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Effects of Vagus Nerve Stimulation on Upper-Limb Motor Function After Stroke: A Systematic Review and Meta-Analysis

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ABSTRACT

Background. Stroke results in persistent upper-limb motor impairment, and survivors experience incomplete recovery despite standard rehabilitation. Vagus nerve stimulation (VNS) has emerged as a potential neuromodulatory adjunct capable of enhancing training-dependent plasticity. This meta-analysis evaluated the effectiveness of VNS combined with upper-limb rehabilitation in improving motor outcomes after stroke.

Methods. A systematic search of PubMed, the Cochrane Library, and CNKI from 2010 to November 2025 identified randomized controlled trials evaluating rehabilitation paired with implanted or transcutaneous VNS. The primary outcome was upper-limb motor recovery measured by Fugl-Meyer Assessment–Upper Extremity (FMA-UE) at the longest follow-up. Standardized mean differences (SMDs) were pooled using a random-effects model, and certainty of evidence was appraised with the GRADE approach.

Results. Eight RCTs involving 262 participants met inclusion criteria. Across all VNS modalities, rehabilitation paired with VNS significantly improved upper-limb motor function (SMD = 0.886, 95% CI: 0.098–1.674, p = 0.028). Subgroup analysis demonstrated that transcutaneous VNS showed a significant pooled effect (SMD = 1.332, 95% CI: 0.034–2.629, p = 0.044), whereas implanted VNS yielded a smaller, nonsignificant effect (SMD = 0.161, 95% CI: −0.166–0.487, p = 0.335). Improvements were directionally consistent across trials, though heterogeneity and small sample sizes limited certainty of evidence.

Conclusions. Vagus nerve stimulation paired with structured upper-limb rehabilitation enhance motor recovery after stroke. While the overall evidence remains constrained by heterogeneity and modest trial sizes, this review synthesizes emerging data supporting VNS as a promising adjunct to post-stroke neurorehabilitation and highlights the need for larger, standardized RCTs.

Keywords: Stroke; Vagus nerve stimulation; Upper-limb rehabilitation; Fugl-Meyer Assessment; Meta-analysis.

Introduction

Stroke is a leading cause of long-term disability worldwide, frequently resulting in persistent upper extremity motor impairment and reduced functional independence [1]. Stroke affects up to one in five people during their lifetime in some high-income countries, and up to almost one in two in low-income countries [2]. While post-stroke motor deficits primarily stem from the disruption of corticospinal pathways, conventional rehabilitation strategies such as physical therapy and robotic-assisted training often yield limited recovery, with only 20–30% of survivors regaining full function. This limitation underscores the need for neuromodulatory adjuncts like vagus nerve stimulation (VNS), which leverages neuroplasticity by acting via vagal afferents to the brainstem and cortex to enhance motor relearning [3, 4]. Recovery after stroke depends largely on neuroplasticity, in which repetitive, task-specific training promotes reorganization of motor networks and functional improvement [5]. Despite intensive rehabilitation, many individuals still fail to achieve full motor recovery, with persistent upper limb weakness continuing to limit their ability to perform daily activities [4, 6].

The burden of post-stroke upper limb impairment is substantial. The World Stroke Organization: Global Stroke Fact Sheet 2025 reports nearly 12 million new strokes annually worldwide. It also highlights that a large proportion of stroke survivors experience motor impairments, including arm weakness as a common initial deficit.(1) Although some regain partial function, a significant proportion remain dependent on others for daily living, resulting in reduced quality of life and increased socioeconomic costs [7, 8]. Accordingly, innovative rehabilitation approaches that enhance motor relearning and cortical reorganization are of growing clinical interest [9, 10].

Conventional stroke rehabilitation, such as task-oriented training, constraint-induced movement therapy, and functional electrical stimulation, remains the mainstay of treatment, but may not sufficiently engage neural circuits for optimal motor recovery [11, 12]. In recent years, neuromodulation techniques such as vagus nerve stimulation (VNS) have emerged as promising adjuncts to rehabilitation for enhancing neuroplasticity and motor outcomes [13-15].

VNS exerts its therapeutic effect through activation of cholinergic and noradrenergic pathways, thereby modulating cortical excitability and facilitating synaptic plasticity when paired with motor training [16, 17]. Two main VNS approaches have been developed: implanted VNS, involving surgical placement of a cervical stimulator, and transcutaneous VNS, a non-invasive method targeting the auricular branch. Both are typically paired with repetitive upper limb rehabilitation to enhance timing-dependent plasticity for motor relearning. Recent studies on auricular VNS suggest that single-session use offers only modest physical benefits and limited standalone efficacy, highlighting the need to combine VNS with intensive, task-specific training for meaningful motor recovery [18, 19].

Recent randomized controlled trials (RCTs) have demonstrated that VNS paired with rehabilitation may improve upper limb motor outcomes, most commonly assessed by the Fugl-Meyer Assessment Upper Extremity (FMA-UE), Preliminary studies using tVNS have also reported encouraging results, though evidence quality and reproducibility remain variable across stimulation parameters and study designs [20-22]. Overall, VNS appears to be safe and well tolerated, with most adverse events being mild or transient [15]. Nevertheless, the magnitude and consistency of treatment effects, as well as potential differences between implanted and transcutaneous modalities, remain to be systematically evaluated.

This meta-analysis aimed to evaluate, in patients with stroke (P: Population), whether rehabilitation combined with vagus nerve stimulation (I: Intervention), either implanted or transcutaneous, compared with sham stimulation or conventional therapy (C: Comparison), improves upper limb motor recovery as measured by the Fugl-Meyer Assessment Upper Extremity (FMA-UE) (O: Outcome). This PICO (Population, Intervention, Comparison, and Outcome) framework guided the study design. Only randomized controlled trials (RCTs) were included to ensure methodological rigor, and subgroup analyses were conducted to compare the effects of implanted versus transcutaneous VNS. By synthesizing current evidence, this study seeks to provide an updated and quantitative summary of the efficacy and safety of VNS as an adjunct to stroke rehabilitation.

Methods

Inclusion and exclusion criteria

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and followed a pre-registered protocol [23] (PROSPERO registration number: CRD420251218925).

