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A systematic review and network meta-analysis of the application effect of neural regulation combined with rehabilitation training in the rehabilitation of neurological diseases

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ADMINISTRATIVE INFORMATION

Support - No.

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 May 2026 and was last updated on 25 May 2026.

INTRODUCTION

Review question / Objective P: Patients with neurological diseases (stroke, SCI, PD) confirmed by clinical diagnosis and imaging examinations, aged ≥18 years; I: Neuromodulation techniques (rTMS/tDCS/VNS/SCS) combined with any form of structured rehabilitation training; C: Rehabilitation training alone / sham stimulation combined with rehabilitation training / routine care; O: Primary outcomes: Fugl-Meyer Assessment (FM), Action Research Arm Test (ARAT), Barthel Index (BI). Secondary outcomes: Modified Ashworth Scale (MAS), Box and Block Test (BBT), Lower Extremity Motor Score (LEMS), Unified Parkinson's Disease Rating Scale Part III (UPDRS-III), 6-Minute Walk Distance (6MWD); S: Randomized Controlled Trials (RCTs).

Condition being studied Neurological diseases are one of the leading global causes of disability. This systematic review and network meta-analysis focuses on three common and disabling neurological conditions: stroke, spinal cord injury (SCI), and Parkinson's disease (PD).

Stroke includes ischemic and hemorrhagic stroke. Among stroke survivors, approximately 70–80% are left with persistent functional impairments, including motor dysfunction, reduced activities of daily living, and impaired walking ability. These deficits severely affect patients' quality of life.

Spinal cord injury can be complete or incomplete according to the American Spinal Injury Association (ASIA) impairment scale. Around 90% of individuals with SCI experience neurological dysfunction, leading to lower extremity motor deficits, spasticity, and gait impairment.

Parkinson's disease is a progressive neurodegenerative disorder characterized by motor symptoms such as bradykinesia, rigidity, tremor, and postural instability. These symptoms are commonly assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III).

All three conditions share the common feature of impaired motor function that limits independence

and rehabilitation outcomes. While conventional rehabilitation training is a cornerstone therapy, its efficacy is limited for patients with moderate-to-severe deficits. Therefore, this study investigates the application of neuromodulation techniques (repetitive transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, and spinal cord stimulation) combined with rehabilitation training to improve motor recovery, activities of daily living, and walking ability in these neurological diseases.

METHODS

Participant or population Patients with confirmed neurological diseases including: (1) stroke (ischemic or hemorrhagic, acute/subacute/chronic phase); (2) spinal cord injury (complete or incomplete, graded by ASIA); (3) Parkinson's disease (UK Brain Bank or MDS criteria). Aged ≥18 years, no sex or nationality restrictions.

Intervention Neuromodulation techniques combined with conventional rehabilitation (CR). Neuromodulation includes: repetitive transcranial magnetic stimulation (rTMS: high-frequency ≥5 Hz, low-frequency ≤1 Hz, iTBS, cTBS); transcranial direct current stimulation (tDCS: anodal, cathodal, bilateral); vagus nerve stimulation (VNS: implantable or transcutaneous auricular VNS); spinal cord stimulation (SCS: epidural or transcutaneous). Rehabilitation includes exercise therapy, occupational therapy, balance/gait training, robot-assisted or virtual reality training.

Comparator Control groups receive one of: (1) rehabilitation training alone; (2) sham stimulation plus rehabilitation training; (3) other neuromodulation techniques plus rehabilitation training; (4) routine care or sham treatment.

Study designs to be included Randomized controlled trials (RCTs), including parallel-design and cross-over design (using only pre-crossover data).

Eligibility criteria Inclusion: RCTs on neurological diseases (stroke, SCI, PD) comparing neuromodulation+rehabilitation vs. control, reporting at least one primary/secondary outcome. Exclusion: non-RCTs; animal/cell/healthy-participant studies; severe comorbidities (heart/liver/kidney, malignancy, mental illness); unclear intervention parameters; duplicate publications; conference abstracts; incomplete/unobtainable data; neuromodulation alone without rehabilitation.

