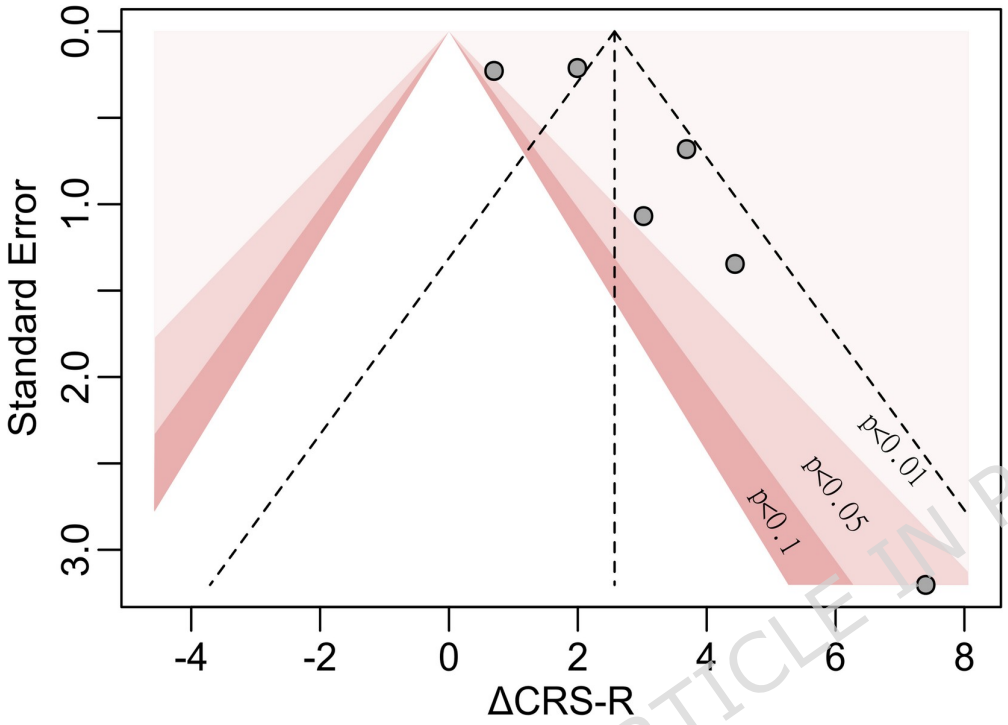
Heterogeneity: I^2 = 86%, τ^2 = 1.5416, p < 0.01











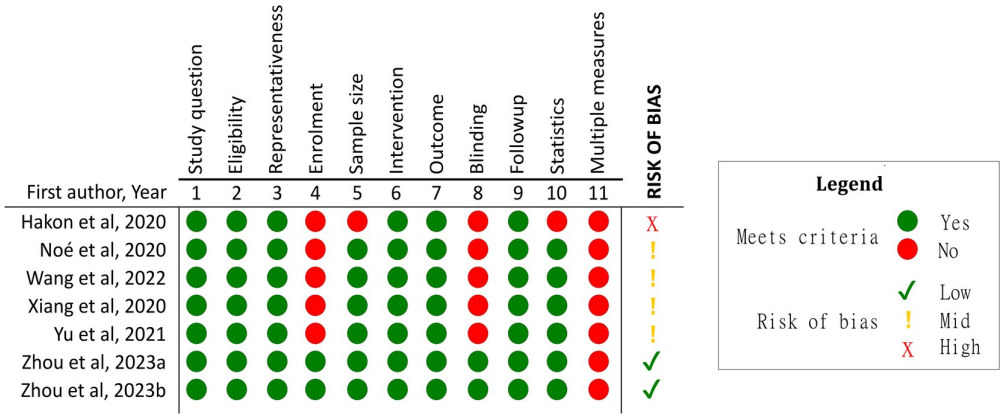


Table 1. Summary of included studies, arranged alphabetically by name of first author. iVNS: implanted VNS (cervical); VNM (vagal nerve magnetic) stimulation; taVNS (trans-auricular VNS).