Eligibility criteria were defined using the PICO (Population, Intervention, Comparison, and Outcome) framework. The population (P) included adults with a confirmed diagnosis of stroke, irrespective of lesion type or hemisphere, who demonstrated residual upper-limb motor impairment. Both ischemic and hemorrhagic stroke and patients in the subacute or chronic phases were eligible. The intervention (I) consisted of vagus nerve stimulation (VNS) delivered through either implanted cervical stimulation or transcutaneous auricular stimulation, administered in conjunction with standard rehabilitation practices. Studies were eligible if they used any form of structured upper-limb rehabilitation paired with VNS or if VNS was administered alongside task-specific motor training. The comparison (C) included sham stimulation, standard rehabilitation without VNS, or any active control condition not involving vagus nerve stimulation. The primary outcome (O) was upper-limb motor impairment measured by the Fugl-Meyer Assessment-Upper Extremity (FMA-UE) scale. Studies were required to report FMA-UE data to be eligible for inclusion.

Only randomized controlled trials were included. Non-randomized studies, case reports, reviews, conference abstracts, and animal studies were excluded. Because multiple high-quality randomized trials are now available in this domain, restricting inclusion to RCTs ensured methodological consistency and minimized bias. For studies reporting several post-intervention time points, the longest follow-up was used for quantitative synthesis, and between-group standardized mean differences (SMDs) were prioritized when both within-group and between-group data were available.

Data sources and search strategy

A comprehensive electronic search was performed in the PubMed, Cochrane Library and China National Knowledge Infrastructure (CNKI) databases, encompassing studies published from 2010 to November 2025. To ensure a comprehensive retrieval of relevant studies, the search strategy combined Medical Subject Headings (MeSH) terms with free-text keywords. Boolean operators such as “AND” and “OR” were applied to structure the queries and ensure precise retrieval of studies relevant to the research question. The PubMed search strategy was formulated according to the PICO framework, with the final query defined as: (“Stroke”[Mesh]) AND “Vagus Nerve Stimulation”[Mesh].

For the Cochrane Library, the strategy consisted of two individual queries: “Stroke” (#1) and “Vagus Nerve Stimulation” (#2), with the final query constructed as #1 AND #2. Equivalent search logic was adapted for CNKI to include Chinese-language studies. The last search was conducted in November 2025. Only randomized controlled trials (RCTs) were included. To maximize completeness, the reference lists of all included studies and relevant systematic reviews were manually examined to identify any additional eligible publications.

Selection strategy

The screening and study selection procedures were carried out with the assistance of EndNote reference management software. Two reviewers first independently screened study titles to eliminate duplicates, non–randomized studies, meta-analyses, systematic reviews, scoping reviews, and case reports. The remaining abstracts were subsequently evaluated independently by both reviewers to determine their eligibility. Inter-rater agreement was assessed using Cohen’s kappa ($\kappa = 0.85$), demonstrating a high level of concordance. Any disagreements at this stage were addressed through discussion until consensus was reached. Full-text articles of all potentially eligible studies were then independently reviewed by both researchers to confirm final inclusion, with any remaining non-RCT designs excluded at this step. All final disagreements were settled through discussion and consensus, ensuring the rigor and reliability of the overall study selection process.

Data extraction

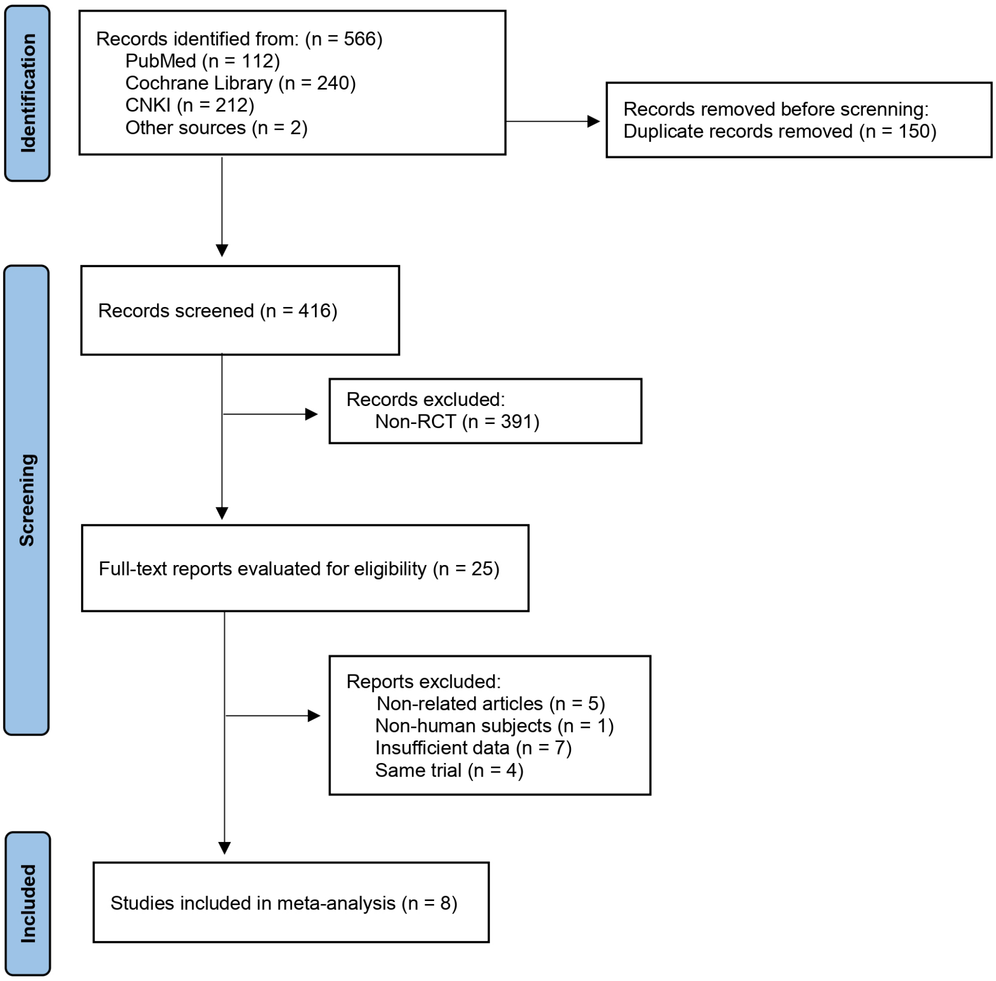
Data used for quantitative analysis were extracted using a standardized form. The information collected included the first author’s name, year of publication, country where the study was conducted, study design, total sample size and group allocation at follow-up, gender distribution, mean age, stroke-related characteristics, types of vagus nerve stimulation used, inclusion and exclusion criteria, and detailed descriptions of the interventions.

Risk of bias of individual studies

The methodological quality of all included studies was independently evaluated by two reviewers using the Risk of Bias 2 (ROB2) tool, as only randomized controlled trials were included. The ROB2 assessment examined potential bias related to the randomization process, deviations from planned interventions, issues related to missing outcome information, approaches to measuring outcomes, and risks of selective reporting. Any disagreements between reviewers were resolved through discussion to achieve consensus [24].