Information sources Electronic databases: PubMed, Embase, Web of Science Core Collection, CINAHL (from inception to April 2026). Trial registries: ClinicalTrials.gov, WHO ICTRP. Supplementary searches: manual screening of reference lists of included studies and relevant systematic reviews; grey literature via Google Scholar; contacting field experts for unpublished/ongoing studies.

Main outcome(s) Primary outcomes (continuous, mean±SD): Fugl-Meyer Assessment (FM) for motor function, Action Research Arm Test (ARAT) for upper limb dexterity, Barthel Index (BI) for activities of daily living. Secondary outcomes: Modified Ashworth Scale (MAS) for spasticity, Box and Block Test (BBT), Lower Extremity Motor Score (LEMS), Unified Parkinson's Disease Rating Scale Part III (UPDRS-III), 6-Minute Walk Distance (6MWD). Effect measure: standardized mean difference (SMD) with 95% confidence/credible intervals.

Quality assessment / Risk of bias analysis The methodological quality of included RCTs will be assessed using the Cochrane Risk of Bias Tool 2.0 (RoB 2.0). Five domains are evaluated: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result. Each domain is rated as "low risk", "some concerns", or "high risk". An overall risk of bias judgment is then assigned based on domain ratings. Two researchers independently perform the assessment, with disagreements resolved by discussion or a third party. Results are visualized using the RobVis tool. The overall quality of evidence for each outcome is further evaluated using the GRADE CINeMA (Confidence in Network Meta-Analysis) framework across six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and inconsistency, resulting in four levels (high, moderate, low, very low).

Strategy of data synthesis A Bayesian random-effects model will be used for network meta-analysis (NMA) via R (netmeta, gemtc), Stata 17.0, and JAGS 4.3.2 (Markov Chain Monte Carlo, MCMC). For continuous outcomes, mean differences (MD) or standardized mean differences (SMD) with 95% credibility intervals are calculated; for binary outcomes, odds ratios or relative risks are used. MCMC settings: four chains, 50,000 iterations per chain (20,000 burn-in), thinning interval = 10. Convergence is assessed by Brooks-Gelman-Rubin diagnostic (PSRF < 1.05),

trace plots, and Monte Carlo error (<5% of posterior SD). The design-by-treatment interaction model is used to assess global consistency; node-splitting and loop-inconsistency tests (p 0.10 and $I^2 < 50\% \rightarrow$ fixed-effects model; otherwise random-effects model). Frequentist analyses are performed in parallel to verify robustness.

Subgroup analysis Subgroup analyses are conducted by disease type (stroke, spinal cord injury, Parkinson's disease) for outcomes that include multiple diseases in the network (specifically Modified Ashworth Scale [MAS] and 6-Minute Walk Distance [6MWD]) to explore differences in relative efficacy across populations. Additionally, where data allow, subgroups by disease phase (acute, subacute, chronic) and by specific neuromodulation parameters (e.g., high-frequency vs. low-frequency rTMS; anodal vs. cathodal tDCS; implanted vs. transcutaneous VNS) are considered. The transitivity assumption is evaluated within each subgroup. Results of subgroup analyses are reported as SUCRA rankings within each disease category and compared with the overall rankings.

Sensitivity analysis Sensitivity analyses are performed to test the robustness of the findings: (1) removing one study at a time (leave-one-out analysis) to assess the influence of individual studies on pooled effect sizes and SUCRA rankings; (2) excluding studies with a high overall risk of bias (RoB 2.0 "high risk" or "some concerns"); (3) excluding small-sample studies ($n < 30$ per arm); (4) comparing fixed-effects versus random-effects models; (5) comparing Bayesian versus frequentist NMA results. If the direction and magnitude of effect estimates and rankings remain unchanged after these exclusions or model changes, the conclusions are considered robust. Any notable changes are reported and discussed as potential sources of bias or heterogeneity.

Country(ies) involved China.

Keywords Neuromodulation; Rehabilitation training; Stroke; Spinal cord injury; Parkinson's disease; Network meta-analysis; Repetitive transcranial magnetic stimulation; Transcranial direct current stimulation; Vagus.

Contributions of each author
Author 1 - Ting Li.
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