Study	N	RCT	Etiology of DoC	Type of VNS	Age, years, mean (SD)	Duration of DoC, days, mean (SD)	Duration of VNS	CRS-R at baseline	Best CRS-R post-VNS, mean (SD)	Follow-up period, months	Country of Study
Case report											
Corazzol et al., 2017[22]	1	-	TBI	iVNS	35	180	6 months	5	8	6 months	France
Osinska et al., 2022[39]	1	-	TBI	taVNS	28	72	6 months	4	7	6 months	Poland
Yu et al., 2017[23]	1	-	HIE	taVNS	73	50	4 weeks	6	13	4 weeks	China
Interventional studies											
Hakon et al., 2020[25]	5	No	5 TBI	taVNS	52 (27)	57 (30)	8 weeks	6.4 (4.4)	13.8 (8.9)	8 weeks	Denmark
Noé et al., 2020[24]	14	No	7 TBI 3 ICH 4 HIE	taVNS	40 (16)	368 (195)	4 weeks	9.4 (2.6)	10.0 (3.1)	8 weeks	Spain
Wang et al., 2022[33]	17	No	5 TBI 9 ICH 3 HIE	VNM	63 (9)	66 (44)	4 weeks	7.9 (2.9)	11.5 (4.9)	4 weeks	China
Xiang et al., 2020[40]	10	No	4 TBI 5 ICH 1 HIE	iVNS	44 (16)	218 (64)	>6 months	11.2 (0.9)	14.2 (3.9)	6 months	China
Yu et al., 2021[41]	10	No	2 TBI 3 ICH 5 HIE	taVNS	37 (15)	79 (83)	4 weeks	6.1 (3.3)	10.6 (5.9)	4 weeks	China
Zhou et	2	Ye	17	taVNS	56	118	4	9.0 (4.0)	10.9	4	China

al., 2023a[42]	8	s	stroke 11 TBI		(10)	(16)	weeks		(5.0)	weeks	
Zhou et al., 2023b[43]	25	Yes	10 TBI 13 stroke 2 HIE	taVNS	56 (11)	48 (42)	4 weeks	10.0 (1.4)	14.0 (8.9)	4 weeks	China

Table 2. Stimulation parameters used across included studies.

Study, Year	VNS Type	Intensity	Frequency	Pulse Width	Stimulation Paradigm
Corazzol et al., 2017[22]	iVNS	0.25–1.5 mA	30 Hz	500 ms	30 s stim + 5 min rest
Osińska et al., 2022[39]	taVNS	0.2–1.5 mA	25 Hz	0.25 ms	30 s on / 30 s off, 4 h/day
Yu et al., 2017[23]	taVNS	4–6 mA	20 Hz	0.5 ms	30 min twice daily
Hakon et al., 2020[25]	taVNS	0.5–1 mA	25 Hz	250 μs	30 s on / 30 s off, 4 h
Noé et al., 2020[24]	taVNS	1.5 mA	20 Hz	0.25 ms	30 min twice daily, 5 days/wk
Wang et al., 2022[33]	VNMM	100% RMT	10 Hz	Not reported	20 min/session, once daily, 5 days/wk
Xiang et al., 2020[40]	iVNS	0.1–0.3 to 1.5 mA	20–30 Hz	250 or 500 μs	30 s stim + 5 min rest
Yu et al., 2021[41]	taVNS	4–6 mA	20 Hz	0.5 ms	30 min twice daily, 5 days/wk
Zhou et al., 2023a[42]	taVNS	1.5 mA	20 Hz	0.2 ms	30 min, twice daily, 6 days/wk, 4 weeks
Zhou et al., 2023b[43]	taVNS	1.5 mA	20 Hz	0.2 ms	30 min, twice daily, 6 days/wk, 4 weeks

RMT: resting motor threshold, taVNS: trans-auricular vagal nerve stimulation, iVNS: invasive vagal nerve stimulation, VNM: vagal nerve magnetic modulation