Data analysis(meta-analysis)

Statistical analyses were conducted using Comprehensive Meta-Analysis version 3.7 (Biostat, Englewood, NJ, USA). Standardized mean differences (SMDs), standard errors (SEs), and 95% confidence intervals (CIs) were calculated to estimate the effects of vagus nerve stimulation on rehabilitation-related



Abbreviations: CNKI, China National Knowledge Infrastructure

Figure 1 – Flow diagram of study selection for randomized controlled trials evaluating vagus nerve stimulation after stroke

Table 1 Baseline characteristics of the studies included in the meta-analysis

Source	Country	Study Design	Age Range	% Female	Phase post-stroke	Mean FMA-UE at Baseline (VNS Group)	Mean FMA-UE at Baseline (Sham)	Experimental Group (VNS)	Control Group (Sham)	Intervention Type	Comparator	Detailed Intervention	Follow-up Duration & Schedule	Adverse events
Dawson et al. (2016)	UK	open-label, assessor-blinded, RCT	VNS Group: 57.9 ± 17.2; Sham: 60.7 ± 10.7	VNS Group 22.2%; Sham 18.2%	Chronic (≥ 6 months)	40.1±9.7	45.3± 8.4	9	11	Implanted Vagus Nerve Stimulation (VNS)	Rehabilitation only	VNS: therapist-triggered 0.5 s train, 15 pulses, 0.8 mA, 100 µs, 30 Hz, left side, once per movement; Duration: 6 weeks (3x/week, total 18 sessions).	30 Days: 1, 7, 30 days post-rehab	Vocal cord palsy, deglutition impairment, gastric distress, dysgeusia, hoarseness, tingling
Capone et al. (2017)	Italy	double-blind, RCT	VNS Group: 53.71 ± 5.88; Sham: 55.60 ± 7.12 #	VNS Group 42.9%; Sham 40.0%	Chronic (≥ 1 year)	22.29 ± 3.51	32.60 ± 6.43	7	5	Transcutaneous Vagus Nerve Stimulation (tVNS)	Sham tVNS	tVNS: left tragus, 20 Hz 0.3 ms, 30 s/5 min × 60 min, intensity above sensory below pain, left only; Duration: 2 weeks (5x/week, total 10 sessions).	Assessment only at the end of treatment	None
Kimberley et al. (2018)	USA	double-blind, RCT	VNS Group: 59.5± 7.4; Sham: 60± 13.5	VNS Group: 50%; Sham: 44.4%	Chronic (≥ 4 months)	29.5±6.4	36.4± 9.4	8	9	Implanted cervical Vagus Nerve Stimulation (VNS)	Sham VNS	Implanted cervical VNS paired: therapist-triggered 0.5-s trains at 30 Hz, 100 µs, 0.8 Ma, one train per movement; Duration: 6 weeks (3x/week, total 18 sessions).	90 Days: 1, 7, 30, 90 days	Surgical site infection, dyspnea, deglutition impairment, dysphonia
Wu et al. (2020)	China	single-blinded, RCT	VNS Group: 64.50 ± 9.97; Sham: 61.82 ± 10.63	VNS Group: 50%; Sham: 27.3%	VNS Group: 36.30 ± 9.23(d); Sham: 35.55 ± 6.47 (d)	17.50± 4.91	16.82± 3.89	10	11	Transcutaneous auricular vagus nerve stimulation (taVNS)	Sham taVNS	taVNS: 600 pulses/train (20 Hz, 0.3 ms), 30 s/5 min cycle, 30 min/day; Duration: 15 days (Daily).	12 Weeks: 4 weeks and 12 weeks	Erythema
Wei et al. (2020)	China	open-label, RCT	VNS Group: 61.31± 11.54; Sham: 57.23± 10.17	VNS Group: 69.2%; Sham: 76.9%	VNS Group: 48.77± 24.74 (d); Sham: 50.38± 22.07(d)	32.85± 12.13	28.31± 13.55	13	13	Transcutaneous left auricular vagus nerve stimulation (taVNS)	Sham taVNS	taVNS: optimum intensity, 25 Hz, 100 µs, lasting 30 s every 30 s; Duration: 4 weeks (5x/week, 20 sessions).	Assessment only at the end of treatment	Nausea, vomiting, ear pain
Zhang et al. (2020)	China	triple-blind, RCT	VNS Group: 66.1± 1.49; Sham: 64.1± 1.03	VNS Group: 47.6%; Sham: 61.9%	VNS Group: 38±15 (d); Sham: 36.86± 2(d)	18.76± 0.94	17.9± 0.76	21	21	Transcutaneous left auricular vagus nerve stimulation (taVNS)	Sham taVNS	taVNS: 0.5 mA, 20 Hz, 30 s every 2 min, total 30 min per session; Duration: 6 weeks (3x/week, total 18 sessions)..	20 Weeks: 12 weeks and 20 weeks post-rehab	None
Dawson et al. (2021)	UK	triple-blind, RCT	VNS Group: 59.1± 10.2; Sham: 61.1 ±9.2	VNS Group: 35.8%; Sham: 34.5%	Chronic (≥ 9 months)	34.4±8.2	35.7± 7.8	53	55	Implanted cervical Vagus Nerve Stimulation (VNS)	Sham VNS	Implanted cervical VNS: Therapist triggered VNS 0.8 mA (two cases 0.7/0.6 mA), 100 µs, 30 Hz, 0.5 s per movement repetition; Duration: 6 weeks (3x/week, 18 sessions; ~90 min/session; ~300+ reps/session).	90 Days: 1, 90 days	Vocal fold paralysis
Badran et al. (2023)	USA	double-blind, RCT	VNS Group: 57.33 ± 8.28 ; Sham: 58.71 ± 6.45	VNS Group: 56%; Sham: 29%	Chronic (≥ 6 months)	36.56 ± 7.94	38.57 ± 10.47	9	7	Transcutaneous Motor-Activated Auricular Vagus Nerve Stimulation (MAAVNS)	unpaired taVNS	MAAVNS: EMG-triggered closed-loop taVNS (<100 ms delay), bilateral cymba conchae + tragus electrodes, 25 Hz, 500 µs, 2× perceptual threshold, 5 s trains repeated, mean 36,070 ± 3,205 pulses; Duration: 4 weeks (3x/week, 12 sessions).	8 Weeks: Post-session 3, 6, 9, 12; 2 weeks and 8 weeks after intervention	None

#The patient's age range in Capone et al. (2017) is provided as Mean ± SE.

Abbreviations: VNS, vagus nerve stimulation; tVNS, transcutaneous vagus nerve stimulation; taVNS, transcutaneous auricular vagus nerve stimulation; RCT, randomized controlled trial; EMG, electromyography; mA, milliampere; Hz, hertz; µs, microsecond; ms, millisecond; s, second; min, minute; SE, standard error.

outcomes. Forest plots were generated to provide a visual summary of effect sizes. A p-value less than 0.05 was considered statistically significant.

To account for both within-study and between-study variability, a random-effects model was applied for all pooled analyses. Heterogeneity was planned to be evaluated using the I^2 statistic and Cochran's Q test, and potential publication bias was to be examined using funnel plots and Egger's regression. However, because the number of eligible studies did not exceed ten, these assessments were not performed in accordance with Cochrane recommendations. Instead, clinical and methodological heterogeneity were qualitatively examined by comparing variations in stimulation modality, intervention parameters, patient characteristics, and outcome measures across included trials.

All included studies employed between-group randomized controlled trial designs; therefore, SMDs were derived using post-intervention means and standard deviations. The overall certainty of evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework, taking into consideration risk of bias, inconsistency, indirectness, imprecision, and potential publication bias.

Results

Study and identification and selection

The PRISMA diagram outlines the identification and screening procedures used in this meta-analysis (Figure 1). A total of 566 records were retrieved from all databases (PubMed, n = 112; Cochrane Library, n = 240; CNKI, n = 212; additional sources, n = 2). After removing 150 duplicate entries, 416 records proceeded to title and abstract screening, during which 391 were excluded because they did not meet the eligibility criteria or were non-randomized designs.

Subsequently, 25 full-text articles were assessed in detail. Of these, 5 were excluded for being unrelated to the research question, 1 was a non-human study, 7 lacked sufficient extractable data, and 4 represented duplicate publications of the same trial.

In the end, 8 randomized controlled trials involving a total of 262 participants met all inclusion criteria and were incorporated into the final quantitative synthesis (Table 1).

Quality assessment of the included studies

Risk of bias for all included randomized controlled trials was evaluated using the ROB2 tool. As illustrated in Figure 2 and Figure 3, none of the studies were rated as having a high risk of bias in any domain. Although a few trials demonstrated some concerns in areas such as the randomization process or missing outcome data, these issues were generally minor and did not materially threaten the internal validity of the findings.

Certainty of evidence (GRADE))

Certainty of evidence was assessed using the GRADE framework [25-32], with detailed evidence profiles presented in Table 2. For the primary functional outcomes, the certainty remains limited. Downgrading was primarily driven by variability in stimulation parameters and intervention protocols across trials, differences in patient characteristics, and imprecision related to small sample sizes with wide confidence intervals. Additionally, the presence of some concerns in certain ROB2 domains contributed to downgrading for risk of bias.

Despite these limitations, the pooled results showed a consistent pattern of improvement in post-stroke motor

Table 2 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment of certainty of evidence

Outcomes	Studies, No.	Participants, No.	Pooled effect (95% CI)	Overall certainty (GRADE)	Reason for downgrades
Upper-limb motor function (all VNS modalities)	8	262	SMD 0.886 (0.098–1.674), p = 0.028	Moderate	Downgraded for risk of bias, inconsistency
Upper-limb motor function (implanted VNS only)	3	145	SMD 0.161 (−0.166–0.487), p = 0.335	Low	Downgraded for imprecision
Upper-limb motor function (transcutaneous VNS only)	5	117	SMD 1.332 (0.034–2.629), p = 0.044	Low	Downgraded for risk of bias, inconsistency and imprecision

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development and Evaluations; VNS, Vagus nerve stimulation; SMD, Standardized Mean Difference; CI, Confidence interval.

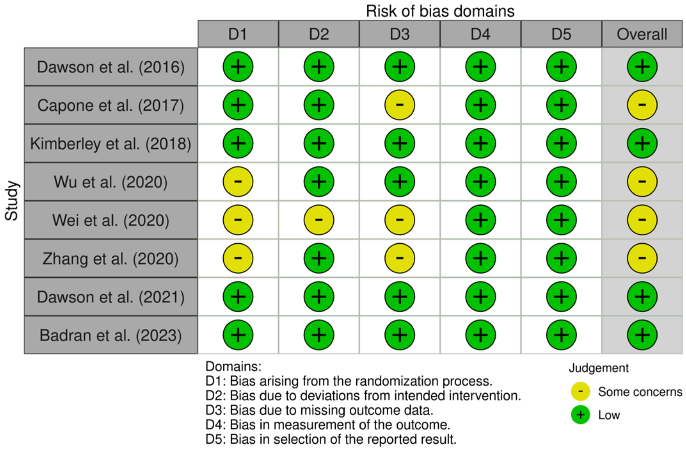


Figure 2 – ROB2 Traffic Light Plot

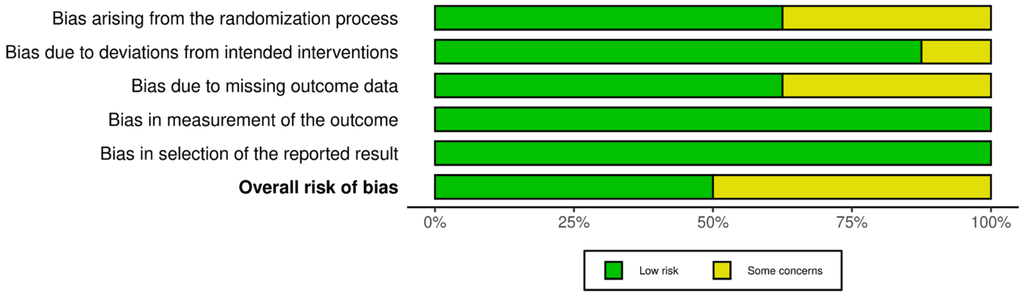
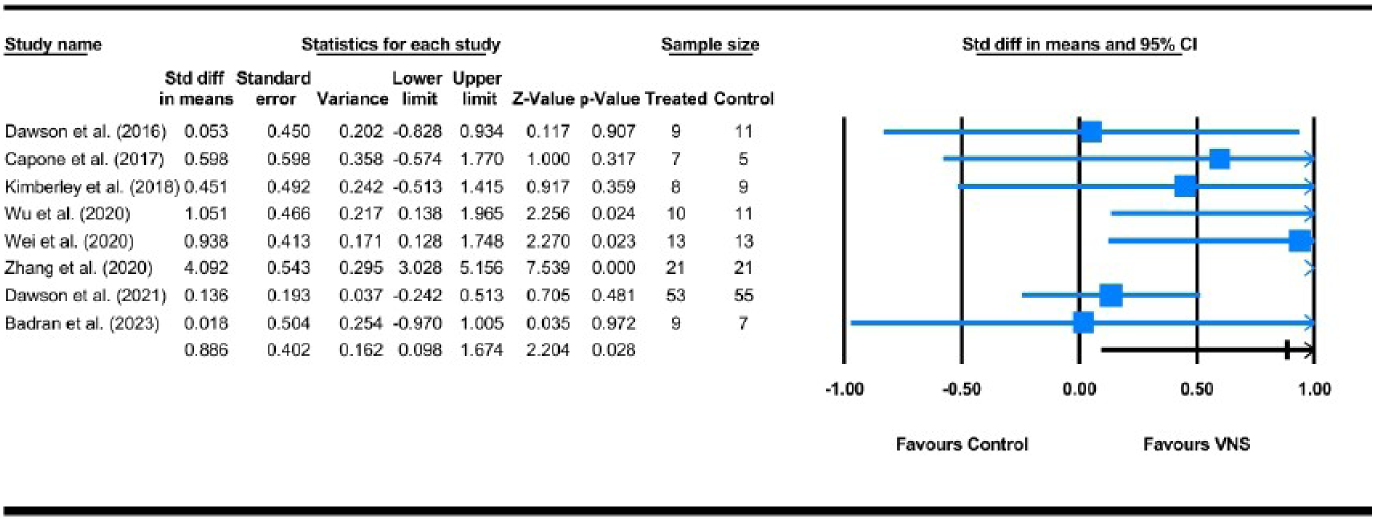
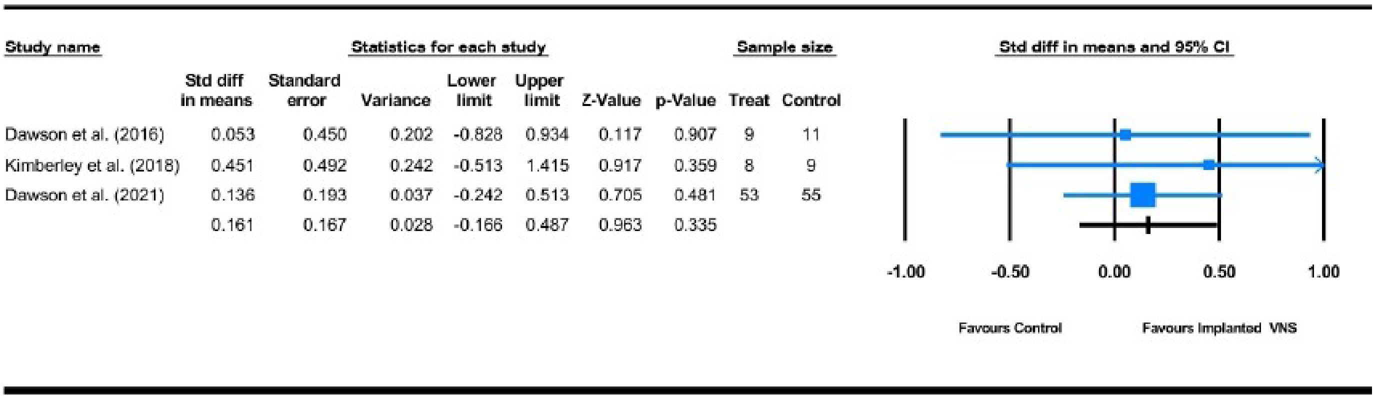


Figure 3 – ROB2 Summary Plot



Study name	Statistics for each study							Sample size	
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Treated	Control
Dawson et al. (2016)	0.053	0.450	0.202	-0.828	0.934	0.117	0.907	9	11
Capone et al. (2017)	0.598	0.598	0.358	-0.574	1.770	1.000	0.317	7	5
Kimberley et al. (2018)	0.451	0.492	0.242	-0.513	1.415	0.917	0.359	8	9
Wu et al. (2020)	1.051	0.466	0.217	0.138	1.965	2.256	0.024	10	11
Wei et al. (2020)	0.938	0.413	0.171	0.128	1.748	2.270	0.023	13	13
Zhang et al. (2020)	4.092	0.543	0.295	3.028	5.156	7.539	0.000	21	21
Dawson et al. (2021)	0.136	0.193	0.037	-0.242	0.513	0.705	0.481	53	55
Badran et al. (2023)	0.018	0.504	0.254	-0.970	1.005	0.035	0.972	9	7
	0.886	0.402	0.162	0.098	1.674	2.204	0.028		

Fig. 4-1. Forest plot depicting the pooled effects of vagus nerve stimulation (all modalities combined) on upper-limb motor function after stroke.



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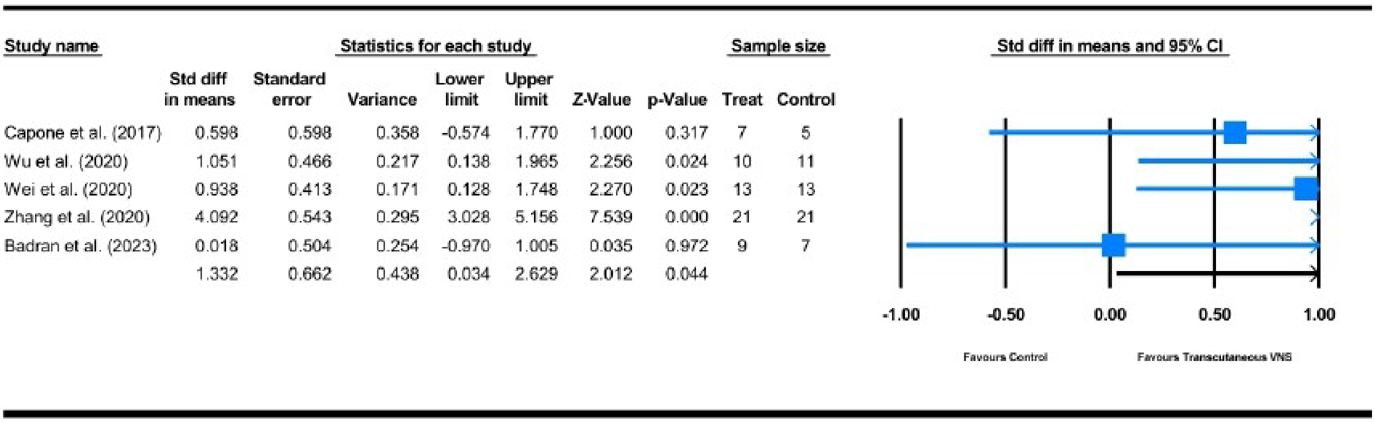
Dawson et al. (2021)	0.136	0.193	0.037	-0.242	0.513	0.705	0.481	53	55
	0.161	0.167	0.028	-0.166	0.487	0.963	0.335		

Fig. 4-2. Forest plot depicting the effects of implanted cervical vagus nerve stimulation on upper-limb motor outcomes compared with control conditions.



Study name	Statistics for each study							Sample size	
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Zhang et al. (2020)	4.092	0.543	0.295	3.028	5.156	7.539	0.000	21	21
Badran et al. (2023)	0.018	0.504	0.254	-0.970	1.005	0.035	0.972	9	7
	1.332	0.662	0.438	0.034	2.629	2.012	0.044		

Fig. 4-3. Forest plot depicting the effects of transcutaneous vagus nerve stimulation on upper-limb motor outcomes compared with control conditions.

Figure 4 – Forest plot depicting the effects of vagus nerve stimulation on upper-limb motor function after stroke

outcomes among participants receiving vagus nerve stimulation compared with control groups. In a research area with a historically small number of randomized trials, this synthesis consolidates emerging evidence and provides important direction for the planning of future studies, including more accurate sample-size estimation, selection of appropriate primary endpoints, and greater standardization of stimulation approaches.

Participants

A total of 262 participants from eight randomized controlled trials were included in this systematic review and meta-analysis (study details extracted from included trials). Sample sizes across studies ranged from 12 to 108 participants. Disease duration (time post-stroke) was reported in most trials and generally exceeded 4 months. Sex distribution varied by study, with reported female proportions ranging from 20% to 73%. Across the included trials, three studies employed implanted vagus nerve stimulation (VNS) [33-35], while five studies utilized transcutaneous VNS (tVNS) [36-40], reflecting variation in stimulation modality. All studies enrolled individuals with upper-limb motor impairment following stroke, with chronic motor deficits representing the predominant clinical profile. Baseline FMA-UE scores across the included trials ranged from 16.82 to 45.3, indicating a spectrum of impairment from severe to moderate [41]. To facilitate clinical interpretation, a standardized classification of FMA-UE scores has been included in the Appendix 1.

Interventions

In this review, all included trials investigated vagus nerve stimulation combined with upper-limb rehabilitation as the primary intervention for patients with chronic stroke. Across the eight randomized controlled trials, three studies [33-35] used implanted cervical VNS, whereas five [36-40] employed transcutaneous auricular VNS, including motor-activated paradigms.(36) In the implanted VNS trials [33-35], stimulation was delivered via a cervical cuff electrode on the left vagus nerve, with therapist-triggered 0.5-second trains at 30 Hz, 100 µs pulse width, and intensities typically around 0.8 mA, paired with task-specific upper-limb movements during in-clinic therapy sessions. In the transcutaneous VNS trials [36-40], stimulation was applied to the tragus or cymba conchae of the auricle, using frequencies between 20 and 25 Hz, pulse widths of 0.3–0.5 ms, and intensities adjusted above sensory threshold but below pain threshold, administered either as continuous or intermittent trains over 30- to 60-minute sessions.

Intervention duration and dosing varied across studies. Some protocols were relatively brief, such as 10-day [37] tVNS, whereas others, particularly those combining implanted VNS with intensive upper-limb training, involved structured programs delivered three times per week over six weeks, with approximately 90-minute sessions and several hundred task repetitions per session [34].

One trial [36] implemented an electromyography-triggered, motor-activaed tVNS paradigm, in which stimulation was automatically delivered within milliseconds of muscle activation during upper-limb tasks, providing a closed-loop pairing of VNS with voluntary movement. Overall, these intervention strategies were designed to enhance experience-dependent plasticity by coupling VNS with repetitive, task-specific upper-limb practice to promote functional motor recovery after stroke.

Comparator interventions

In the trials included in this review, comparator conditions were designed to control for both rehabilitation dose and nonspecific effects of device use. Several studies used standard upper-limb rehabilitation alone as the control condition, with no active VNS delivered.

In the implanted VNS trials [33-35], control groups received sham stimulation through deactivated or subtherapeutic device settings while undergoing the same task-specific training as the active VNS group. In the transcutaneous VNS trials [36-40], sham tVNS was commonly applied by placing electrodes at the same auricular locations but delivering no current or ineffective stimulation parameters, or by using unpaired stimulation that was not temporally linked to movement. Across all studies [33-40], control participants received comparable contact time and rehabilitation exposure, ensuring that any between-group differences could be attributed primarily to the presence or absence of effective VNS rather than differences in therapy intensity or attention.

Meta-analysis

A synthesis of eight randomized controlled trials encompassing 262 participants demonstrated consistent improvements in upper-limb motor function favoring vagus nerve stimulation over control conditions (Figure 4-1). The pooled standardized mean difference (SMD) for all VNS modalities combined was 0.886, with a 95% confidence interval from 0.098 to 1.674 and a p value of 0.028, indicating a statistically significant benefit associated with VNS. Individual trial effects varied, ranging from very small or negligible effects in studies such as Dawson et al. (2016) [35], Dawson et al. (2021) [34], and Badran et al. (2023) [36] to a very large effect in Zhang et al. (2020) [39], which contributed strongly to the upper bound of the pooled estimate. The forest plot illustrates study-specific SMDs and corresponding weights, with larger samples contributing more heavily to the overall result. Between-study variation is apparent and is likely related to differences in stimulation parameters, VNS modality, rehabilitation intensity, and participant characteristics across trials.

In the subgroup of trials employing implanted cervical VNS, the combined effect on upper-limb motor outcomes was small and not statistically significant (Figure 4-2). The pooled SMD was 0.161, with a 95% confidence interval from −0.166 to 0.487 and a p value of 0.335, suggesting that any additional benefit of implanted VNS beyond control conditions remains uncertain based on current evidence. Some studies in this subgroup reported modest gains [33], whereas others showed effects close to zero [34, 35] , and their relative weights reflected differences in sample size, with the largest implanted VNS trial [34] contributing most to the pooled estimate. These findings indicate that implanted VNS may have, at most, a modest effect on motor recovery within the contexts studied.

By contrast, the subgroup analysis of five trials using transcutaneous VNS (tVNS) showed a larger pooled effect size on upper-limb motor function (Figure 4-3). The pooled SMD was 1.332, with a 95% confidence interval from 0.034 to 2.629 and a p value of 0.044, consistent with a statistically significant and potentially large treatment effect, albeit with substantial imprecision. Zhang et al. (2020) [39] reported the largest SMD, whereas other tVNS studies such as Capone et al. (2017) [37], Wu et al. (2020) [40], and Wei et al. (2020) [38] demonstrated moderate benefits, and Badran et al. (2023) [36] reported a minimal effect. Taken together, these findings suggest that tVNS may be associated with greater motor gains than implanted VNS, although the wide confidence intervals and heterogeneity across trials underscore the influence of factors such as stimulation modality, intensity, treatment duration, and baseline motor impairment, and highlight the need for larger, head-to-head randomized trials to clarify differences between VNS approaches.

Secondary Outcomes and Other Effects

Beyond the primary FMA-UE scores, several trials evaluated secondary motor and sensory outcomes. The Wolf

Motor Function Test (WMFT) was utilized in studies included Dawson (2021) , Kimberley (2018) , and Badran (2023). Participants in the VNS groups demonstrated faster completion of distal tasks, including picking up small objects (e.g., paper clips), turning keys, and hand-eye coordination tasks. Muscle stiffness and spasticity were assessed using the Modified Ashworth Scale (MAS); however, most studies, including the pivotal Dawson (2021) trial, reported no significant difference in spasticity between the VNS group and the control group [33-36].

Safety and Adverse Events

VNS was generally well-tolerated, with profiles varying by modality. For implanted VNS (iVNS), adverse events included minor surgical site infections and transient hoarseness. Serious events, such as vocal cord paresis, were rare (e.g., 7% in the VNS-REHAB trial) and typically resolved [33-35]. Transcutaneous VNS (tVNS) showed an excellent safety profile, with minor side effects limited to local skin irritation (erythema or tingling) and rare systemic symptoms like nausea, without significant autonomic changes [36-40].

Discussion

This meta-analysis demonstrated that vagus nerve stimulation, when added to conventional upper-limb rehabilitation, is associated with greater improvements in motor outcomes after stroke compared with control conditions. When all VNS modalities were combined, the pooled effect size fell within the moderate-to-large range, indicating a clinically meaningful advantage for VNS-enhanced rehabilitation. These results reinforce the therapeutic potential of pairing neuromodulation with structured task-specific training to optimize post-stroke motor recovery.

Across the eight included randomized controlled trials, three investigated implanted cervical VNS [33-35] and five examined transcutaneous auricular VNS [36-40]. Implanted VNS showed small, generally modest improvements, whereas the tVNS subgroup demonstrated a larger pooled effect size, suggesting the possibility of greater benefit with non-invasive stimulation under certain conditions. Although variation existed across individual trials, the overall direction of effects consistently favored VNS over control, supporting its role as an adjunctive therapy to enhance upper-limb rehabilitation after stroke.

The variability observed across studies is likely shaped by several interacting factors. Stimulation parameters differed substantially in frequency, pulse width, current amplitude, and train duration, and the timing of stimulation relative to motor activity was not consistent. Some protocols used therapist-triggered stimulation delivered precisely during task-specific movements [33-35], whereas others relied on continuous or intermittently scheduled tVNS without strict alignment to task performance [36-40]. Intervention dosage also varied across trials, and patient characteristics such as stroke chronicity, lesion location, baseline motor ability, and cognitive function further contributed to differences in responsiveness. Preclinical and translational evidence supports pairing VNS with rehabilitation [42, 43]. These effects are mediated through neuromodulatory systems, including norepinephrine, acetylcholine, and serotonin, which create a biochemical environment that supports long-term potentiation and synaptic remodeling [42, 44]. Closed-loop VNS delivered during or immediately after successful motor attempts activates widespread networks across cortical, subcortical, and spinal levels, promoting task-specific synaptic modifications in damaged motor circuits [44, 45]. VNS also increases brain-derived neurotrophic factor (BDNF), upregulates plasticity-related genes such as Arc, and increases synaptic spine density, mechanisms that are crucial for motor learning and recovery [46, 47]. Importantly, these effects occur only when VNS is paired with task-specific training; stimulation delivered without behavioral engagement yields minimal benefit [42].

This mechanistic foundation directly correlates with the functional improvements observed across several trials. The faster completion of distal tasks in the Wolf Motor Function Test (WMFT) reported in studies included Dawson (2021), Kimberley (2018), and Badran (2023) suggests that the synaptic modifications facilitated by VNS are particularly effective at enhancing distal limb coordination, such as picking up small objects and turning keys. Because VNS is specifically paired with motor tasks to drive motor cortex reorganization, its effects are primarily focused on motor recruitment rather than sensory or spasticity modulation. This explains why most included studies reported significant motor gains without corresponding changes in tactile sensitivity, proprioception , or muscle stiffness as measured by the Modified Ashworth Scale (MAS) [33, 34, 36].

Collectively, this evidence supports the interpretation of VNS as a neuromodulatory “amplifier” rather than a stand-alone intervention. In both animal and human studies, VNS paired with rehabilitation has been shown to produce greater improvements in upper limb function than rehabilitation alone, suggesting an added benefit of stimulation beyond training, although the precise contribution of stimulation timing requires further clarification [36, 48]. This aligns with observations in the included stroke trials, where both intervention and control groups received structured upper-limb rehabilitation, and between-group differences reflect neuromodulatory enhancement of training effects [49, 50]. VNS acts as a neuromodulatory amplifier whose efficacy depends on precise pairing with high-intensity therapy, often requiring several hundred repetitions per session. Clinical benefits are further influenced by baseline impairment; patients with FMA-UE scores between 20–50 are typically targeted to avoid floor and ceiling effects. Additionally, VNS focuses on enhancing motor recruitment rather than modulating severe muscle spasticity, as reflected by the lack of significant change in MAS scores. Inter-individual variability in treatment response likely reflects differences in neurobiological reserve and cognitive engagement [33-36, 38].

Inter-individual variability in treatment response likely reflects differences in neurobiological reserve and cognitive engagement. Patients with greater preservation of corticospinal pathways, moderate baseline impairment, or intact cognitive function may respond more robustly to VNS-augmented therapy. Conversely, severe impairment, apraxia, or attention deficits may limit the ability to pair stimulation with meaningful task performance [45]. Although all included trials enrolled predominantly chronic stroke patients, preclinical data suggest that earlier intervention may enhance responsiveness, though benefits can still occur in later stages when training intensity is adequate [42, 51]. Future studies should include detailed imaging, neurophysiological markers, and cognitive assessments to better identify responder profiles.

Mechanistic evidence aligns with core principles of neurorehabilitation. Repetitive, task-specific practice promotes use-dependent plasticity, while VNS enhances this effect by increasing neuromodulatory activity at key moments of learning [52]. Closed-loop stimulation enhances movement-specific plasticity in primary motor cortex, strengthens motor unit recruitment patterns, and increases motor drive to alpha motor neurons. These mechanisms provide a biological foundation for the motor improvements observed across VNS trials [45].

Clinical considerations further differentiate implanted and transcutaneous approaches. Implanted VNS allows precise, therapist-guided stimulation synchronized with motor tasks, facilitating timing-dependent plasticity [43]. A double-blind trial in individuals with chronic cervical spinal cord injury demonstrated meaningful improvements using implanted closed-loop VNS combined with high-intensity rehabilitation, although invasiveness, surgical risk, and cost remain limitations [45]. In contrast, tVNS is non-invasive and more scalable but shows greater variability in stimulation precision, and its comparative efficacy remains uncertain, although studies suggest it can improve motor function and daily activities when paired with exercise. Rigorous comparative effectiveness trials are needed to define its relative benefits, limitations, and cost-effectiveness across rehabilitation settings [4, 53].

Future studies should emphasize the use of consistent stimulation parameters, unified motor training protocols, and thorough outcome evaluation incorporating impairment-level measures, functional performance tests, kinematic analyses, neurophysiological indices, and patient-reported assessments. The integration of electromyography-triggered closed-loop tVNS, home-based stimulation systems, and telerehabilitation platforms may further expand access and increase training dose. Combinations of VNS with other neuromodulatory or pharmacologic strategies may enhance recovery through complementary mechanisms [54].

Importantly, our meta-analysis provides direct evidence that VNS-enhanced rehabilitation yields significantly greater improvements in upper-limb motor function compared with conventional therapy alone. Both implanted and transcutaneous approaches demonstrated directionally favorable outcomes, and tVNS in particular produced a statistically significant pooled effect size. These findings reinforce that VNS meaningfully augments the benefits of task-specific training and offer early clinical validation of the biological mechanisms highlighted above. As such, the results of this study strengthen the rationale for integrating VNS into contemporary neurorehabilitation practice and underscore its potential value as an effective therapeutic adjunct for post-stroke motor recovery.

Limitations

Despite the encouraging findings, several limitations should be acknowledged. The number of eligible randomized trials was small, and most studies enrolled relatively modest sample sizes, which reduces statistical power and limits the precision and generalizability of the results. Although all included trials used randomized designs, there was substantial methodological variation in stimulation parameters, the timing of VNS delivery relative to motor practice, the duration of treatment, and the structure of the rehabilitation programs. These inconsistencies likely contributed to variability across studies and make direct comparison more difficult.

A notable limitation relates to the substantial variation in effect sizes, particularly within the transcutaneous VNS subgroup where wide confidence intervals suggest imprecision and the potential influence of small-study effects. Differences in participant characteristics, including age, baseline motor function, stroke chronicity, and lesion characteristics, may have influenced individual responses. However, incomplete reporting in several trials limited the ability to perform more detailed subgroup analyses. The use of standardized mean differences allowed pooling across different motor outcome scales, but this approach may reduce clarity regarding the true magnitude of clinical improvement.

Risk-of-bias considerations also temper confidence in the findings. The ROB2 assessment indicated that several studies had some concerns in domains related to randomization procedures, missing outcome data, or the selection of reported outcomes. Although no trial was rated as high risk of bias, these uncertainties may still affect the overall reliability of the evidence. Although all included trials employed the FMA-UE as a primary outcome measure, enabling a consistent pooled analysis of motor impairment, there was substantial variation in the supplementary assessment tools used across studies (such as the Wolf Motor Function Test or Action Research Arm Test). The lack of standardized secondary measures across all trials, combined with variable follow-up durations, adds challenges to a more comprehensive interpretation of functional recovery beyond impairment scales. The possibility of publication bias should also be considered, since studies with null or negative findings are less likely to be published. Practical adoption of VNS faces hurdles, including the high cost and surgical risks associated with implanted systems. While tVNS is non-invasive and more scalable, its comparative efficacy and the requirement for intensive, therapist-guided training protocols remain challenges for widespread clinical implementation.

Overall, these limitations emphasize the need for larger and more methodologically rigorous randomized controlled trials that employ consistent stimulation parameters, harmonized motor outcome measures, and comprehensive reporting of participant and intervention characteristics. Such improvements are essential to strengthen the evidence base regarding the role of VNS in stroke rehabilitation.

Conclusion

This meta-analysis shows that vagus nerve stimulation, when paired with structured upper-limb rehabilitation, yields meaningful improvements in post-stroke motor recovery. Our findings confirm that VNS-augmented rehabilitation provides significantly greater gains in upper-limb motor function compared with rehabilitation alone, although the magnitude of benefit varied across studies, particularly between implanted and transcutaneous stimulation modalities. The observed variability is likely attributable to differences in stimulation parameters, timing of pairing with motor tasks, intervention dose, and patient characteristics such as stroke chronicity and baseline impairment. Despite this heterogeneity, the overall evidence consistently supports the effectiveness of VNS as an adjunct that enhances the motor gains achievable through task-specific rehabilitation.

These findings underscore the importance of integrating neuromodulatory approaches such as VNS into contemporary post-stroke rehabilitation frameworks, particularly when delivered alongside high-quality, repetitive, and goal-directed upper-limb training. A treatment model that combines evidence-based rehabilitation with targeted neuromodulation has the potential to amplify experience-dependent plasticity and maximize functional recovery in appropriately selected patients.

Future research should address current limitations by employing larger, well-powered randomized trials, standardizing stimulation protocols, and harmonizing outcome measures across studies. Identifying clear responder profiles through neuroimaging, neurophysiological markers, and cognitive assessment will further refine patient selection and optimize treatment precision. Collaborative efforts among neurologists, physiatrists, physiotherapists, and neuromodulation specialists will be essential for designing holistic and scalable treatment pathways. By adopting a structured and individualized approach, clinicians may better leverage the synergistic effects of VNS and rehabilitation to improve upper-limb function, promote long-term recovery, and enhance quality of life for individuals living with chronic stroke.

Supplementary materials

The Supplementary information includes:

- Appendix 1. Classification of Fugl-Meyer Assessment Upper Extremity (FMA-UE) Severity Levels.

This supplemental material has been provided by the authors to give readers additional information about their work.

The file can be accessed using: https://www.editorialpark.com/download/article-supp/761/Appendix-1.-Classification-of-Fugl-Meyer-Assessment-Upper-Extremity-(FMA-UE)-Severity-Levels.docx.

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